Hypoxia-inducible factor prolyl hydroxylase inhibitors for anaemia in chronic kidney disease: a document by the European Renal Best Practice board of the European Renal Association

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ABSTRACT

Anaemia is a common complication of chronic kidney disease (CKD) and is associated with poor long-term outcomes and quality of life. The use of supplemental iron, erythropoiesis stimulating agents (ESAs) and blood transfusions has been the mainstay of treatment of anaemia in CKD for more than three decades. Despite available treatments, CKD patients with anaemia are undertreated and moderate-to-severe anaemia remains prevalent in the CKD population. Anaemia has consistently been associated with greater mortality, hospitalisation, cardiovascular events, and CKD progression in patients with CKD, and the risk increases with anaemia severity.

Hypoxia-inducible factor (HIF) prolyl hydroxylase (PH) inhibitors have a novel mechanism of action by mimicking the body's response to hypoxia and have emerged as an alternative to ESAs for the treatment of anaemia in CKD. Their

efficacy in correcting and maintaining haemoglobin has been demonstrated in over 30 phase 3 clinical trials. Additionally, HIF activation results in various pleiotropic effects beyond erythropoiesis with cholesterol reduction and improved iron homeostasis and potential anti-inflammatory effects. The long-term safety of these agents, particularly with respect to cardiovascular and thromboembolic events, and their possible effect on tumor growth requires to be fully elucidated.

This document presents in detail the effects of HIF-PH inhibitors, describes their mechanisms of action and pharmacologic properties, and discusses their place in the treatment of anaemia in CKD according to the available evidence.

Keywords: anaemia, chronic kidney disease, erythropoietin, erythropoiesis stimulating agents, hypoxia-inducible factor prolyl hydroxylase inhibitors

Epidemiology and outcomes of anaemia in the CKD population

Anaemia is a clinical hallmark of chronic kidney disease (CKD) and its prevalence and severity increases with progression of CKD.[1-3] It is twice as prevalent in patients with CKD compared to the general population[1], and is a substantial health care burden associated with increased health care resource utilisation.[4-6]

Patients with CKD who develop anaemia have an increased risk of adverse health outcomes including major cardiovascular events, hospitalisation, progression to kidney failure, and mortality.[7-11] Despite the prevalence of anaemia in CKD and its significant consequences for patient outcomes, it is often undertreated worldwide[1, 3] and typically less than half of patients with anaemia receive conventional anaemia medication within a year of nephrology follow-up.[12]

Following the establishment of the role of the hypoxia-inducible factor (HIF) pathway in the physiological response to hypoxia, HIF prolyl hydroxylase (HIF-PH) enzyme inhibitors have been developed as an alternative to ESAs for the treatment of anaemia in CKD. Although they have been approved and utilised in many countries worldwide, some of the molecules have only recently been licensed by the European Medicines Agency (EMA), Medicines and Healthcare products Regulatory Agency (MHRA) and the US Food and Drug Administration (FDA).

This review outlines the HIF-PH inhibitors (HIF-PHi) mechanism of action and considers their role in the management of anaemia in CKD by presenting the evidence from several phase 3 randomised clinical trials.

Treatment of anaemia in CKD in the pre-HIF-PHi era

The key facets of managing anaemia of CKD include iron supplementation, recombinant human erythropoietin (EPO) and its analogues, referred to as ESAs, and red blood cell (RBC) transfusion.[13, 14] An overview of the evolution of anaemia management in CKD is shown in **Supplementary Figure 1**.

Iron

Iron is essential for erythropoiesis, intra-cellular oxygen transportation and oxidative reactions needed for metabolic processes. Absolute and functional iron deficiency are common in CKD, driven by reduced dietary intake, reduced intestinal absorption, increased iron losses, and altered iron homeostasis, including elevated levels of the regulator protein hepcidin due to chronic inflammation and poor kidney clearance.[15] Addressing iron deficiency with supplementation is the first-line

therapy for anaemia of CKD[14] and it reduces the exposure to ESA therapy and RBC transfusion requirements.[16, 17]

The FIND-CKD study indicated that the use of IV ferric carboxymaltose to target higher ferritin levels (400-600 vs 100-200 µg/L) was more efficacious for increasing haemoglobin in non-dialysis CKD patients and delayed time to initiation of other anaemia management (blood transfusion, ESA, other iron therapy), with no safety concerns in terms of cardiovascular events or infections.[18] The PIVOTAL trial demonstrated that pro-active high-dose IV iron sucrose supplementation in incident haemodialysis patients (held if ferritin >700 µg/L or TSAT ≥40%) lowered the composite risk of all-cause death, nonfatal myocardial infarction (MI), nonfatal stroke, and heart failure (HF) hospitalisation compared with a reactive low-dose regimen[19] without increasing the risk of infections.

Erythropoiesis-stimulating agents (ESAs)

Erythropoietin derivatives have been studied since 1989 and transformed the treatment of anaemia in CKD by effectively increasing haemoglobin levels and avoiding regular blood transfusions.[20]

Landmark clinical trials in anaemia showed no improvements in clinical outcomes with normalisation of haemoglobin with ESAs in patients with CKD.[21-24] The Normal Hematocrit Cardiac Trial (NHCT) in haemodialysis patients with cardiovascular disease (CVD) was stopped early for futility after results of interim analysis were nearing the statistical boundary of a higher mortality rate in the normal-haematocrit group.[21] In patients with non-dialysis CKD correction of haemoglobin to levels greater than 13g/dL was associated with increased risk of cardiovascular events in the CHOIR[22] and no cardiovascular benefit in the

CREATE[23] and TREAT[24] trials. The increased cardiovascular events however may be related to ESAs dosing rather than the haemoglobin level per se[25-27] or to fluctuations of haemoglobin level.[28]

Mechanism of action of HIF-PHi

The HIF pathway is an exquisite oxygen-sensing mechanism enabling adaptation according to the oxygen content by controlling the transcription of over 1000 hypoxia-responsive genes.[29] Among its functions, HIF coordinates response to hypoxia by stimulating erythropoietin production in the kidneys and liver and favouring intestinal iron absorption and availability.[30]

HIF is a heterodimeric DNA-binding complex composed of two basic helix-loop-helix proteins: one hypoxia-inducible α-subunit (HIF-1α, HIF-2α, HIF-3α) and the constitutive HIF-β.[31] Whilst HIF-α subunits are highly inducible by hypoxia, HIF-β subunit is a non-oxygen-responsive nuclear protein with other roles in transcription processes.[32] The HIF-2α subunit has been recognised as the primary mediator of erythropoiesis.[33] HIF is regulated by a family of prolyl hydroxylase domain (PHD) enzymes, of which there are 3 isoforms (PHD1, PHD2, and PHD3) and serve as cellular oxygen sensors. In the presence of oxygen and/or iron, PHD enzymes hydroxylate prolines in HIF-α, thereby targeting it for proteasomal degradation.[30, 34] Under hypoxic conditions or iron deficiency, PHD enzymes activity is supressed and the HIF-α escapes proteasomal degradation and accumulates.[35] It then translocates to the nucleus and dimerises with HIF-β forming the HIF α/β heterodimer, which binds to the hypoxia response elements of target genes inducing, amongst other responses, erythropoiesis.[36] **(Figure 1**)

HIFs are the main regulators of EPO production and iron availability via the following mechanisms: (1) upregulation of EPO receptors and endogenous EPO production; (2) increase in intestinal iron absorption; (3) increase in iron uptake by proerythrocytes and promotion of erythrocyte maturation; and (4) inhibition of hepcidin production in the liver.[37, 38] Prolyl hydroxylation can be pharmacologically inhibited by HIF-PHi - also referred to as HIF stabilisers - thereby stimulating these effects and enhancing erythropoiesis.[39, 40] The clinically available compounds have various degrees of inhibition of PHD isoforms in vitro but to some degree this depends on the assay utilised.[33, 41, 42] They all appear to be potent inhibitors of PHD1-3, although PHD2 is considered the most important isoform from a physiological perspective.[33, 42] In a direct comparison of cellular assays vadadustat was less potent at inhibiting PHD2 compared with roxadustat, daprodustat and molidustat. Differences in the effect on HIF-1α and HIF-2α are also apparent between the compounds, with vadadustat having a preference for HIF-2α > HIF-1α and roxadustat demonstrating the highest efficacy on HIF-stabilisation.[42]

