Novel anemia therapies in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Anemia is common in patients with chronic kidney disease 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 chronic kidney disease. 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 2 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.

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Received 2 March 2023; revised 11 May 2023; accepted 15 May 2023

Kidney International (2023) ■, ■–■; https://doi.org/10.1016/j.kint.2023.05.009

KEYWORDS: anemia; chronic kidney disease; dialysis; erythropoiesis-stimulating agents; hypoxia-inducible factor-prolyl hydroxylase inhibitors; major adverse cardiovascular events

Anemia is common in patients with chronic kidney disease (CKD), and it 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 (KDIGO; 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; therefore, a reevaluation of the 2012 KDIGO guideline is required. In December 2019, KDIGO held the first of 2 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

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 taken orally, risk of poor gastrointestinal tolerance and non-adherence to therapy • If i.v., risk of allergic/anaphylactic reaction • If i.v., potential risk of increasing oxidative stress • If i.v., potential risk of hemosiderosis

ADPKD, autosomal dominant polycystic kidney disease; CKD, chronic kidney disease; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; i.v., intravenous.

and safety data. Given the historical nomenclature, we continue to refer to epoetins—that is, recombinant human EPO and its derivatives, but not HIF-PHIs—as ESAs throughout this document, 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 the levels in 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, although 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, though this may be infrequent for longer-acting ESAs, may be important for patients not on dialysis or those 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, and on drug dosing and 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 measure, and the advantages of HIF-PHIs therefore must be balanced against their 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] Currently, 6 HIF-PHIs are available in various jurisdictions, including daprodustat, desidustat, enarodustat, molidustat, roxadustat, and vadadustat (Tables 2 and 3).[9,20–51]

Most published phase 2 and phase 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

Table 2 | Efficacy data from phase 3 HIF-PHI clinical trials in patients with CKD not on dialysis therapy

Study; location	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 wk	Difference in mean Hb, wk 40–52: DAPRO: 12 g/dl EBP: 11.9 g/dl Difference: 0.1 g/dl (–0.1, 0.3)	Hb within target range (11–13 g/dl) during wk 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 wk	Difference in mean ΔHb, wk 28–52: DAPRO: 0.74 g/dl DPO: 0.66 g/dl Difference: 0.08 g/dl (0.03, 0.13)	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 wk	Difference in mean ΔHb, wk 16–24: DESI: 1.95 g/dl DPO: 1.83 g/dl LSMD: 0.11 g/dl (–0.12, 0.35)	Hb within target range (10–12 g/dl) during wk 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 wk	Difference in mean Hb, wk 20–24: ENARO: 10.96 g/dl DPO: 10.87 g/dl Difference: 0.09 g/dl (–0.07, 0.26)	Hb within target range (10–12 g/dl) during wk 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 wk	Difference in mean Hb, wk 30–36: MOLI: 11.28 g/dl DPO: 11.70 g/dl Difference in mean ΔHb, wk 30–36: MOLI: 1.32 g/dl DPO: 1.69 g/dl LSMD: –0.38 g/dl (–0.67, –0.08)	Hb within target range (11–13 g/dl), responder rate during wk 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 wk	Difference in mean Hb, wk 30–36: MOLI: 11.67 g/dl DPO: 11.53 g/dl Difference in mean ΔHb, wk 30–36: MOLI: 0.36 g/dl DPO: 0.24 g/dl LSMD: 0.13 g/dl (–0.15, 0.40)	Hb within target range (11–13 g/dl), responder rate during wk 30–36: MOLI: 72.0% DPO: 76.8%

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Table 2 | (Continued) **Efficacy data from phase 3 HIF-PHI clinical trials in patients with CKD not on dialysis therapy**

Study; location	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]
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 wk DB, then 18 wk OL	Difference in mean ΔHb, wk 7–9: ROXA: 1.9 g/dl PBO: –0.4 g/dl Difference: 2.2 g/dl (1.9, 2.6)[k]	Hb target: 10–12 g/dl; pts with >10 g/dl and increase in ΔHb of 1–2 g/dl at wk 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 wk	Difference in mean ΔHb, wk 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 wk	Difference in mean ΔHb, wk 18–24: ROXA: 0.15 g/dl DPO: 0.22 g/dl LSMD: –0.07 g/dl (–0.23, 0.10)	Hb within target range (10–12 g/dl), maint. rate during wk 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 wk	EMA endpoint,[g] first 24 wk: ROXA: 79.2% PBO: 9.9% Odds ratio: 34.74% (20.48%, 58.93%)[k] FDA endpoint,[h] wk 28–52: ROXA: 1.99 g/dl PBO: 0.3 g/dl LSMD: 1.69 g/dl (1.52, 1.86)[k]	Hb target: 10–12 g/dl, maint.; mean ΔHb without rescue therapy, wk 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 wk	EMA endpoint,[g] first 24 wk: ROXA: 86.0% PBO: 6.6% Odds ratio: 77.6% (44.7%, 134.5%)[k] FDA endpoint,[h] wk 28–52: ROXA: 2.00 g/dl PBO: 0.16 g/dl LSMD: 1.85 g/dl (1.74, 1.97)[k]	Hb target: 10–12 g/dl, maint.; mean ΔHb without rescue therapy, wk 28–36 (exploratory): ROXA: 2.02 g/dl PBO: 0.20 g/dl LSMD: 1.88 (1.73, 2.04) g/dl[k]
OLYMPUS[31] (NCT02174627); Global AstraZeneca	R, DB, PC; ESA-naïve; $n = 2781$; 1:1	ROXA 70 mg TIW vs. PBO; 164 wk	FDA endpoint,[h] wk 28–52: ROXA: 1.75 g/dl PBO: 0.4 g/dl LSMD: 1.35 g/dl (1.27, 1.43)[k]	Hb target: 10–12 g/dl, maint.; EMA endpoint,[g] first 24 wk: ROXA: 77% PBO: 8.5% Odds ratio: 9.12 (7.63, 10.89),[k] comparable results in iron-replete vs. 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 wk	EMA endpoint,[g] first 24 wk: 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 wk: ROXA: 96.4% (iron-replete)[i] DPO: 84.3% (iron-replete)[i] ROXA: 80.2% (non-replete)[i] DPO: 71.4% (non-replete)[i]

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Table 2 | (Continued) **Efficacy data from phase 3 HIF-PHI clinical trials in patients with CKD not on dialysis therapy**

Study; location	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]
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 wk	Difference in mean Hb, wk 20 and 24: VADA: 11.66 g/dl DPO: 11.93 g/dl LSMD: –0.26 g/dl (–0.50, –0.02)	Hb within target range (11–13 g/dl) at wk 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 300 mg QD, then adjusted to 150, 450, or 600 mg QD vs. DPO; 168 wk	Difference in mean ΔHb, wk 24–36: VADA: 1.43 g/dl DPO: 1.38 g/dl LMSD: 0.05 g/dl (–0.04, 0.15) Difference in mean ΔHb, wk 40–52[j]: VADA: 1.52 g/dl DPO: 1.48 g/dl LSMD: 0.04 g/dl (–0.06, 0.14)	Hb target range: US, 10–11 g/dl / non-US, 10–12 g/dl; Hb at target, wk 24–36: VADA: 50.4% DPO: 50.2% Hb at target, wk 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 wk	Difference in mean ΔHb, wk 24–36: VADA: 0.41 g/dl DPO: 0.42 g/dl LSMD: –0.01 g/dl (–0.09, 0.07) Difference in mean ΔHb, wk 40–52[j]: VADA: 0.43 g/dl DPO: 0.44 g/dl LSMD: 0.00 g/dl (–0.10, 0.09)	Hb target range: US, 10–11 g/dl / non-US, 10–12 g/dl; Hb at target, wk 24–36: VADA: 60.1% DPO: 60.7% Hb at target, wk 40–52: VADA: 50.7% DPO: 49.0%