The peritubular interstitial EPO-producing cells are predominantly located in a zone of the kidney with relative hypoxia[43] where small decreases in blood oxygen stimulate upregulation of the HIF-2α leading to increased transcription of the EPO genes and increased levels of circulating EPO. There is evidence that HIF is activated spontaneously in haemodialysis patients living 1300-1400m above sea level, as they have higher haemoglobin levels despite requiring lower ESA and iron doses.[44] Similarly, in patients with CKD the risk of anaemia was lower at higher altitude.[45]

A major class of genes moderated by HIFs include those involved in iron handling and metabolism. The impact of the HIF pathway on iron homeostasis is

modulated by HIF-2α stimulation of iron absorption in the duodenum and by suppression of hepcidin.[43] Hepcidin reduces dietary iron absorption and blocks release of stored iron from macrophages and the liver by decreasing the expression of ferroportin, an iron exporter, leading to reduced circulating iron levels.[46]

HIF activation results in a broad physiologic response with various pleiotropic effects (beneficial, neutral, or harmful). Many of these effects are context dependent and can go in opposite directions depending on the duration and severity of the hypoxic state. In animal studies pharmacological inhibition of HIF-PH had a renoprotective effect from ischemic injury caused by AKI[47, 48] though other experimental studies showed increased fibrosis following HIF activation.[49] Many of the genes involved in angiogenesis such as vascular growth factors (VEGF) are directly induced by HIF-1α.[50] The molecular mechanisms underlying cancer metabolism are significantly influenced by HIF-1α[36] however, studies on gene expression have so far failed to establish the impact of HIF-1α on tumor angiogenesis and growth.[51, 52] On the contrary, under certain experimental conditions, PHD inhibition reconstituted tumour vessels and normalised the tumour microenvironment, which are essential for response to chemotherapy.[53]

Therapeutic use of HIF-PHi in the management of anaemia in non-dialysis dependent CKD (NDD-CKD)

The search strategy used to identify phase 3 trials of HIF-PHi in adult CKD patients with anaemia is described in **Supplementary material** and **Supplementary Table 1**.

All available phase 3 trials of HIF-PHi versus placebo in non-dialysis dependent CKD (NDD-CKD) are summarised in **Table 1** and the trials of HIF-PHi versus ESAs in **Table 2**.

Haemoglobin correction and maintenance

In the placebo-comparator trials, roxadustat and daprodustat were superior in achieving and maintaining target haemoglobin levels for up to 4 years and minimised the requirements for rescue RBC transfusion or ESA therapy.[54-59] A pooled analysis of the ALPS[56], ANDES[54] and OLYMPUS[55] trials of roxadustat versus placebo in 4,277 patients showed a greater increase in haemoglobin (1.9 vs 0.2g/dL), greater haemoglobin response (80 vs 9%), and less requirement for rescue therapy in the first 52 weeks of treatment (9 vs 31%) in the roxadustat arm.[59]

HIF-PHi have consistently shown non-inferiority compared to ESAs in improving and maintaining haemoglobin levels.[60-69] The ASCEND-ND global trial of daprodustat versus darbepoetin alfa including 3,872 patients demonstrated a non-inferior change in haemoglobin over 52 weeks with a between group difference of 0.08g/dL (95% CI 0.03-0.13).[62] The PRO_2TECT trials showed non-inferiority of vadadustat versus darbepoetin in ESA-naive (between group difference in haemoglobin change 0.04g/dL; 95% CI -0.06-0.14) and ESA-treated patients (difference 0.00g/dL; 95% CI -0.10-0.09).[64] A meta-analysis of ESA-comparator daprodustat clinical trials including 4,406 patients showed a non-significant mean difference in haemoglobin change between the daprodustat and ESA groups (-0.01g/dL; 95% CI -0.38-0.35).[70]

The potential for rapid haemoglobin increases with HIF-PHi therapy has been noted in some of the trials. In a Japanese trial of daprodustat at a starting dose of 4

mg/day versus epoetin beta pegol, 13% of ESA-naive patients on daprodustat had a haemoglobin rise by >2g/dL in the first 4 weeks requiring early daprodustat protocol adjustment.[63] In the ESA-comparator desidustat trial, 48% of patients on desidustat overshot the haemoglobin target compared with 40.8% on ESAs.[69] Although in the phase 3 clinical trials, larger increases in haemoglobin levels were observed for roxadustat compared to daprodustat and vadadustat,[71] no difference in haemoglobin change from baseline among different HIF-PHi was observed in a recent meta-analysis.[72] The sharp increases in haemoglobin levels do not necessarily imply improved efficacy but rather the choice of a relatively high starting dose.

Effects on iron homeostasis and hepcidin

The main effects of HIF-PHi on iron homeostasis are summarised in **Figure 2**.

In placebo-comparator trials of roxadustat, most studies showed a reduction in ferritin levels with roxadustat.[54, 55, 57] Serum iron and TSAT were unchanged or increased and total iron-binding capacity (TIBC) was increased in the roxadustat group.[54-57] These changes overall reflect an increase in erythropoiesis and iron mobilisation with roxadustat.

In the ESA-comparator trials, HIF-PHi demonstrated a similar[60-63, 69] or greater[65-67] decrease in ferritin levels compared to ESA therapy. A single trial showed increased ferritin levels with HIF-PHi.[73] Iron levels were relatively unchanged in both groups in 3 trials[60-62], similarly increased in 2 trials[66, 67], increased with ESA therapy in 2 trials[63, 69], or increased with HIF-PHi in 1 trial.[73] Among the ESA-controlled RCTs, TSAT was higher with ESA therapy in 6 trials[62, 63, 65-67, 69], and relatively unchanged with both HIF-PHi and ESA therapy in 3

trials[60, 61, 73]. HIF-PHi had a greater effect in increasing TIBC[61-63, 65, 67, 73] and transferrin levels[61, 63] compared to ESAs.

Phase 3 trials have noted a significant decrease in hepcidin levels in patients treated with HIF-PHi in comparison to placebo and ESAs.[54-57, 60-63, 65-67, 69]

HIF-PHi have been shown to reduce the requirements for IV iron supplementation, however this finding was not universally replicated in the trials. It should be underlined that protocols for iron administration were not standardised in phase 3 trials introducing inconsistency in prescription practices. Two studies found less need for IV iron utilisation in patients on roxadustat compared to placebo.[54, 55] Patients in the roxadustat arm of the DOLOMITES study required less supplemental IV iron compared to patients on ESA therapy.[60] However, the iron protocol differed between treatment groups, with a preference for the oral route as first line in the roxadustat group, which likely introduced bias in favour of roxadustat. Lower dosing of IV iron was used in the molidustat compared to darbepoetin alfa group in two studies.[66, 68] On the contrary, the ASCEND-ND and SYMPHONY-ND studies of daprodustat and enarodustat versus darbepoetin alfa demonstrated similar IV iron requirements in both groups.[62, 67] Whether the potential advantage of a reduced requirement for IV iron therapy with HIF-PHi translates to reduced number of IV iron infusions, which would be more relevant particularly in NDD-CKD patients, remains to be confirmed.

Efficacy in elevated inflammatory states

The efficacy of HIF-PHi therapy in achieving and maintaining a haemoglobin response was not impaired by the presence of elevated CRP levels.[54, 55, 61] A pooled analysis of three randomised controlled trials (RCTs) in patients with CRP

greater than the upper limit of normal comparing roxadustat with placebo showed a haemoglobin change of 2g/dL in the roxadustat versus 0.3g/dL in the placebo group.[59] In a post-hoc analysis of a study of roxadustat vs darbepoetin alfa, low-grade inflammation (CRP ≥3 mg/L) was associated with a requirement for higher doses of darbepoetin but not roxadustat.[74] The MIYABI ND-C molidustat trial showed similar haemoglobin levels in the subgroups of patients with high (>3 mg/L) and low (≤3 mg/L) CRP.[66] These findings should be interpreted with caution as trials excluded patients with chronic inflammatory states.

Effect on cholesterol

Roxadustat, daprodustat and desidustat significantly decreased total cholesterol and low-density lipoprotein (LDL)[54-57, 60, 63, 69] but also slightly decreased high-density lipoprotein (HDL) cholesterol[54, 56] in comparison to placebo and ESA therapy. This likely reflects the role of HIF in the activity of acetyl coenzyme-A and 3-hydroxy-3-methylglutaryl coenzyme-A reductase, which are essential in cholesterol synthesis.[46]

In the pooled analysis of the placebo-comparator roxadustat trials, ALPS[56], ANDES[54] and OLYMPUS[55], the change in LDL cholesterol over 12 to 28 weeks was -17.3mg/dL in the roxadustat versus +2.6mg/dL in the placebo group.[59]

In the ESA-comparator trials, a Japanese study showed a decrease in LDL and HDL cholesterol in the daprodustat compared to no change in the ESA group.[63] DREAM-ND found a significant decrease in LDL cholesterol with desidustat compared to darbepoetin alfa but no significant change in HDL, total cholesterol, triglyceride and apolipoproteins A1 and B.[69] MIYABI ND-C showed no

difference in the total cholesterol levels between patients treated with molidustat and darbepoetin.[66]

It is unclear whether the decrease in serum cholesterol translates in a positive effect on atherosclerotic plaque stabilisation, as it is the case for statins.

Health-related quality of life

Phase 3 trials comparing roxadustat to placebo demonstrated no significant change in health-related quality of life (HRQoL) or functional health scoring.[54-56] In the DOLOMITES study, roxadustat was non-inferior to darbepoetin alfa for changes in patient-reported HRQoL measurements.[60]

The ASCEND-NHQ trial reported a greater mean change in the SF-36 vitality score in the daprodustat than in the placebo group (7.3 vs 1.9 points), which translates to an improvement in fatigue with daprodustat.[58] However, patients receiving daprodustat achieved higher haemoglobin levels. The DREAM-ND trial demonstrated an increase in HRQoL scoring in patients taking desidustat but this was no different from the ESA arm.[69]

Kidney transplant recipients

The efficacy and safety of HIF-PHi in kidney transplant recipients is poorly investigated. Roxadustat has been reported to be effective in treating posttransplant anaemia in small case series from Japan[75, 76] and China[77, 78], however studies with long follow-up are required to investigate potential effects on the immune system and interactions with immunosuppressive drugs.

Therapeutic use of HIF-PHi in the management of anaemia in dialysis dependent CKD (DD-CKD)

All available phase 3 trials of HIF-PHi versus ESAs in dialysis-dependent CKD are summarised in **Table 3**.

Haemoglobin correction and maintenance

The phase 3 trials demonstrated that all six HIF-PHi (roxadustat, daprodustat, vadadustat, molidustat, desidustat, and enarodustat) were non-inferior to ESAs in haemoglobin correction and maintenance in studies of incident[79-83] or prevalent[73, 80, 81, 83-92] dialysis-dependent CKD (DD-CKD) patients. The ROCKIES trial of 2,133 dialysis patients showed non-inferiority of roxadustat to epoetin alfa (mean haemoglobin increase 0.77 vs 0.68g/dL) and a similar proportion of time spent with a haemoglobin of >10g/dL.[80] In the ASCEND-D trial of 2,964 dialysis patients, daprodustat was non-inferior to ESA therapy in correcting haemoglobin (mean haemoglobin increase 0.28 vs 0.10g/dL).[86] In the INNO$_2$VATE trials including 3,923 dialysis patients, vadadustat was non-inferior to darbepoetin alfa in haemoglobin efficacy (between group difference in haemoglobin change -0.07g/dL in the incident and -0.18g/dL in the prevalent dialysis trial).[83]

Roxadustat compared to ESAs did not meet the non-inferiority criterion for the secondary endpoint of RBC transfusion in the HIMALAYAS[79] (4.3 vs 3.5 per 100 patient-exposure years) whereas it was non-inferior in the ROCKIES[80] (9.8 vs 13.2%) and superior in the SIERRAS[81] (12.5 vs 21.1%) and PYRENEES[84] (9.2 vs 12.9%) trials. Higher use of ESA rescue was shown in the roxadustat group in the ROCKIES[80] (3.7 vs 0.2%) and PYRENEES[84] (1.5% vs 0%) trials. A similar rate

of rescue therapy was administered in both the daprodustat and ESA groups in the ASCEND-D[86], ASCEND-ID[82] and ASCEND-TD[87] trials. In the incident $INNO_2VATE$ trial more patients in the vadadustat group required ESA rescue (20.4 vs 16%), whereas in the prevalent trial more patients in the ESA group required ESA rescue (27.6% vs 30.2%).[83]

Effects on iron homeostasis and hepcidin

The main effects of HIF-PHi on iron homeostasis are a) an increase in iron, transferrin and TIBC, and b) a reduction in ferritin and hepcidin.

The roxadustat trials showed a reduction in ferritin in both the roxadustat and ESA groups, although the decrease was larger in the roxadustat group.[79-81, 84, 91] The SIERRAS trial noted greater reductions in patients with higher baseline ferritin levels.[81] The daprodustat trials showed a similar reduction in ferritin compared to ESAs.[82, 86-88] The $INNO_2VATE$ incident dialysis trial showed stable ferritin levels in both the vadadustat and ESA groups but a greater reduction in ferritin was shown in the vadadustat group in the $INNO_2VATE$ prevalent dialysis trial.[83]

HIF-PHi maintained or increased serum iron compared to ESAs in most clinical trials.[73, 79-82, 85-88]

TSAT was overall stable or reduced at the same rate in both the HIF-PHi and ESA groups.[79-88]

The TIBC and transferrin levels were elevated from baseline in the HIF-PHi compared to the ESA groups.[73, 79, 80, 82, 85-88, 92, 93]

HIF-PHi were found to reduce hepcidin levels more than the comparator ESAs.[73, 79-85, 87, 88, 91-93] In the $INNO_2VATE$ trials a greater decrease in

hepcidin was noted in the vadadustat group of prevalent compared with incident dialysis patients.[83]

Phase 3 trials demonstrated lower requirements for oral or IV iron supplementation with HIF-PHi compared to ESAs.[79-82, 84-88, 93] In the pooled analysis of the PYRENEES, SIERRAS, HIMALAYAS, and ROCKIES trials, patients on roxadustat required a mean of 5.3 IV iron administrations per patient year compared with 9.6 for ESA patients.[94] Two trials found similar iron requirements between the HIF-PHi and ESA groups.[73, 91] As for NDD-CKD, protocols for iron administration were not standardised in the trials making it difficult to draw conclusions on IV iron needs.

Efficacy in elevated inflammatory states

Efficacy of haemoglobin response to HIF-PHi therapy was maintained in the context of elevated CRP in a number of trials of roxadustat, daprodustat, vadadustat, and enarodustat.[73, 79, 81, 82, 84, 92, 93] Three roxadustat trials demonstrated superior haemoglobin response in the context of an elevated CRP for the roxadustat versus the ESA group.[80, 85, 92] In other roxadustat trials, dose requirements were similar for both the high and low CRP roxadustat groups, but patients with a higher CRP treated with epoetin required increased doses and often achieved lower haemoglobin levels.[79, 81, 85, 91] A recent pooled analysis of four RCTs comparing roxadustat with ESA in patients stratified by quintiles of CRP at baseline showed a greater haemoglobin increase in the roxadustat group regardless of baseline CRP levels without requirement for higher doses.[95]

In the ASCEND-TD trial, patients classified as ‘ESA hyporesponders’ did not respond better to daprodustat compared to their previous ESA treatment.[87] In

other studies, patients with a higher baseline erythropoietin resistance index required higher doses of daprodustat for achieving haemoglobin targets[88] and enarodustat did not show difference in dose needs compared to darbepoetin alfa in those with high CRP values (≥3 mg/L).[73] Vadadustat, however, improved haemoglobin levels in patients that had not achieved targets with previous ESA therapy.[93]