AC, active-controlled; ALPS, Roxadustat in the Treatment of Anemia in Chronic Kidney Disease Patients Not Requiring Dialysis; ANDES, Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat for the Treatment of Anemia in CKD Patients; ASCEND-ND, Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Non-Dialysis; DAPRO, daprodustat; DB, double-blind; DESI, desidustat; DOLOMITES, Roxadustat in the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients, Not on Dialysis, in Comparison to Darbepoetin Alfa; DPO, darbepoetin alfa; DREAM-ND, Desidustat in Anemia due to Non-Dialysis-Dependent Chronic Kidney Disease: A Phase 3 Study; EBP, epoetin beta pegol; eGFR, estimated glomerular filtration rate; EMA, European Union European Medicines Agency; ENARO, enarodustat; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; FDA, US Food and Drug Administration; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; LSMD, least-squares mean difference; maint., maintenance; MIYABI ND-C, Molldustat Once Daily Improves Renal Anaemia by Inducing Erythropoietin Non-Dialysis-Correction; MIYABI ND-M, MIYABI Non-Dialysis Maintenance; MOLI, molidustat; NC, non-comparative; OL, open-label; OLYMPUS, Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients With CKD, Not on Dialysis; pts, patients; PBO, placebo; PC, placebo-controlled; PRO_2TECT, Study to Evaluate Vadadustat for the Correction of Anemia in Participants with Non-dialysis-dependent Chronic Kidney Disease; QD, once daily; R, randomized; RBC, red blood cell; ROXA, roxadustat; SYMPHONY ND, Phase 3 Study of Enarodustat in Anemic Patients with CKD Not Requiring Dialysis; TIW, 3 times weekly; TSAT, transferrin saturation; VADA, vadadustat; US, United States.

[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]For the 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 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy (i.e., RBC transfusion, ESA, or i.v. iron administration) prior to Hb response.

[h]For the FDA, the primary efficacy endpoint was the mean change in Hb from baseline to the average Hb level during the evaluation period (defined as wk 28–52), regardless of rescue therapy.

[i]Iron status: iron replete, TSAT ≥ 20% and ferritin ≥ 100 ng/ml; non-replete, TSAT ≤ 20%, and ferritin ≤ 100 ng/ml.

[j]Key secondary endpoint.

[k]Statistical significance reported.

Adapted from Haase.[9] Funding sources are indicated either with drug name or with individual studies. 95% confidence intervals are shown in parentheses. ESA-naïve is defined as no use of ESA for a study-defined period of time prior to start of study.

Table 3 | Efficacy data from phase 3 HIF-PHI clinical trials in patients on dialysis therapy

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 wk	Difference in mean Hb, wk 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 wk 40–52: DAPRO: 88% DPO: 90%
ASCEND-ID[36] (NCT03029208); Global	R, OL, AC; ESA-naïve and ESA-treated (limited exposure <6 wk), I-DD; $n = 312$; 1:1	DAPRO 1–4 mg QD[c] vs. DPO; 52 wk	Difference in mean ΔHb, wk 28–52: DAPRO: 1.02 g/dl DPO: 1.12 g/dl Difference: 0.10 g/dl (–0.34, 0.14)	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 wk)	Difference in mean ΔHb, wk 28–52: DAPRO: 0.28 g/dl ESA: 0.10 g/dl Difference: 0.18 g/dl (0.12, 0.24)	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 wk	Difference in mean ΔHb, wk 28–52: DAPRO: –0.04 g/dl Epoetin alfa: 0.02 g/dl Difference: –0.05 g/dl (–0.21, 0.10)	Hb target 10–11 g/dl Hb within analysis range of 10–11.5 g/dl during wk 28–52: DAPRO: 80% Epoetin alfa: 64%[l]
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 × per wk); $n = 392$; 1:1	DESI 100 mg TIW (ESA-naïve); 100, 125, or 150 mg TIW[d] (ESA-treated) vs. epoetin alfa; 24 wk	Difference in mean ΔHb, wk 16–24: DESI: 0.95 g/dl Epoetin alfa: 0.80 g/dl LSMD: 0.14 g/dl (–0.13, 0.42)	Hb within target range (10–12 g/dl) during wk 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 wk	Difference in mean Hb, wk 20–24: ENARO: 10.73 g/dl DPO: 10.85 g/dl Difference: –0.12 g/dl (–0.33, 0.10)	Hb within target range (10–12 g/dl) during EOT period: ENARO: 77.9% DPO: 88.4%

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Table 3 | (Continued) **Efficacy data from phase 3 HIF-PHI clinical trials in patients on dialysis therapy**

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]
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 wk	Difference in mean Hb, wk 33–36: MOLI: 10.63 d/dl DPO: 10.77 g/dl Difference in mean ΔHb, wk 33–36: MOLI: –0.14 g/dl DPO: –0.07 g/dl LSMD: –0.13 g/dl (–0.46, 0.19)	Hb within target range (10–12 g/dl): MOLI: 61.2%–77.8% during wk 18–52 DPO: 68.7%–88.7% during wk 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 wk	Difference in mean ΔHb, wk 23–27: ROXA: 0.7 g/dl Epoetin alfa: 0.5 g/dl Difference: 0.2 g/dl (–0.02, 0.5)	Hb target: 10–12 g/dl Hb of ≥10 g/dl, wk 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 wk, ESA-treated); $n = 239$	ESA-naïve: ROXA 50 or 70 mg TIW[c]; 24 wk ESA-treated: ROXA 70 or 100 mg TIW[d]; 52 wk	Difference in mean ΔHb, wk 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 wk 18–24 ESA-treated: 79.1% at wk 18–24 and 71.2% at wk 46–52
Akizawa *et al.*, 2020[44] (NCT02780726); Japan Astellas Pharma, Inc.	R, OL, NC; ESA-naïve ($n = 13$) and ESA-treated, PD (>4 wk); $n = 56$	ROXA 50 or 70 mg TIW[c] (ESA-naïve) or ROXA 70 or 100 mg TIW[d] (ESA-treated); 24 wk	Difference in mean Hb, wk 18–24: ESA-naïve: 1.69 g/dl ESA-treated: 0.14 g/dl	Hb within target range (10–12 g/dl) during wk 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 wk	Difference in mean Hb, wk 18–24: ROXA: –0.04 g/dl DPO: –0.03 g/dl Difference: –0.02 g/dl (–0.18, 0.15)	Hb within target range (10–12 g/dl) during wk 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 wk), I-DD; $n = 1043$; 1:1	ROXA 70–100 mg TIW[g,j] vs. epoetin alfa; 52 wk	EMA endpoint,[h] first 24 wk: ROXA: 88.2% Epoetin alfa: 84.4% Difference: 3.5% (–0.7%, 7.7%) FDA endpoint,[i] wk 28–52: ROXA: 2.57 g/dl Epoetin alfa: 2.36 g/dl LSMD: 1.18 g/dl (0.08, 0.29)[l]	Hb at target (10–12 g/dl), first 24 wk (US second. endpoint): ROXA: 84.3% Epoetin alfa: 79.5% ΔHb, wk 28–52 (EU second. endpoint): ROXA: 2.62 g/dl Epoetin alfa: 2.44 g/dl[l]