Effect on cholesterol

A consistent superior reduction in LDL cholesterol was reported in DD-CKD patients treated with HIF-PHi compared to ESAs.[79-81, 84, 85, 90] In the HIMALAYAS trial, roxadustat also decreased HDL, non-HDL cholesterol, and triglycerides.[79] In the ROCKIES[80] and Chen et al.[85] trials of roxadustat, a greater reduction in HDL and triglycerides was noted compared with epoetin alfa. In the DREAM-D trial, patients treated with desidustat had significantly lower apolipoprotein-B levels compared to those treated with ESAs.[90]

Health-related quality of life

The PYRENEES trial of roxadustat versus ESA therapy in prevalent dialysis patients found a greater improvement on patient-reported HRQoL questionnaire in the roxadustat group.[84] However, in this trial haemoglobin levels increased more rapidly and to higher levels in the roxadustat than in the ESA arm. The DREAM-D trial found no difference in HRQoL scoring between the desidustat and ESA groups.[90]

Safety profile of HIF-PHi in non-dialysis and dialysis dependent CKD

The broad spectrum of metabolic functions of the HIF pathway has raised safety concerns regarding its continuous activation from HIF-PHi.[46] Furthermore the effect of HIF-PHi on signalling pathways in metabolic processes other than the HIF pathway and their potential for epigenetic gene regulation is not fully understood.[13, 46]

In the placebo-comparator trials in NDD-CKD patients for roxadustat and daprodustat, there were broadly comparable incidences of adverse events between placebo and HIF-PHi, and participants were more likely to withdraw due to adverse events in the placebo arms.[54, 55, 57, 58] Phase 3 active-comparator trials in NDD and DD-CKD generally noted comparable adverse events to ESA therapy, although participants were more likely to withdraw from study due to adverse events in the HIF-PHi arms.[60, 61, 64, 65, 68, 80, 81, 83-85, 91, 93]

Clinically important adverse events of different HIF-PHi from pooled analyses and meta-analyses are summarised in **Table 4**.

All-cause mortality

A meta-analysis of 46 studies including 27,338 patients across all the currently available HIF-PHi found no significant differences in mortality compared with placebo or ESAs in both the DD-CKD and NDD-CKD subgroups.[96] A meta-analysis of eight studies comparing daprodustat with ESAs showed no difference in mortality in the DD-CKD and NDD-CKD groups.[70]

A pooled analysis of 4,277 patients in ANDES[54], ALPS[56] and OLYMPUS[55] trials for roxadustat versus placebo in NDD-CKD patients showed non-inferiority for all-cause mortality.[59]

Similarly, a pooled analysis of the PYRENEES[84], SIERRAS[81], ROCKIES[80] and HIMALAYAS[79] roxadustat ESA-comparator trials in DD-CKD patients demonstrated non-inferiority of roxadustat for all-cause mortality.[94] There was a numerically higher risk of all-cause mortality in the subgroup of stable dialysis patients converted from ESA to roxadustat compared with incident dialysis patients treated with roxadustat (HR 1.23; 95% CI 1.02-1.49 vs HR 0.83; 95% CI 0.57-1.19). This is confounded by the change of ESA to a new therapy and the possible impact this may have had on haemoglobin levels.

Cardiovascular safety

The majority of phase 3 trials demonstrated non-inferiority of HIF-PHi to placebo and ESA therapy for major cardiac events in NDD-CKD and DD-CKD patients.[55, 60, 62, 79-81, 84, 86] A Cochrane meta-analysis of 51 studies including 30,994 NDD-CKD and DD-CKD patients showed little or no difference between HIF-PHi and ESAs for CV death (RR 1.05; 95% CI 0.88-1.26), nonfatal MI (RR 0.91; 95% CI 0.76-1.10), and nonfatal stroke (RR 1.06; 95% CI 0.71-1.56).[97]

A pooled analysis of ANDES[54], ALPS[56] and OLYMPUS[55] trials of roxadustat compared to placebo in NDD-CKD patients found roxadustat to be non-inferior for major adverse cardiovascular events (MACE; composite of death, non-fatal MI and/or stroke) (HR 1.10; 95% CI 0.96-1.27) and expanded MACE (MACE plus hospitalisation for either HF or unstable angina or MACE plus hospitalisation for either HF or a thromboembolic event) (HR 1.07; 95% CI 0.94-1.21).[59] In the

dialysis population, a pooled analysis of four roxadustat ESA-comparator clinical trials (PYRENEES[84], SIERRAS[81], ROCKIES[80] and HIMALAYAS[79]) revealed non-inferiority for MI, unstable angina, stroke, and HF requiring hospitalisation.[94]

In a meta-analysis of eight clinical trials including 3,839 DD-CKD and 4,406 NDD-CKD patients, daprodustat compared to ESAs was associated with a significantly reduced incidence of MACE (RR 0.89; 95% CI 0.89-0.98) in DD-CKD patients but not in the NDD-CKD cohort (RR 1.05; 95% CI 0.94-1.18).[70] The reduced incidence in MACE in the DD-CKD group was driven by a decrease in incidence of MI (RR 0.74; 95% CI 0.59-0.92). A post-hoc analysis of three Japanese phase 3 trials in NDD-CKD and DD-CKD patients comparing daprodustat to ESAs found no difference in incidence of MACE (RR 0.86; 95% CI 0.29-2.52).[98]

A meta-analysis comparing vadadustat with placebo or darbepoetin alfa including NDD-CKD and DD-CKD patients found no difference in incidence of cardiac events (RR 1.03, 95% CI 0.88-1.20), or non-fatal stroke (RR 0.92, 95% CI 0.55-1.57).[99] By contrast, a pooled analysis of the PRO_2TECT NDD-CKD trials of 3,471 patients comparing vadadustat with darbepoetin alfa showed higher risk for MACE (HR 1.17; 95% CI 1.01-1.36) in the vadadustat group.[64] This appeared to be driven by the subset of patients enrolled outside of the US randomised to a higher haemoglobin target (10-12g/dL vs 10-11g/dL).

Thrombotic events

In a pooled analysis of trials in NDD-CKD patients, roxadustat was associated with an increased incidence of arteriovenous (AV) access thrombosis (1.5 vs 0.9/100 patient-years), DVT (0.7 vs 0.2/100 patient-years) and PTE (0.3 vs 0.1/100 patient-years) compared to placebo.[59] A meta-analysis of roxadustat in NDD-CKD trials

noted an increased risk of DVT compared to placebo (RR 3.80; 95% CI 1.50-9.64).[100] In the ASCEND-ND trial, more patients treated with daprodustat developed vascular access thrombosis compared to ESAs (2.1 vs 1.5%).[62]

In patients on dialysis, phase 3 trials have noted higher rates of AV dialysis access thrombosis in patients treated with HIF-PHi compared to ESAs.[79-81, 83, 84] However, other studies have found similar or less AV access thrombosis episodes with HIF-PHi.[73, 85, 87] A pooled analysis of Japanese phase 3 trials of daprodustat found a similar incidence of thromboembolic events between the daprodustat and ESA groups.[98]

Malignancy

In a recent meta-analysis of 26 studies with 24,387 NDD and DD-CKD patients, the risk of cancer was similar between HIF-PHi and ESAs (RR 0.93; 95% CI 0.76-1.13).[72] A post-hoc analysis from three phase 3 Japanese studies in NDD and DD-CKD patients noted similar cancer-related adverse events in the daprodustat and ESA groups (1.28 vs 1.53/100 patient-years, respectively).[98]

In the ASCEND-ND trial, cancer-related outcomes (death or tumor progression or recurrence) were more frequent with daprodustat compared to ESAs (3.7 vs 2.5%, RR 1.47; 95% CI 1.03-2.10);[62] the imbalance for cancer-related events between the two treatment groups was attenuated in post-hoc analyses taking into account the longer darbepoetin dosing intervals.[101] A pooled analysis of studies on roxadustat compared to placebo in patients with NDD-CKD showed no increased risk of malignancy with roxadustat.[59]

In dialysis patents, the MIYABI HD-M trial demonstrated an increased incidence of neoplasm episodes (9.8 vs 5.3%) in the molidustat arm compared with

darbepoetin.[89] However, the trial sample size was rather small and the follow-up short for assessing reliably the risk of malignancy.

Retinopathy

The neo-vascularisation effect of HIF-PHi has been postulated to worsen ocular pathology, such as diabetic retinopathy.[13, 46] For this reason, most of the phase 3 clinical trials excluded patients with severe retinopathy.