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Table 3 | (Continued) **Efficacy data from phase 3 HIF-PHI clinical trials in patients on dialysis therapy**

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]
Roxadustat (FibroGen, Inc.; Astellas Pharma, Inc.; AstraZeneca)				
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[d] vs. ESA (epoetin alfa or DPO); 52–104 wk	Difference in mean ΔHb, wk 28–36: ROXA: 0.43 g/dl ESA: 0.19. g/dl LSMD: 0.23 g/dl (0.13, 0.34)[l] Difference in mean ΔHb, wk 28–52: ROXA: 0.36 g/dl ESA: 0.19 g/dl LSMD: 0.17 g/dl (0.082, 0.261)[l]	Hb within target range (10–12 g/dl) at wk 28 to 36: 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 wk	Difference in mean ΔHb, wk 28–52: ROXA: 0.77 g/dl Epoetin alfa: 0.68 g/dl LSMD: 0.09 g/dl (0.01, 0.18)[l]	Proportion of time with Hb ≥10 g/dl during wk 28–52: ROXA: 79% Epoetin alfa: 76%
SIERRAS[49] (NCT02273726); US; FibroGen, Inc.	R, OL, AC; ESA-treated, M-DD and I-DD ($n = 71$); total $n = 741$; 1:1	ROXA 70–200 mg TIW[d,j] vs. epoetin alfa; 52 wk	Difference in mean ΔHb, wk 28–52: ROXA: 0.39 g/dl Epoetin alfa: –0.09 g/dl LSMD: 0.48 g/dl (0.37, 0.59)[l]	Hb target range: 10–12 g/dl Hb ≥10 g/dl, wk 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 wk	Difference in mean Hb, wk 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 wk 24 and 52: VADA: 75.4% and 75.7% DPO: 75.7% and 86.5%
$INNO_2VATE$[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 wk	Difference in mean ΔHb, wk 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, wk 40–52[k]: VADA: 1.42 g/dl DPO: 1.50 g/dl LSMD: –0.07 g/dl (–0.34, 0.19)	Hb target range: US, 10–11 g/dl / non-US, 10–12 g/dl; Hb at target, wk 24–36: VADA: 43.6% DPO: 56.9% Hb at target, wk 40–52: VADA: 39.8% DPO: 41.0%

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Table 3 | (Continued) **Efficacy data from phase 3 HIF-PHI clinical trials in patients on dialysis therapy**

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]
Vadadustat (Akebia Therapeutics; Otsuka Pharmaceuticals)				
$INNO_2VATE$[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 wk	Difference in mean ΔHb, wk 24–36: VADA: 0.19 g/dl DPO: 0.36 g/dl LSMD: –0.17 g/dl (–0.23, –0.10) Difference in mean ΔHb, wk 40–52[k]: VADA: 0.23 g/dl DPO: 0.41 g/dl LSMD: –0.18 g/dl (–0.25, –0.12)	Hb target range: US, 10–11 g/dl / non-US, 10–12 g/dl; Hb at target, wk 24–36: VADA: 49.2% DPO: 53.2% Hb at target, wk 40–52: VADA: 44.3% DPO: 50.9%

AC, active-controlled; ASCEND, Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat; ASCEND-D; ASCEND dialysis; ASCEND-ID, ASCEND Incident Dialysis; ASCEND-TD, ASCEND 3 times weekly dosing in dialysis; DAPRO, daprodustat; DB, double-blind; DESI, desidustat; DPO, darbepoetin alfa; DREAM-D, Desidustat in the Treatment of Anemica in CKD on Dialysis Patients; EMA, European Union European Medicines Agency; ENARO, enarodustat; EOT, end of treatment; ESA, erythropoietin-stimulating agent; FAS, full analysis set; FDA, US Food and Drug Administration; Hb, hemoglobin; HD, hemodialysis; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; HIMALAYAS, Safety and Efficacy Study of Roxadustate (FG-4592) for the Treatment of Anemia in ESRD Newly Initiated Dialysis Participants; I-DD, incident dialysis (HD and PD); I-HD, incident hemodialysis; $INNO_2VATE$, Efficacy and Safety Study to Evaluate Vadadustat for the Maintenance Treatment of Anemia in Participants with Dialysis-dependent Chronic Kidney Disease; LSMD, least-squares mean difference; M-DD, maintenance/stable dialysis (HD and PD); M-HD, maintenance/stable hemodialysis; MOLI, molidustat; MIYABI HD-N, Molldustat Once Daily Improves Renal Anaemia by Inducing Erythropoietin, Hemodialysis-Maintenance; NC, non-comparative; OL, open-label; PBO, placebo; PC, placebo-controlled; PD, peritoneal dialysis; pts, patients; PYRENEES, Roxadustat in the Treatment of Anemia in ESRD Patients on Stable Dialysis; QD, once daily; QW, once weekly; R, randomized; RBC, red blood cell; ROCKIES, Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients with Chronic Kidney Disease, on Dialysis; ROXA, roxadustat; SIERRAS, Study to Evaluate the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Participants with ESRD on Stable Dialysis; SYMPHONY HD, Phase 3 Study of Enarodustat in Anemic Patients with CKD, Hemodialysis; TIW, 3 times weekly; US, United States; VADA, vadadustat.

[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 kg or 120 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 kg.

[h]For 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 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without rescue therapy (i.e., RBC transfusion, ESA, or i.v. iron administration) prior to Hb response.

[i]For the 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.

[l]Statistical significance reported.

Adapted from Haase.[9] Funding sources are indicated either with drug name or with individual studies. 95% confidence intervals are shown in parentheses. ESA-naïve is defined as no use of ESA for a study-defined period of time prior to start of study.

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 patients with CKD not on dialysis and those on dialysis therapy (Tables 2 and 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 (Supplementary Table S1).

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 prespecified margin. This margin ideally should be based on the observed adverse event rate of the standard therapy versus placebo in randomized controlled trials (RCTs), or be one 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 prespecified 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 3 major, phase 3 programs that have examined the cardiovascular safety of HIF-PHIs have all used non-inferiority trial designs.

EFFICACY OF HIF-PHIs IN THE CORRECTION OF ANEMIA

The general consensus among the attendees was that HIF-PHIs are superior to placebo and non-inferior to ESAs in increasing and maintaining hemoglobin (Hb) concentration among CKD patients not on dialysis and those on dialysis therapy.[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 patients with CKD not on dialysis and in incident and prevalent dialysis patients (Tables 2 and 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 given 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 are generally lower than the rates among those receiving placebo.[19]

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

OPTIMAL HEMOGLOBIN TARGETS FOR THE CORRECTION OF ANEMIA

Current targets that 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, revealing that 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, 1 trial comparing a high Hb target with placebo (and a conservative rescue strategy) in CKD patients with diabetes not on dialysis found an increased rate of stroke.[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 and 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 levels between treatment arms, differences in the proportion of patients with baseline iron deficiency, and baseline imbalances in iron and hepcidin status and relevant comorbidities.

Notwithstanding the limitations in trials thus far, higher serum transferrin levels in patients treated with HIF-PHIs, as measured either directly[20,26–28,35,42–45,63–65] or indirectly by calculating total iron binding capacity, were reported across different compounds. In contrast, the effects on serum iron,

hepcidin, transferrin saturation, 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 and 5.[21,29–32,34,36–38,46–49,51]

Although the potential exists for a reduction in i.v. iron treatment, the general consensus was that HIF-PHI therapy will not eliminate the need for iron replacement in dialysis 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 health-related quality of life, higher rates of cardiovascular events, and a higher incidence of mortality.[66,67]

In summary, conference participants agreed that clinically meaningful differences in iron utilization have not been demonstrated so far using HIF-PHIs. Iron therapy will likely have a continued role in CKD patients not on dialysis and those on dialysis therapy treated with HIF-PHIs.