The pooled Japanese daprodustat analysis of trials in ND and DD-CKD patients found no increased risk for retinal events or aggravation of underlying retinal disease.[98]

The SYMPHONY-ND study demonstrated increased VEGF levels and increased retinal adverse events of enarodustat compared to ESAs (3.7 vs 0.9%).[67] All the remaining Japanese NDD-CKD trials showed no increased risk of ocular disorders related to HIF-PHi therapy.[61, 63, 65, 91]

The SYMPHONY-HD trial reported an increased risk of retinal adverse events with vadadustat (6.9 vs 3.5%), although the VEGF levels were lower in the vadadustat compared to the darbepoetin group.[73] The ASCEND-ID trial also reported an increased incidence of ocular adverse events with daprodustat compared to ESAs (3.4 vs 0.79/100 patient-years).[82]

Hypertension

Although hypertension is an established complication of ESA therapy, comparator trials of HIF-PHi versus ESAs in NDD-CKD patients have not shown significant differences in the development of hypertension.[61, 64, 69] A meta-analysis of NDD-CKD roxadustat trials noted a higher incidence of hypertension in

the roxadustat group compared to placebo (RR 1.37; 95% CI 1.13-1.65).[59] Another meta-analysis of NDD-CKD patients has, however, reported a lower risk of hypertension with HIF-PHi compared with ESAs (RR 0.89; 95% CI 0.81-0.98).[102]

In comparator trials of DD-CKD patients there were no significant differences in the development of hypertension between HIF-PHi and ESA groups.[73, 79, 81, 84, 86, 90]

Other studies in both ND and DD-CKD patients suggest a beneficial effect of HIF-PHi on blood pressure compared to ESAs, such as fewer requirements for titration of anti-hypertensives.[63, 65, 85, 87, 88, 93]

Other potential adverse effects

Other less commonly reported potential adverse effects are described in **Supplementary material**.

Approved HIF-PHi

Currently approved HIF-PHi are summarised in **Supplementary Table 2**.

Roxadustat was the first-in-class HIF-PHi approved for treatment of anaemia in patients with DD-CKD and NDD-CKD and is the most studied globally. Roxadustat was granted marketing authorisation by the EMA in August 2021 for patients with anaemia associated with CKD, whether they are on dialysis or not (EMA/453588/2021). It was rejected on safety concerns by the FDA in July 2021. More specifically, the efficacy and safety of roxadustat was assessed by FDA and EMA in a phase 3 programme of eight multi-centre randomised studies involving 9,600 patients with anaemia of CKD worldwide. Although both agencies considered

the evidence provided for efficacy of roxadustat substantial, the FDA raised significant safety concerns. The safety of roxadustat was assessed by FDA using pooled analyses of studies of roxadustat versus placebo[54-56] or darbepoetin alfa[60] in NDD-CKD and roxadustat versus ESA[79-81, 84] in DD-CKD. Using on-treatment analyses (as opposed to intention-to-treat analyses) that were requested by the FDA to minimise the effect of including unexposed person-times or events, the risk of MACE was higher for roxadustat compared to placebo in the NDD-CKD population (HR 1.38, 95% CI 1.11-1.70) and similar to ESA in the DD-CKD population (HR 1.02, 95% CI 0.88-1.20).[103] Of note, in the US, ESAs are not used as frequently as in Europe for the treatment of anaemia in NDD-CKD (28% in the US compared to 57% in Germany).[104] Roxadustat was also associated with a higher risk for thrombotic events, vascular access thrombosis and seizures compared to placebo in the NDD-CKD population and ESA in the DD-CKD population. The FDA did not approve roxadustat and called for an additional clinical trial on the safety of roxadustat in both the NDD and DD-CKD populations. By contrast, EMA concluded that the CV and mortality risks appeared to be similar to ESA based on data from the 'haemoglobin correction studies' in NDD and DD-CKD and considered that evaluation in other data pools (including comparison to placebo and in stable dialysis patients) are associated with methodological and study design issues complicating interpretation. Thus, the risk of MACE, MACE+ and all-cause mortality in the 'haemoglobin correction studies' was similar compared to ESAs (HR 0.79, 95% CI 0.61-1.02, HR 0.78, 95% CI 0.62 -0.98 and HR 0.78, 95% CI 0.57-1.05, respectively) and the benefits were considered greater than its risks.[105]

Vadadustat was granted marketing authorisation by the EMA in April 2023 for treatment of anaemia in patients with DD-CKD (EMA/100938/2023) with a warning

on the risk of thromboembolic events. In the NDD-CKD population, the non-inferiority of vadadustat compared to darbepoetin alfa for MACE was not demonstrated. Vadadustat has been rejected by the FDA on safety concerns regarding thromboembolic events and a case of severe drug-induced liver injury reported in phase 2 trial data.

Daprodustat was approved for use by the FDA in February 2023 for patients with DD-CKD with a boxed warning for an increased risk of thrombotic events. It was not approved for NDD-CKD patients due to insufficient safety data in this population. On 22nd June 2023, the EMA Committee for Medicinal Products for Human Use (CHMP) recommended granting of a marketing authorisation for daprodustat only for DD-CKD (EMEA/H/C/005746). On 12th July 2023, the pharmaceutical company withdrew its application.

Roxadustat, vadadustat and daprodustat are commercialised in other countries outside the EU and the US; of note, the local regulatory authorities did not require extensive phase 3 data for the approvals.

Molidustat was submitted for EMA approval but was withdrawn in August 2019 with the company indicating its strategic plans to focus on the Japanese market.

The remaining two HIF-PHi have not been submitted to the EMA. Desidustat was approved for use in India in March 2022 and Enarodustat in Japan in September 2020 for the treatment of anaemia in NDD-CKD and DD-CKD patients.

Ongoing studies with HIF-PHi in CKD

Although HIF-PHi have shown promise in haemoglobin correction and maintenance efficacy, long-term safety data are required to establish their role in the management of anaemia of CKD. At the moment, only a limited number of new clinical trials have been designed.

A study focusing on long-term safety outcomes of molidustat in Japanese patients is currently recruiting (ClinicalTrials.gov Identifier: NCT04899661) with an estimated completion date in June 2027. A post-marketing phase 4 study will evaluate long-term safety of desidustat in dialysis and non-dialysis patients but is not yet recruiting (NCT05515367).

Specific groups of patients were excluded from phase 3 clinical trials including patients with a kidney transplant, those with significant CVD including HF, and those with active inflammatory disease. A study comparing roxadustat combined with sacubitril/valsartan versus recombinant human erythropoietin combined with ACEI or ARB in Chinese patients with cardiorenal syndrome and anaemia is currently recruiting (NCT05053893). Another study examining the safety and efficacy of roxadustat in the treatment of HF in patients with CKD and anaemia (NCT05691257) is expected to start recruiting this year in China and Japan. A meta-analysis of studies evaluating the efficacy and safety of HIF-PHi compared with ESAs in patients with CKD and HF[106] is expected to publish its results later this year.

Suggestions for clinical practice

The Asian Pacific Society of Nephrology (APSN) has published recommendations for the use of HIF-PHi.[107] The KDIGO recently published its conclusions from the 2021 controversies conference on novel anaemia therapies in CKD; however, the scope of the KDIGO report was not to provide specific recommendations on their use.[108]

Major clinical trials have failed to conclusively demonstrate that, as a class, HIF-PHi are non-inferior to placebo or ESAs for cardiovascular, thrombotic or cancer complications. Given the mechanism of action for HIF-PHi, patients with known malignancy occurring in the five years preceding enrolment were excluded from clinical trials and the median follow up of phase 3 studies was short to reliably assess a pro-oncogenic effect. The same holds true for patients with polycystic kidney disease, as the rate of cyst growth was not assessed systematically in the trials.

Potential explanations for the different effects of different trials and agents include imbalances in patients' characteristics and ethnicity, haemoglobin at baseline, prior ESA exposure, and type of analyses performed (intention-to-treat versus on-treatment analyses). Although a class-effect is plausible, drug-specific effects may also contribute to differences in efficacy and safety outcomes.