EFFECT OF HIF-PHIs ON HEALTH-RELATED QUALITY OF LIFE

Several large, phase 3 HIF-PHI trials have included assessments of quality of life 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 Medical Outcomes Study 36-item Short-Form Survey Physical Functioning subscore, were reported in the OLYMPUS trial, which compared roxadustat to placebo.[31] Data from the smaller, dedicated Anemia Studies in Chronic Kidney Disease (CKD): Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor (PHI) Daprodustat in Non-Dialysis Subjects Evaluating Hemoglobin (Hgb) and Quality of Life (ASCEND-NHQ) study in patients with ND-CKD, which evaluated the effects of daprodustat versus placebo on quality of life using the Medical Outcomes Study 36-item Short-Form Survey Vitality score, suggested that those receiving daprodustat had a higher vitality score (improvement in fatigue).[68]

The patient representatives in attendance felt that although health-related quality of life was important, a new treatment ideally should 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 regarding 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 nondialysis populations within target ranges recommended for ESAs.

Patients with CKD not on dialysis therapy. Roxadustat was the first HIF-PHI to be reviewed by the FDA. Data submitted in support of the FDA New Drug Application included 3 separate trials comparing roxadustat with placebo that were pooled for meta-analyses in the CKD population not on dialysis ($n = 4270$).[70,71] Data from a fourth study, comparing roxadustat to darbepoetin alfa, were analyzed separately.[28] The pooled analyses for roxadustat did not have prespecified non-inferiority margins that were agreed upon with the FDA.[71,72] A comparison of the upper limits of the 95% confidence interval (CI), against the prespecified non-inferiority margin in the daprodustat and vadadustat trials (hazard ratio [HR] 1.25), revealed that roxadustat would not have met the criteria for non-inferiority in pooled analyses of MACE in the CKD population not on dialysis, 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) that were 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] In an assessment of events occurring while patients were on treatment and for 1 week after treatment discontinuation (on-treatment + 7 days analyses), 277 events (7.2%) were recorded in the roxadustat arm, compared with 131 events (5.6%) in the placebo arm (HR 1.38; 95% CI: 1.11–1.70). A caveat in these analyses is the higher dropout rate in the placebo arm, compared to that in the roxadustat arm, with a potential for bias that may have disadvantaged roxadustat.

Data from vadadustat phase 3 trials of ESA-treated ($n = 1725$) and ESA-untreated ($n = 1751$) patients with CKD not on dialysis were pooled, as prespecified, with darbepoetin alfa treatment as the comparator arm in both trials.[34] The primary MACE analysis did not meet the prespecified HR = 1.25 non-inferiority margin (HR 1.17; 95% CI: 1.01–1.36), and it showed a higher risk of MACE in the vadadustat arm. The excess risk was accounted for by nonfatal myocardial infarction and death from noncardiovascular causes. Subgroup analyses found a regional difference in the study results, with the increased MACE risk observed in non-US study sites (HR 1.30; 95% CI: 1.05–1.62) but no difference in risk observed in the US study sites (HR 1.06; 95% CI: 0.87–1.29).[34]

Daprodustat non-inferiority trials met the prespecified non-inferiority margins of an HR of 1.25 in primary analyses of the CKD population not on dialysis 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 receive daprodustat had a higher incidence of MACE than those randomized to receive an ESA in the ND-CKD study (14.1% vs. 10.5%; HR 1.40; 95% CI:

Table 4 | Iron parameters from phase 3 HIF-PHI clinical trials in patients with CKD not on dialysis therapy

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 per 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	i.v. iron: 13% in HIF-PHI vs. 11% in ESA between wk 36–48	Hepcidin: decreased from median (IQR) 105.6 ng/ml (61.7–165.9) to 82.7 ng/ml (43.0–142.4) in HIF-PHI vs. 105.3 ng/ml (61.2–169.8) to 120.1 ng/ml (66.5–201.1) 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 ng/ml (164.0–456.0) to 240.0 ng/ml (135.0–425.0) in HIF-PHI vs. 275.0 ng/ml (171.0–449.0) to 262.0 (150.5–447.5) in ESA TIBC: 45.0 mmol/l (40.0–50.0) to 50.0 mmol/l (45.0–55.0) in HIF-PHI vs. 44.0 mmol/l (40.0–49.0) to 44.0 mmol/l (39.0–49.0) in ESA Iron: 13.0 mmol/l (10.0–16.0) to 14.0 mmol/l (11.0–17.0) in HIF-PHI vs. 13.0 mmol/l (10.0–16.0) to 14.0 mmol/l (11.0–18.0) in ESA
Roxadustat (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)				
ALPS[29] (NCT01887600); Europe Astellas Pharma, Inc. *N* = 594	eGFR <60 ml/min per 1.73 m^2 ESA naïve Ferritin ≥30 ng/ml TSAT ≥5%	Oral iron recommended i.v. iron as rescue if Hb <8.5 g/dl and ferritin <100 ng/ml or TSAT <20%	Not reported	Hepcidin: decreased from 37.9 mg/l (36.6) to 24.6 mg/l (30.1) in HIF-PHI and from 41.2 mg/l (37.6) to 39.4 mg/l (37.8) 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 per 1.73 m^2 Hb ≤10 g/dl Ferritin ≥30 ng/ml TSAT ≥5%	Oral iron encouraged i.v. iron rescue	% receiving i.v. iron: 2.5% HIF-PHI vs. 4.9% placebo; HR 0.39 (95% CI 0.15–0.81)	Hepcidin: −22.1 mg/l (80.9) in HIF-PHI and 3.9 mg/l (80.9) in placebo; LSMD of −25.7 μg/l (95% CI −38.5 to −12.9) TIBC: increased in HIF-PHI and decreased in placebo; LSMD 38.65 μg/dl (95% CI 31.9–45.5) TSAT: LSMD −0.1% (95% CI −2.0, 1.7) Iron: LSMD 8.3 mg/l (95% CI 2.9, 13.6) Ferritin: LSMD −57.5 ng/ml (95% CI −92.8, −22.3)
OLYMPUS[31] (NCT02174627); Global AstraZeneca *N* = 2781	ESA naïve eGFR <60 ml/min per 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 i.v. 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 i.v. 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: LSMD −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)

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Table 4 | (Continued) **Iron parameters from phase 3 HIF-PHI clinical trials in patients with CKD not on dialysis therapy**

Study; location	Entry criteria	Iron strategy	Iron utilization	Changes in markers of iron metabolism
Roxadustat (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)				
DOLOMITES[32] (NCT02021318); Europe Astellas Pharma, Inc. $N = 616$	ESA naïve eGFR <60 ml/min per 1.73 m^2 Mean of 2 recent Hb ≤10.5 g/dl	Oral iron recommended in HIF-PHI and i.v. 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 i.v. iron required if ferritin <100 ng/ml or TSAT <20% in ESA	i.v. iron: 6.2% HIF-PHI, 12.7% ESA Monthly dose 34.7 mg (30.0) HIF-HI 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 pmol/l (521.4) HIF-PHI vs. –72.4 pmol/l (459.3) ESA TSAT: 1.3% (11.8%) HIF-PHI vs. 5.2% (13.2%) Iron: 1.1 mmol/l (5.9) HIF-PHI vs. 2.2 pmol/l (6.8) ESA
Vadadustat (Akebia Therapeutics; Otsuka Pharmaceuticals)				
PRO_2TECT[34] (NCT02648347); Global $N = 1751$	ESA naïve eGFR ≤60 ml/min per 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 per 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

ALPS, Roxadustat in the Treatment of Anemia in Chronic Kidney Disease Patients Not Requiring Dialysis; ANDES, Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat for the Treatment of Anemia in CKD Patients; ASCEND-ND, Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Non-Dialysis; CI, confidence interval; DOLOMITES, Roxadustat in the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients, Not on Dialysis, in Comparison to Darbepoetin Alfa; eGFR, estimated glomerular filtration rate; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; HR, hazard ratio; IQR, interquartile range; i.v., intravenous; LSMD, least squares mean difference; OLYMPUS, Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients With CKD, Not on Dialysis; PRO_2TECT, Study to Evaluate Vadadustat for the Correction of Anemia in Participants with Non-dialysis-dependent Chronic Kidney Disease; TIBC, total iron binding capacity; TSAT, transferrin saturation; US, United States.

Table 5 | Iron parameters from phase 3 HIF-PHI clinical trials in patients on dialysis therapy

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 i.v. dose: 139.2 mg (171.1) to 90.8 mg (SE 3.3) HIF-PHI vs. 137.4 mg (174.7) to 99.9 mg (SE 3.3) 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	Mean monthly i.v dose: 159.3 mg (207.1) to 142 mg (161) HIF-PHI vs. 180.1 mg (209.9) to 128 mg (137) 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 i.v. iron: Wk 28–52: 38% in HIF-PHI vs. 40% in ESA Wk 1–52: 51% HIF-PHI vs. 51% ESA Mean monthly dose: Wk 28–52: 104.9 mg (222.5) HIF-PHI vs. 103.1 mg (244.7) ESA Wk 1–52: 99.0 mg (187.1) HIF-PHI vs. 104.4 mg (210.8) ESA Mean treatment difference: –8.1 mg (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 wk Mean of last 2 Hb ≤10 g/dl ferritin ≥100 ng/ml TSAT ≥20%	Oral iron encouraged; i.v. iron allowed if Hb response inadequate and ferritin ≤100 ng/ml and TSAT <20%	% receiving i.v. iron: Wk 28–52: 83.7% HIF-PHI vs. 85.4% ESA Mean monthly i.v. dose: Difference: –4.4 mg (95% CI –20.7, 12.0) Mean monthly oral dose: 290.7 mg (95% CI –463.2, 1044.5)	Hepcidin: –64.8 mg/l (95% CI –74.3, –55.3) HIF-PHI vs. –54.1 mg/l (95% CI –63.4, –44.7) ESA; difference –10.7 mg/l (95% CI –23.2, 1.77) Ferritin: –191.3 ng/ml (95% CI –234.4, –148.2) HIF-PHI vs. –130.0 ng/ml (95% CI –172.9, –87.2) ESA; difference –61.3 ng/ml (95% CI –117.0, –5.6) 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 mg/dl (95% CI 33.3, 42.1) HIF-PHI vs. 1.7 mg/dl (95% CI –2.7, 6.0) ESA; difference 36.1 mg/dl (95% CI 30.2, 41.9) Iron: 2.1 mg/dl (95% CI –1.2, 5.5) HIF-PHI vs. –4.7 mg/dl (95% CI –8.0, –1.5) ESA; difference 6.9 mg/dl (95% CI 2.4, 11.3)
PYRENEES[47] (NCT02278341); Europe	ESA users ferritin ≥100 ng/ml TSAT ≥20%	For patients on HIF-PHI, oral iron was permitted. i.v. iron was allowed only if Hb did not respond	Mean monthly i.v. dose: HIF-PHI: 21.6 mg	Hepcidin: –32.7 (42.3) HIF-PHI vs. –17.5 (47.3) ESA at wk 52 Ferritin: lower in HIF-PHI and TSAT levels similar; exact changes not reported

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Table 5 | (Continued) **Iron parameters from phase 3 HIF-PHI clinical trials in patients on dialysis therapy**

Study; location	Entry criteria	Iron strategy	Iron utilization	Changes in markers of iron metabolism
Roxadustat (FibroGen, Inc.; Astellas Pharma, Inc.; AstraZeneca)				
Astellas Pharma, Inc. Prevalent HD *N* = 3188		adequately after 2 consecutive dose increases or if the maximum dose was reached and ferritin <100 ng/ml or TSAT <20% or the patient was intolerant to oral iron	ESA: 53.5 mg Difference: −31.9 (95% CI −41.4, −22.4)	TIBC: 10.0 mmol/l (8.8) HIF-PHI vs. 2.7 mmol/l (6.4) ESA Iron: −0.3 mmol/l (7.4) HIF-PHI vs. −1.2 mmol/l (6.3) 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, i.v. iron permitted if Hb did not increase sufficiently after ≥2 doses and ferritin <100 ng/ml or TSAT <20%	Mean monthly i.v. dose: 58.7 mg HIF-PHI vs. 91.4 mg ESA Oral iron use 20.7% HIF-PHI vs. 18.0% ESA	Hepcidin: −45.0 ng/ml (95% CI −57.5, −32.5) HIF-PHI vs. −16.8 ng/ml (95% CI −29.2, −4.4) ESA; difference: −18.2 ng/ml (95% CI −42.0, −14.5) 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 mg/l (95% CI −126.2, −82.8) HIF-PHI vs. −41.2 mg/l (95% CI −62.1, −20.3) ESA; difference −63.3 mg/l (95% CI −87.4, −39.2) TIBC: 35.0 mg/dl (95% CI 31.8, 38.2) HIF-PHI vs. −2.4 (95% CI −5.5, 0.7) ESA; difference 37.4 mg/dl (95% CI 33.8, 41.0) Iron: 6.6 mg/dl (95% CI 4.5, 8.7) HIF-PHI vs. −5.5 mg/dl (95% CI −7.6, −3.5) ESA; difference 12.1 mg/dl (95% CI 9.8, 14.5)
SIERRAS[49] (NCT02273726); US FibroGen, Inc. Prevalent HD *N* = 741	ESA users Ferritin ≥100 ng/ml TSAT ≥20%	Oral iron encouraged i.v. iron if oral not tolerated or if iron deficient	Mean monthly i.v. dose: 17.1 mg (53.4) HIF-PHI vs. 37.0 mg (106.8) ESA Difference: −20.1 (95% CI −33.8, −6.45)	Hepcidin: decreased in both groups; difference: −19.12 ng/ml (95% CI −39.52, 1.28) Ferritin: decreased in both groups; difference: −41.71 ng/ml (95% CI −96.51, 13.09) Iron: increased in roxadustat; difference: 6.33 mg/dl (95% CI 2.20, 10.45) 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 ng/ml (140.1) to 137.4 ng/ml (119.9) in HIF-PHI vs. 190.4 ng/ml (135.9) to 158.2 ng/ml (123.4) in ESA Ferritin: 846.8 ng/ml (562.7) to 787.3 ng/ml (550.2) in HIF-PHI vs. 840.7 ng/ml (538.5) to 828.9 ng/ml (565.8) 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 wk 40–52: Hepcidin: 122.4 ng/ml (109.5) to 95.7 ng/ml (72.1) in HIF-PHI vs. 126.9 ng/ml (111.2) to 101.1 ng/ml (95.6) in ESA Ferritin: 469.7 ng/ml (316.9) to 555.5 ng/ml (453.2) in HIF-PHI vs. 527.8 ng/ml (401.1) to 559.4 ng/ml (458.5) 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

ASCEND, Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat; ASCEND-D, ASCEND dialysis; ASCEND-ID, ASCEND incident dialysis; ASCEND-TD, ASCEND 3 times weekly dosing in dialysis; CI, confidence interval; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; HD, hemodialysis; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; HIMALAYAS, Safety and Efficacy Study of Roxadustate (FG-4592) for the Treatment of Anemia in ESRD Newly Initiated Dialysis Participants; $INNO_2VATE$, Efficacy and Safety Study to Evaluate Vadadustat for the Maintenance Treatment of Anemia in Participants with Dialysis-dependent Chronic Kidney Disease; IQR, interquartile range; PYRENEES, Roxadustat in the Treatment of Anemia in ESRD Patients on Stable Dialysis; ROCKIES, Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients with Chronic Kidney Disease, on Dialysis; SIERRAS, Study to Evaluate the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Participants with ESRD on Stable Dialysis; TIBC, total iron binding capacity; TSAT, transferrin saturation; US, United States.