Collectively, given the degree of uncertainty about the benefits and harms of HIF-PHi, the principle of shared decision making should be applied to ensure that the values of patients with diverse needs and perspectives are respected. Definitive answers on whether there is a specific population in which HIF-PHi should be

preferred or avoided will evolve from comprehensive assessment of post-marketing surveillance data and a mandate for a registry has been proposed.[109]

Based on existing evidence, our summary of suggestions for clinical practice is shown in **Table 5**. Potential advantages of the use of HIF-PHi compared to ESA therapy in different CKD populations are shown in **Figure 3**.

Conclusions and future directions

HIF-PHi offer an alternative pharmacological approach for anaemia correction in CKD but also mediate a number of metabolic pathways beyond anaemia correction that could improve patients' outcomes and prognosis. However, HIF stabilisation is not highly specific and may lead to metabolic cascades and gene expression with unfavourable effects. The phase 3 programme of HIF-PHi is one of the largest global investigative programs ever conducted in CKD with a plethora of data generated, which require careful analyses and vigilance as these agents are approved for use in clinical practice.

Although several large phase 3 trials have been published, they evaluate adverse events over a relatively short treatment period (52-104 weeks). Evidence for MACE noninferiority compared with ESAs has been demonstrated in patients receiving dialysis[59, 83, 85, 88, 91] but questions remain in patients with non-dialysis CKD for some HIF-PHi.[64, 110] In fact, EMA has approved only roxadustat for use in NDD-CKD. The reported data in thromboembolic events from phase 3 trials raise concerns of increased thrombotic risk with HIF□PHi.[59, 62, 79-81, 83, 84, 100] There is a theoretical potential for oncogenesis based on the putative mechanisms of action of HIF-PHi, with conflicting evidence in patients with NDD-

CKD.[54, 62] Regarding diabetic retinopathy, the available data from some of the phase 3 trials[88] are reassuring. Hyperkalaemia is an unexpected but relatively rare adverse effect of HIF-PHi therapy[59, 85, 110] and requires further evaluation. Finally, elucidation of potential benefits of HIF-PHi in ESA-hyporesponsive patients, inflammation, iron metabolism, alleviation of hypoxic kidney injury, rate of kidney function loss and quality of life is needed.

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DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article.

CONFLICT OF INTEREST STATEMENT

None declared.

Table 1. Non-dialysis dependent CKD (NDD-CKD): HIF-PHi vs placebo							
Study	**Comparator**	**Number of patients**	**Population**	**Treatment period**	**Target Hb (g/dL)**	**Efficacy endpoints**	**Safety endpoints**
ROXADUSTAT						**Roxadustat vs placebo**	**Roxadustat vs placebo**
ALPS[56] (Europe)	Placebo	594	CKD 3-5	52-104 weeks	10-12	□ Mean Hb change at 28-52 wk: 1.99 vs 0.30 g/dL □ % patients with Hb response at 24 wk: 79.2 vs 9.9%	□ Hypertension: 22.3 vs 13.8% □ Nausea: 9.5 vs 3.0% □ Diarrhoea: 8.4 vs 3.4%
ANDES[54] (Global)	Placebo	922	CKD 3-5	52-208 weeks	10-12	□ Mean Hb change at 28-52 wk: 2.00 vs 0.16 g/dL □ % patients with Hb response at 24 wk: 86.0 vs 6.6% □ Rescue therapy at 52 wk: 8.9 vs 28.9% □ RBC transfusion at	□ Hypertension: 15.5 vs 8.9% □ Hyperkalaemia: 18.2 vs 13.4% □ Constipation: 17.2 vs 11.1%

						52 wk: 5.6 vs 15.4% □ IV iron use at 52 wk: 2.5 vs 4.9% □ ESA rescue at 52 wk: 2.1 vs 6.7%	
OLYMPUS[55] (Global)	Placebo	2782	CKD 3-5	52-208 weeks	10-12	□ Mean Hb change at 28-52 wk: 1.75 vs 0.40 g/dL □ % patients with Hb response at 24 wk: 77.0 vs 8.5% □ Rescue therapy: 18.4 vs 41.7% □ RBC transfusion: 12.7 vs 23.3% □ IV iron use: 4.3 vs 7.9% □ ESA rescue: 4.7 vs 23.6%	□ UTI: 12.8 vs 8.0% □ Hypertension: 11.5 vs 9.1% □ Hyperkalaemia: 8.5 vs 6.9%
Chen, 2019[57] (China)	Placebo	154	CKD 3-5	8 weeks (followed by an	≥10	□ Mean Hb change at 7-9 wk: 1.90 vs -	□ Hyperkalaemia: 16 vs 8%

				18-week open-label period)		0.40 g/dL □ % patients with mean Hb ≥10 g/dL at 7-9 wk: 67 vs 6% □ Rescue therapy: 3 vs 12% □ Mean hepcidin change at 9 wk: -56.1 vs -15.1 ng/mL	□ Metabolic acidosis: 12 vs 2%
DAPRODUSTAT						**Daprodustat vs placebo**	**Daprodustat vs placebo**
ASCEND-NHQ[58] (Global)	Placebo	614	CKD 3-5	28 weeks	11-12	□ Mean Hb change at 24-28 wk: 1.58 vs 0.19 g/dL □ % patients with Hb increase of ≥1 g/dL at 28 wk: 77 vs 18% □ Rescue therapy: <1 vs 10% □ Change in the SF-36 vitality (fatigue)	□ Hypertension: 7 vs 5% □ Retinal disorder: <1 vs 3.0%

						score at 28 wk: 7.3 vs 1.9 points	

Table 1 details HIF-PHi versus placebo phase 3 trials in the non-dialysis dependent CKD (NDD-CKD) population. This includes four trials of roxadustat (two global[54, 55], one from Europe[56], one from China[57]) and one daprodustat trial (global[58]).

Hb, haemoglobin; UTI, urinary tract infection; IV, intravenous; ESA, erythropoiesis stimulating agent

Table 2. Non-dialysis dependent CKD (NDD-CKD): HIF-PHi vs ESAs							
Study	Comparator	Number of patients	Population	Treatment period	Target Hb (g/dL)	Efficacy endpoints	Safety endpoints
ROXADUSTAT						**Roxadustat vs ESAs**	**Roxadustat vs ESAs**
DOLOMITES[60] (Europe)	Darbepoetin alfa	616	CKD 3-5	104 weeks	10-12	□ % patients with Hb response at 24 wk: 89.5 vs 78.0% □ Mean monthly IV iron use at 1-36 wk: 34.7 vs 69.6 mg □ Time to 1st use of IV iron at 1-36 wk: HR 0.46 (0.26-0.78)	□ MACE: 11.8 vs 14.0%, HR 0.81 (0.52-1.25) □ MACE+: 16.7 vs 18.1%, HR 0.90 (0.61-1.32) □ VTE: 2.5 vs 0.7%, HR 3.63 (0.76-17.20)
Akizawa, 2021[61] (Japan)	Darbepoetin alfa	334	CKD 2-5	24 weeks	10-12	□ Mean Hb change at 18-24 wk: 0.15 vs 0.22 g/dL □ % patients with	□ Hypertension: 2.3 vs 3.8% □ Hyperkalaemia: 3.8 vs 3.8%

						target Hb at 18-24 wk: 77.1 vs 85.5%	□ Nasopharyngitis: 19.1 vs 26.0% □ Retinal haemorrhage: 31.4 vs 39.8%
DAPRODUSTAT						**Daprodustat vs ESAs**	**Daprodustat vs ESAs**
ASCEND-ND[62] (Global)	Darbepoetin alfa	3872	CKD 3-5	52 weeks	10-11	□ Mean Hb change at 28-52 wk: 0.74 vs 0.66 g/dL □ Use of rescue therapy: 2.0 vs 3.3% □ RBC transfusion: 12.8 vs 13.5%	□ MACE (ITT analysis): 19.5 vs 19.2%, HR 1.03 (0.89-1.19) □ MACE (on-treatment analysis): 14.1 vs 10.5%, HR 1.40 (1.17-1.68) □ Cancer-related death or tumor progression or recurrence: 3.7 vs 2.5%, RR 1.47 (1.03-2.10) □ Oesophageal or gastric erosions: 3.6 vs 2.1%, RR 1.70 (1.16-2.49)

Nangaku, 2021[63] (Japan)	Epoetin beta pegol	299	CKD 3-5	52 weeks	11-13	□ Mean Hb level at 40-52 wk (ITT): 12.0 vs 11.9 g/dL □ % patients with target Hb at 40-52 wk: 92 vs 92%, OR 1.01 (0.33-3.04)	□ Hypertension: 3.0 vs 5.0% □ Hyperkalaemia: 8.0 vs 5.0% □ Nasopharyngitis: 33.0 vs 37.0%
VADADUSTAT						**Vadadustat vs ESAs**	**Vadadustat vs ESAs**
PRO_2TECT[64] (Global)	Darbepoetin alfa	3476	CKD 3-5	52 weeks	10-11 (US) 10-12 (non-US)	□ Mean Hb change at 24-36 wk: 0.74 vs 0.66 g/dL □ RBC transfusion 24-36 wk: 2.7 vs 2.2% (ESA-untreated), 1.6 vs 1.2% (ESA-treated) □ ESA rescue 24-36 wk: 4.6 vs 12.8% (ESA-untreated), 5.0 vs 13.4% (ESA-treated)	□ MACE: 22.0 vs 19.9%, HR 1.17 (1.01-1.36) □ MACE+: 25.9 vs 24.5%, HR 1.11 (0.97-1.27) □ Hypertension: 17.7 vs 22.1% (ESA-untreated), 14.4 vs 14.8% (ESA-treated) □ Hyperkalaemia: 12.3 vs 15.6% (ESA-untreated), 9.4 vs 9.9%

							(ESA-treated)
Nangaku, 2021[65] (Japan)	Darbepoetin alfa	304	CKD 3-5	52 weeks	11-13	□ Mean Hb level at 20-24 wk: 11.7 vs 11.9 g/dL □ % patients with target Hb at 52 wk: 71.4 vs 84.5% (ESA non-users), 79.2 vs 76.6% (ESA users)	□ Adverse drug reaction (≥1): 13.2 vs 4.6% □ Hypertension: 1.3 vs 7.2% □ Nasopharyngitis: 24.5 vs 28.1%
ENARODUSTAT						**Enarodustat vs ESAs**	**Enarodustat vs ESAs**
SYMPHONY-ND[67] (Japan)	Darbepoetin alfa	216	CKD 3-5	24 weeks	10-12	□ Mean Hb level at 20-24 wk: 10.96 vs 10.87 g/dL □ % patients with target Hb at 24 wk: 88.6 vs 87.9%	□ Retinal disorders: 3.7 vs 0.9% □ Upper respiratory tract infection: 17.8 vs 22.9% □ Hypertension: 4.7 vs 4.6%
MOLIDUSTAT						**Molidustat vs ESAs**	**Molidustat vs ESAs**
MIYABI ND-C[66]	Darbepoetin	162	CKD 3-5	52 weeks	11-13	□ Mean Hb level at	□ Serious TEAE: 17.1

(Japan)	alfa					30-36 wk: 11.28 vs 11.70 g/dL □ Mean Hb change at 30-36 wk: 1.32 vs 1.69 g/dL □ % patients with target Hb at 30-36 wk: 68.3 vs 85.0% □ Mean IV iron use: 2.89 vs 11.22 mg/week	vs 7.6% □ MACE: 7.3 vs 0.0% □ Hyperkalaemia: 12.2 vs 11.4% □ Nasopharyngitis: 31.7 vs 26.6%
MIYABI ND-M[68] (Japan)	Darbepoetin alfa	164	CKD 3-5	52 weeks	11-13	□ Mean Hb level at 30-36 wk: 11.67 vs 11.53 g/dL □ Mean Hb change at 30-36 wk: 0.36 vs 0.24 g/dL □ % patients with target Hb at 30-36 wk: 72.0 vs 76.8%	□ Serious TEAE: 32.9 vs 26.8% □ MACE: 3.7 vs 1.2% □ Hyperkalaemia: 2.4 vs 8.5% □ Hypertension: 2.4 vs 6.1% □ Diabetic retinopathy: 3.7 vs 1.2%
DESIDUSTAT						**Desidustat vs ESAs**	**Desidustat vs ESAs**

DREAM-ND[69] (India & Sri Lanka)	Darbepoetin alfa	588	CKD 3-5	24 weeks	10-12	□ Mean Hb change at 16-24 wk: 1.95 vs 1.83 g/dL □ Mean Hb level at 16-24 wk: 10.90 vs 10.77 g/dL □ % patients with Hb response at 24 wk: 77.8 vs 68.5% □ Mean hepcidin change at 24 wk: -12.0 vs 7.8 ng/mL	□ Serious TEAE: 8.2 vs 6.1% □ Hypertension: 1.7 vs 5.8%

Table 2 outlines details of phase 3 comparator trials with ESA therapy, including two roxadustat (one from Europe[60], one from Japan[61]), two daprodustat (one global[62], one from Japan[63]), two vadadustat (one global[64], one from Japan[65]), two molidustat (Japan[66, 68]), one enarodustat (Japan[67]) and one desidustat (South Asia[69]).

Hb, haemoglobin; ITT, intention-to-treat; OR, odds ratio; HR, hazard ratio; MACE, major adverse cardiac event (composite of death, non-fatal myocardial infarction and/or stroke); MACE+, expanded major adverse cardiac event (MACE plus hospitalisation for either heart failure or unstable angina or MACE plus hospitalisation for either heart failure or a thromboembolic event); IV, intravenous; ESA, erythropoiesis stimulating agent; TEAE, treatment emergent adverse event

Table 3. Dialysis-dependent CKD (DD-CKD): HIF-PHi vs ESAs							
Study	**Comparator**	**Number of patients**	**Population**	**Treatment period**	**Target Hb (g/dL)**	**Efficacy endpoints**	**Safety endpoints**
ROXADUSTAT						**Roxadustat vs ESAs**	**Roxadustat vs ESAs**
HIMALAYAS[79] (Global)	Epoetin alfa	1043	Incident HD and PD (90/10%)	52 weeks	≥11	□ Mean Hb change at 28-52 wk: 2.57 vs 2.36 g/dL (US), 2.62 vs 2.44 g/dL (Europe) □ % patients with Hb response: 84.3 vs 79.5% (US), 88.2 vs 84.4% (Europe) □ RBC transfusion: 7.3 vs 6.4% □ Monthly IV iron use per PEM: 58.1 vs 88.7 mg	□ Fatal TEAEs: 12.1 vs 11.4% □ Hypertension: 19 vs 17% □ Diarrhoea: 13.8 vs 7.4% □ AVF thrombosis: 11.3 vs 8.9%

SIERRAS[81] (US)	Epoetin alfa	741	Incident and prevalent HD and PD (95/5%)	52 weeks	~11	□ Mean Hb change at 28-52 wk: 0.39 vs -0.09 g/dL □ % patients with mean Hb ≥10g/dL: 66.1 vs 58.6% □ RBC transfusion: 12.5 vs 21.1% □ Monthly IV iron use per PEM: 17.1 vs 37 mg	□ Fatal TEAEs: 16.8 vs 15.7% □ Nausea: 17 vs 16.2% □ Hypertension: 16.8 vs 12.7%
ROCKIES[80] (Global)	Epoetin alfa	2133	Incident and prevalent HD and PD (89/11%)	52 weeks	~11	□ Mean Hb change at 28-52 wk: 0.77 vs 0.68 g/dL □ % patients with mean Hb ≥10 g/dL: 85.3 vs 89.2% □ RBC transfusion: 9.8 vs 13.2% □ Mean monthly IV iron use: 58.7 vs	□ Acute MI: 3.7 vs 3.9% □ Hypertension: 8.8 vs 8.9% □ Pneumonia: 8.7 vs 9.6% □ AVF thrombosis: 7.4 vs 5.4%