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]

A general view among conference participants is that major clinical trials have failed to conclusively demonstrate that HIF-PHIs are non-inferior to placebo or conventional ESAs for cardiovascular outcomes in patients with CKD not on dialysis (Table 6).[9,21,27,29–31,34] In fact, variable results have been reported for different HIF-PHIs and for different study settings, depending on the type of analyses being performed (e.g., intention-to-treat vs. on-treatment analyses). Potential explanations for the differential effects on MACE outcomes of different trials and different agents may result from imbalances in patient characteristics or geographic location at baseline, or from nonmatching intervals of follow-up assessment after the last study drug dose in different randomized groups.[73]

Dialysis population. In contrast to the trial results seen in patients with CKD not on dialysis, the consensus was that HIF-PHIs in general met non-inferiority criteria for MACE in cardiovascular outcome trials in the dialysis populations (Table 7),[9,36–38,42–51] although controversies surrounding interpretation of the data were discussed. Moreover, in most clinical trials, the efficacy and safety of HIF-PHIs were 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 results of 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 being statistically significant for non-inferiority. A fourth trial,[47] 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- versus ESA-treated patients (8.9 per 100 patient-years [PYs] vs. 6.3 per 100 PYs; HR 1.54; 95% CI: 1.04–2.28).[70] In a published analysis of the 4 roxadustat trials in the dialysis population,[74] the frequency of MACE and MACE+ (a composite of MACE plus unstable angina or congestive heart failure requiring hospitalization) in the on-treatment plus 7 day analyses was different between incident and prevalent dialysis patients suggesting benefit in incident patients but harm in prevalent patients. Non-inferiority of roxadustat versus ESA (MACE, MACE+ and all cause mortality) was reported in a pooled analysis of incident dialysis patients from 3 roxadustat trials (Himalayas, Rockies, and Sierras) that also included patients not on dialysis from the Dolomites (vs. darbepoetin alfa) trial.[74a]

Vadadustat dialysis phase 3 trials pooled results from 2 studies of prevalent ($n = 3554$) and incident ($n = 369$) patients, with darbepoetin alfa treatment as the comparator group (Table 3).[51] Pooled results showed similar MACE rates in the 2 arms and met non-inferiority criteria (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 prespecified non-inferiority margin of 1.25 in primary analyses of the dialysis populations (HR: 0.93; 95% CI: 0.81–1.07).[21,37] The on-treatment sensitivity analysis of the dialysis population produced results similar to those of the primary analysis (Table 7).

In most clinical trials, the 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 a similar risk of MACE (HR 0.83; 95% CI: 0.61–1.13) and a 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 dialysis patients and prevalent dialysis patients was not reported.

Despite the overall consensus that HIF-PHI met non-inferiority criteria for MACE in cardiovascular outcome trials involving dialysis populations, the controversy that has surrounded interpretation of the relevant data for roxadustat in this context was recognized. This controversy 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 administration of 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—that is, upregulation of transferrin,[78] or the interference of HIF with the coagulation system, as, for example, through increased expression of plasminogen activator inhibitor—may contribute to thrombotic risk.[79]

Roxadustat showed an excess risk of thrombosis for trials involving both CKD patients not on dialysis (vs. placebo) and those on dialysis therapy (vs. ESA).[70] A pooled analysis of roxadustat trials showed higher risks of thromboembolic events that were associated with the rate of Hb rise.[71] 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 is unclear. Concerns surrounding the thrombotic risk with vadadustat were

Table 6 | Cardiovascular safety data from phase 3 non-inferiority HIF-PHI clinical trials in patients with CKD not on dialysis therapy

Study; location; sponsor	Study design; no. of patients; randomization	Treatment; starting dose[a]; study duration	Primary outcome HR; non-inferiority margin (95% CI)	Other outcome HRs (95%CI)
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 wk	First occurrence of adjudicated MACE (composite of death, nonfatal myocardial infarction, or nonfatal stroke): HR 1.03 (95% CI 0.89–1.19) Non-inferiority 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 wk	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) Non-inferiority 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 0.94–1.21) MACE, on treatment + 7 d: 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 wk		
OLYMPUS[31] (NCT02174627); Global AstraZeneca	R, DB, PC; ESA-naïve; $n = 2781$; 1:1	ROXA 70 mg TIW vs. PBO, 164 wk		
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 wk	(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 (95% CI 1.01–1.36) Non-inferiority 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 wk		

AC, active-controlled; ALPS, Roxadustat in the Treatment of Anemia in Chronic Kidney Disease Patients Not Requiring Dialysis; ANDES, Phase 3, Randomized, Double-Blind, Placebo Controlled Study of the Efficacy and Safety of Roxadustat for the Treatment of Anemia in CKD Patients; ASCEND-ND, Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Non-Dialysis; CI, confidence interval; DAPRO, daprodustat; DB, double-blind; DPO, darbepoetin alfa; EBP, epoetin beta pegol; eGFR, estimated glomerular filtration rate; EMA, European Medicines Agency; EOT, end of treatment; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; HR, hazard ratio; MACE, major adverse cardiovascular event; maint., maintenance; NC, non-comparative; OL, open-label; OLYMPUS, Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients With CKD, Not on Dialysis; PBO, placebo; PC, placebo-controlled; PRO_2TECT, Study to Evaluate Vadadustat for the Correction of Anemia in Participants with Non-dialysis-dependent Chronic Kidney Disease; QD, once daily; R, randomized; ROXA, roxadustat; TIW, 3 times weekly; VADA, vadadustat; US, United States.

[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,[27] 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.

Adapted from Haase.[9] Funding sources are indicated either with drug name or with individual studies. 95% CIs are shown in parentheses. ESA-naïve is defined as no use of ESA for a study-defined period of time prior to start of study.

Table 7 | Cardiovascular safety data from phase 3 non-inferiority HIF-PHI clinical trials in patients on dialysis therapy

Study; location; sponsor	Study design; no. of patients; randomization	Treatment; starting dose[a]; study duration	Primary outcome HR; non-inferiority margin (95% CI)	Other outcome HRs (95% CI)
Daprodustat (GlaxoSmithKline)				
ASCEND-ID[36] (NCT03029208); Global	R, OL, AC; ESA-naïve and ESA-treated (limited exposure <6 wk), I-DD; $n = 312$; 1:1	DAPRO 1–4 mg QD[b] vs. DPO; 52 wk	Exploratory analysis: first occurrence of adjudicated MACE (composite of death from any cause, nonfatal myocardial infarction or nonfatal 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 wk	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 wk	First occurrence of adjudicated MACE: Absolute rate difference per 100 PYs 2.3 (95% CI –4.4 to 9.0)	Worsening hypertension (*post hoc*): DAPRO vs. epoetin: relative risk 0.83 (0.50–1.39)
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 wk	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 wk, ESA-treated); $n = 239$	ESA-naïve: ROXA 50 or 70 mg TIW[b]; 24 wk ESA-treated: ROXA 70 or 100 mg TIW[c]; 52 wk	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 wk); $n = 56$	ROXA 50 or 70 mg TIW[b] (ESA-naïve) or ROXA 70 or 100 mg TIW[c] (ESA-treated); 24 wk	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 wk	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 wk), I-DD; $n = 1043$; 1:1	ROXA 70–100 mg TIW[e,f] vs. epoetin alfa; 52 wk	Pooled analysis of HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS MACE (myocardial infarction, stroke, and all-cause mortality)	Arteriovenous fistula thrombosis: ROXA $n = 39$ (7.5%) vs. $n = 21$ (4.1%) Pooled analysis of HIMALAYAS, PYRENEES, ROCKIES, and SIERRAS:

(*Continued on following page*)

Table 7 | (Continued) **Cardiovascular safety data from phase 3 non-inferiority HIF-PHI clinical trials in patients on dialysis therapy**

Study; location; sponsor	Study design; no. of patients; randomization	Treatment; starting dose[a]; study duration	Primary outcome HR; non-inferiority margin (95% CI)	Other outcome HRs (95% CI)
Roxadustat (FibroGen Inc.; Astellas Pharma, Inc.; AstraZeneca)				
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 wk	HR 1.09 (95% CI 0.95–1.26) Non-inferiority margin: HR 1.30	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)
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 wk		
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 wk		
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 wk	Cardiovascular event, cardiac failure VADA: 13 (8.0%); DPO 15 (9.3%)	Retinal disorder: VADA 21 (13.0%); DPO 16 (9.9%)
$INNO_2VATE$[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 wk	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, 0.84–1.10) Death from cardiovascular causes: HR 0.96 (95% CI, 0.77–1.20) All-cause death: HR 0.95 (95% CI, 0.81–1.12) Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: HR 0.95 (95% CI, 0.80–1.14)
$INNO_2VATE$[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 wk		

AC, active-controlled; ASCEND, Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat; ASCEND-D; ASCEND dialysis; ASCEND-ID, ASCEND incident dialysis; ASCEND-TD, ASCEND 3 times weekly dosing in dialysis; BP, blood pressure; CI, confidence interval; 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; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; HIMALAYAS, Safety and Efficacy Study of Roxadustate (FG-4592) for the Treatment of Anemia in ESRD Newly Initiated Dialysis Participants; HR, hazard ratio; I-DD, incident dialysis (HD and PD); I-HD, incident hemodialysis; $INNO_2VATE$, Efficacy and Safety Study to Evaluate Vadadustat for the Maintenance Treatment of Anemia in Participants with Dialysis-dependent Chronic Kidney Disease; N/A, not applicable; MACE, major adverse cardiovascular event; M-DD, maintenance/stable dialysis (HD and PD); M-HD, maintenance/stable hemodialysis; MOLI, molidustat; N/A, not applicable; NC, non-comparative; OL, open-label; PBO, placebo; PC, placebo-controlled; PD, peritoneal dialysis; PY, person-year; PYRENEES, Roxadustat in the Treatment of Anemia in ESRD Patients on Stable Dialysis; QD, once daily; QW, once weekly; R, randomized; ROCKIES, Safety and Efficacy Study of Roxadustat to Treat Anemia in Patients with Chronic Kidney Disease, on Dialysis; ROXA, roxadustat; SIERRAS, Study to Evaluate the Efficacy and Safety of Roxadustat in the Treatment of Anemia in Participants with ESRD on Stable Dialysis; TIW, 3 times weekly; VADA, vadadustat.

[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 or 120 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 kg.

[f]Titrated to achieve an Hb level of 11 g/dl and to maintain Hb levels of 10–12 g/dl.

Adapted from Haase.[9] Funding sources are indicated either with drug name or with individual studies. 95% CIs are shown in parentheses. ESA-naïve is defined as no use of ESA for a study-defined period of time prior to start of study.

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 an active comparator.[21,37]

Hypertension

Preclinical 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 (Anemia Study in Chronic Kidney Disease (CKD): Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor (PHI) Daprodustat-Blood Pressure [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 that are focused specifically on the interactions between HIF-PHIs and lipid metabolism have not yet been conducted, significant and consistent reductions in total cholesterol, and in low-density and high-density lipoprotein cholesterol levels were reported in patients treated with roxadustat or daprodustat (those not on dialysis and those on dialysis therapy).[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 assessed in studies conducted so far.

Kidney disease progression

Pharmacologic HIF activation has been studied in multiple kidney disease models.[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 appear to be context-dependent and less consistent.[4] This lack of consistency has raised concerns that anemia therapy with HIF-PHIs may worsen CKD in certain subgroups of patients. In 1 trial of molidustat versus ESA, the risk of CKD progression was higher with molidustat, but whether this finding is specific to molidustat is unclear.[25]

Prespecified secondary analyses of phase 3 trials of daprodustat and vadadustat in CKD patients not on dialysis showed no beneficial or harmful effects of either drug on CKD outcomes, including the need for dialysis, kidney transplantation, or >40% decline in estimated glomerular filtration rate.[21,34] A phase 3 trial of roxadustat[31] suggested that its use was associated with greater decline in kidney function, compared with placebo. The annual rate of change in estimated glomerular filtration rate 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 to −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 they 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 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.

Although 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 a 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 no consistent signal is present across the HIF-PHIs of an excess risk of malignancy-related adverse events. However, 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 that for 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 to provide longer-term follow-up data; 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 CKD patients not on dialysis (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. These findings may be due to the molecular structure of roxadustat, which is similar to that of triiodothyronine (T3), so that its binding to thyroid hormone receptor β may lead to the downregulation of thyrotropin-releasing hormone (TRH). To our knowledge, no report has been made of hypothyroidism as a complication in patients treated with other HIF-PHIs.

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

No trials have conducted head-to-head comparison of the different HIF-PHIs in patients with CKD not on dialysis or those on dialysis therapy. 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. The consensus among conference participants was that the appropriate dose depends on the drug and that patients should follow label recommendations. A general consensus was also that the starting HIF-PHI dose should be lower for those who are ESA-naïve versus the dose for 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 level 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 stepwise fashion similar to that in trial protocols based on the current Hb level and its rate of change.

USE OF HIF-PHIs IN SUBPOPULATIONS OF INTEREST

Patients hyporesponsive to ESAs

By lowering hepcidin levels, HIF-PHIs theoretically may 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 levels, the same may not be true for HIF-PHIs.[16,45] However, C-reactive protein 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 the data on the effect of HIF-PHIs in ESA-hyporesponsive patients are limited.

Although the use of HIF-PHIs in combination with ESAs theoretically might be advantageous for patients who are ESA hyporesponsive, no available data support this strategy in clinical practice at present.[102] As with all drugs, a risk for drug–drug interactions is present with HIF-PHIs, particularly when they are used in combination with other oral agents (Supplementary Table S2).

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 hospitalization.[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 the data are insufficient to support 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 enhances 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

Although 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-PHI use could potentially promote graft rejection or increase the risk of malignancy.[108] Experience is limited in 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 discussed further here.[3] In

analogy with HIF-PHIs, sodium–glucose cotransporter-2 (SGLT2) inhibitors also are considered to stimulate endogenous EPO production.

SGLT2 inhibitors

In addition to their antidiabetic and beneficial cardiovascular and kidney effects, SGLT2 inhibitors have been shown to increase Hb in patients with kidney disease and/or heart failure.[109–114] Because increased Hb in patients treated with SGLT2 inhibitors appears to be independent of diuretic use and/or rate of intravascular volume depletion,[115] SGLT2 inhibitor–induced changes in Hb are no longer believed to simply reflect hemoconcentration due to diuresis.[116] In fact, SGLT2 inhibitor administration was associated with transient increases in serum EPO concentrations (30%–40%), an increase in reticulocyte counts or hematocrit levels,[116a] and a decrease in ferritin and hepcidin, indicating erythropoietic stimulation.[117–120] These pro-erythropoietic actions have been hypothesized to have contributed to SGLT2 inhibitor–mediated protective effects on heart failure outcomes and kidney disease progression.[109–111] Although current data suggest that SGLT2 inhibitors 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.

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 vs. ESAs for patients with CKD not on dialysis and those on dialysis therapy
- Conduct 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, and patients with PKD or acute kidney injury in future HIF-PHI studies
- Identify 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, patient 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 recurrence 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

CKD, chronic kidney disease; ESA, erythropoietin-stimulating agent; Hb, hemoglobin; HIF-PHI, hypoxia-inducible factor–prolyl hydroxylase inhibitor; HRQoL, health-related quality of life; MACE, major adverse cardiovascular events; PKD, polycystic kidney disease.

CONCLUSIONS

In summary, HIF-PHIs are non-inferior to conventional ESAs in increasing and maintaining Hb concentrations in patients with CKD patients not on dialysis and those on dialysis therapy, and reduce transfusion requirements, compared with placebo. In terms of cardiovascular safety, HIF-PHIs are inferior to, 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 currently available do not support the concept that use of HIF-PHIs will reduce the need for i.v. or oral iron supplementation among patients with CKD not on dialysis or those on dialysis therapy or that they 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 that varied widely. Studies examining alternative iron-dosing strategies in patients receiving HIF-PHIs are needed. Currently, the data are insufficient to determine whether use of HIF-PHIs improves quality of life in patients with CKD not on dialysis. Further research recommendations are provided in Table 8.

APPENDIX

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 H. 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; and Muh Geot Wong, Australia.

DISCLOSURE

EK declared receiving grants from CareDx, National Institutes of Health (NIH), and Natera; participating in leadership roles for the *American Journal of Kidney Disease* Editorial Board and the American Kidney Fund Health Equity Coalition; gifts from patient families (Lang and Grimes); and stock in Edison, Inc. LDV declared receiving speaker honoraria from Amgen, Astellas, AstraZeneca, Bayer, and Vifor; participating on data safety monitoring or advisory boards for Travere; and serving as a national leader on the ASCEND (Anemia Studies in Chronic Kidney Disease: Erythropoiesis Via a Novel Prolyl Hydroxylase Inhibitor Daprodustat-Non-Dialysis) trial. K-UE declared receiving grants from Amgen, AstraZeneca, Bayer, Evotec, and Vifor; consulting fees from Akebia, AstraZeneca, Bayer, Otsuka, and Retrophin; and speakers honoraria from AstraZeneca and Bayer. VHH declared receiving consulting fees from Akebia, AstraZeneca, and GlaxoSmithKline (GSK); and speaker honoraria from AstraZeneca. KLJ declared receiving grants from National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); consulting fees from Akebia and CSL Vifor; participating on a trial steering committee and advisory board for GSK; speaker honoraria from GSK; payment for expert testimony from GSK; and serving as Associate Editor of the *Journal of the American Society of Nephrology*. MN declared receiving grants from Astellas, Bayer, Chugai, Daiichi-Sankyo,

Japan Tobacco, Kyowa Kirin, Mitsubishi Tanabe, Takeda, and Torii; consulting fees from Astellas, Boehringer Ingelheim, Daiichi-Sankyo, Japan Tobacco, Kyowa Kirin, and Mitsubishi Tanabe; and speaker honoraria from Astellas, AstraZeneca, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, GSK, Kyowa Kirin, and Mitsubishi Tanabe. NT declared receiving grants from AstraZeneca, Bayer, Boehringer Ingelheim, Canadian Institutes of Health Research (CIHR), Janssen, and Kidney Foundation of Canada (KFOC); consulting fees from AstraZeneca, Bayer, Boehringer Ingelheim, GSK, Janssen, Otsuka, ProKidney, and Roche; a patent pending on a microfluidic device for point-of-care detection of urine albumin; participating on advisory boards for AstraZeneca, Boehringer Ingelheim/Lilly, Jansen, National Kidney Foundation (NKF), and Otsuka; and stock or stock options from ClinPredict, Klinrisk, Marizyme, ProKidney, pulseData, and Quanta. SSW declared receiving grants from Johnson & Johnson, Natera, Pfizer, and Vertex; consulting fees from Bain, BioMarin, CANbridge, Goldfinch, Google, GSK, Ikena, NovoNordisk, PepGen, Sironax, Strataca, and Wolters Kluwer; and payment for expert testimony from Aurinia, DaVita, Decher, and Pfizer. AW declared receiving consulting fees from GSK for serving as a Steering Committee Member of the ASCEND study and MEDICE for serving as a Scientific Committee Member of the NOPHOS (Efficacy and tolerability of nicotinamide as add-on therapy compared to placebo in dialysis-dependent patients with hyperphosphatemia) study; speaker honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Chiesi, Fresenius, and Sandoz; and participating on advisory boards for Astellas, Fresenius Kabi, and Hansa Biopharma. MJ declared receiving the following payments to his institution: grants from AstraZeneca; consulting fees from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, CSL Vifor, GSK, and Vertex; speaker honoraria from AstraZeneca, Bayer, and Boehringer Ingelheim; and payment for expert testimony from Astellas and STADA- Eurogenerics. MJ also discloses travel support from AstraZeneca and Boehringer Ingelheim and serving as volunteer co-chair for KDIGO. WCW declared receiving grants or contracts from the NIH; speaker honoraria from Pharmacosmos, GSK, and multiple universities and medical schools; participating on data safety monitoring or advisory boards for Akebia/Otsuka, Ardelyx, AstraZeneca, Bayer, Boehringer Ingelheim/Lilly, GSK, Merck Sharp & Dohme, Reata Pharmaceuticals, Unicycive, and Zydus Lifesciences; and serving as co-chair of KDIGO and associate editor of the *Journal of the American Medical Association*. DCW declared receiving grants from National Institute of Health Research and Kidney Research UK; consulting fees from Astellas, AstraZeneca, Eledon, Galderma, GSK, Merck, Pharmacosmos, ProKidney, Tricida, and Zydus; speakers honoraria from Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Gilead, GSK, Janssen, Merck Sharp & Dohme, and Vifor; travel support from Astellas and AstraZeneca; participating on data safety monitoring or advisory boards for Eledon, Galderma, Merck, and ProKidney; and serves as Advancing Clinical Trials Chair for the International Society of Nephrology and as National Specialty Lead, Renal Disorders, for National Institute of Health Research. MC declared no competing interests.

ACKNOWLEDGMENTS

The conference was sponsored by KDIGO and was supported in part 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.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Table S1. Availability of hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs).

Supplementary Table S2. Drug–drug interactions of hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF-PHIs).

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