						91.4 mg	
PYRENEES[84] (Europe)	Epoetin alfa or darbepoetin alfa	836	Prevalent HD and PD (94/6%)	52-104 weeks	10-12	□ Mean Hb change at 28-36 wk: 0.43 vs 0.19 g/dL □ % patients with target Hb at 28-36 wk: 84.2 vs 82.4% □ Mean monthly IV iron use: 12 vs 44.8 mg	□ Fatal TEAEs: 16.2 vs 13.1% □ Hypertension: 17.9 vs 18.8% □ AVF thrombosis: 12.1 vs 7.4% □ All-cause death: 18.8 vs 14%
Chen et al.[85] (China)	Epoetin alfa	305	Prevalent HD and PD (89/11%)	26 weeks	10-12	□ Mean Hb change: 0.7 vs 0.5 g/dL □ % patients with mean Hb ≥10 g/dL: 87 vs 88.5% □ Mean hepcidin change: -30.2 vs -2.3 ng/mL □ Mean TSAT change: -5.7 vs -	□ Upper respiratory infection: 18.1 vs 11% □ Hyperkalaemia: 7.4 vs 1% □ AVF complication: 2.9 vs 3%

						7.6%	
Akizawa et al.[91] (Japan)	Darbepoetin alfa	303	Prevalent HD	24 weeks	10-12	□ Mean Hb change: -0.04 vs -0.03 g/dL □ % patients with target Hb: 79.3 vs 83.4% □ IV iron use: 22.7 vs 20.4%	□ Serious TEAEs: 20.7 vs 14.5% □ Nasopharyngitis: 34.7 vs 26.3% □ Vomiting: 6.7 vs 2% □ Shunt stenosis: 7.3 vs 8.6%
Hou et al.[92] (China)	Erythropoiesis-stimulating agents	129	Prevalent PD	24 weeks	10-12	□ Mean Hb change: 2.5 vs 2.2 g/dL □ % patients with Hb response: 96 vs 92% □ Mean hepcidin change: -46.6 vs -5.9 ng/mL	□ Hypertension: 6 vs 7% □ Hyperkalaemia: 8 vs 2% □ Insomnia: 6 vs 0%
DAPRODUSTAT						**Daprodustat vs ESAs**	**Daprodustat vs ESAs**

ASCEND-ID[82] (Global)	Darbepoetin alfa	312	Incident HD and PD (81/19%)	52 weeks	10-11	□ Mean Hb change at 28-52 wk: 1.02 vs 1.12 g/dL □ Mean monthly IV iron use: 142 vs 128 mg □ Mean hepcidin change: -29.8 vs -11.4 ng/mL	□ First occurrence of MACE: 12 vs 10% □ Hypertension: 18 vs 16% □ Diarrhoea: 9 vs 7%
ASCEND-D[86] (Global)	Epoetin alfa or darbepoetin alfa	2964	Prevalent HD and PD (88.5/11.5%)	52 weeks	10-11	□ Mean Hb change at 28-52 wk: 0.28 vs 0.10 g/dL □ RBC transfusion: 15.7 vs 18.3% □ Mean monthly IV iron use: 90.8 vs 99.9 mg	□ First occurrence of MACE: 25.2 vs 26.7% □ Rapid increase in Hb: 4.1 vs 1.6% □ Vascular access thrombosis: 10.4 vs 12.5%
ASCEND-TD[87] (Global)	Epoetin alfa	407	Prevalent HD	52 weeks	10-11	□ Mean Hb change: -0.04 vs 0.02 g/dL □ % patients with	□ First occurrence of MACE: 12 vs 10% □ Hypertension: 9

						mean Hb 10-11.5 g/dL: 80 vs 64% □ RBC transfusion: 8 vs 12% □ Mean monthly IV iron use: 98.1 vs 106.2 mg	vs 11% □ Non-fatal stroke: 3 vs 0%
Akizawa et al.[88] (Japan)	Darbepoetin alfa	271	Prevalent HD	40-52 weeks	10-12	□ Mean Hb change: 0 vs 0 g/dL □ % patients with target Hb: 88 vs 90% □ Mean monthly IV iron use: 14 vs 25 mg □ Mean hepcidin levels: 37.9 vs 51.5 ng/mL □ Mean TSAT change: 0.3 vs -	□ Diarrhoea: 15 vs 9% □ Contusion: 13 vs 8% □ Nasopharyngitis: 42 vs 54% □ Pain in extremity: <1 vs 7%

						2.1%	
VADADUSTAT						**Vadadustat vs ESAs**	**Vadadustat vs ESAs**
INNO$_2$VATE[83] (Global)	Darbepoetin alfa	3923	Incident and prevalent HD and PD	52 weeks	10-11 (US) 10-12 (non-US)	□ Mean Hb change at 24-36 wk: 1.26 vs 1.58 g/dL (incident), 0.19 vs 0.36 g/dL (prevalent) □ % patients with target Hb at 24-36 wk: 43.6 vs 56.9% (incident), 49.2 vs 53.2% (prevalent) □ RBC transfusion at 24-36 wk: 1.3 vs 1.8% (incident), 2 vs 1.3% (prevalent) □ ESA rescue at 0-23 wk: 20.4 vs 16% (incident),	□ First occurrence of MACE: 18.2 vs 19.3% □ Serious AEs: 49.7 vs 56.5% (incident), 55 vs 58.3% (prevalent) □ Drug-related AEs: 3.9 vs 2.7% (incident), 9.6 vs 3.8% (prevalent) □ AVF thrombosis: 3.4 vs 5.4% (incident), 6 vs 4.4% (prevalent)

						27.6 vs 30.2% (prevalent)	
Nangaku et al.[93] (Japan)	Darbepoetin alfa	323	Prevalent HD	20-24 weeks	10-12	□ Mean Hb level: 10.61 vs 10.65 g/dL □ % patients with target Hb: 75.4 vs 75.7% □ IV iron use: 30.9 vs 33.3%	□ Adverse drug reaction: 11.1 vs 3.7% □ Nasopharyngitis: 45.7 vs 45.3% □ Shunt stenosis: 14.2 vs 16.1% □ Retinal disorder: 13 vs 9.9%
ENARODUSTAT						**Enarodustat vs ESAs**	**Enarodustat vs ESAs**
SYMPHONY-HD[73] (Japan)	Darbepoetin alfa	173	Prevalent HD	20-24 weeks	10-12	□ Mean Hb level: 10.73 vs 10.85 g/dL □ % patients with target Hb: 77.9 vs 88.4% □ Mean IV iron	□ Vomiting: 10.3 vs 2.3% □ Retinal disorder: 6.9 vs 3.5%

						use: 74 vs 70.2 mg	
MOLIDUSTAT						**Molidustat vs ESAs**	**Molidustat vs ESAs**
MIYABI HD-M[89] (Japan)	Darbepoetin alfa	229	Prevalent HD	52 weeks	10-12	□ Mean Hb change at 33-36 wk: -0.14 vs -0.07 g/dL □ % patients with target Hb at wk 52: 74.6 vs 81.5% □ % patients with a rise in Hb of >0.5 g/dL/week: 49% vs 47.3% □ Use of rescue treatment: 11.1 vs 1.3% □ Mean weekly IV iron use: 18.2 vs 15.2 mg	□ Serious TEAE: 24.2 vs 18.4% □ Neoplasms: 9.8 vs 5.3% □ % patients with MACE: 3.3 vs 2.6% □ Ocular TEAE: 30.1 vs 18.4%
DESIDUSTAT						**Desidustat vs ESAs**	**Desidustat vs ESAs**

DREAM-D[90] (India)	Epoetin alfa	392	Prevalent HD	24 weeks	10-12	□ Mean Hb change at 16-24 wk: 0.95 vs 0.80 g/dL □ % patients with target Hb: 59.2 vs 48.4% □ Median time to achieve target Hb: 4 vs 8 wk	□ At least one TEAE: 48 vs 46.4% □ Nausea: 3.6 vs 1.5% □ Hyperkalaemia: 2.6 vs 0.5% □ Oedema: 2 vs 0.5%

Table 3 details HIF-PHi versus ESA comparator phase 3 trials in the dialysis dependent (DD) population. This includes six trials of roxadustat (two global[79, 80], one US[81], one Europe[84], one Japan[91], & one China[85]), four trials of daprodustat (three global[82, 86, 87], one Japan[88]), one trial of molidustat (Japan[89]), three trials of vadadustat (2 global[83], 1 Japan[93]), one enarodustat (Japan[73]) and one desidustat (South Asia[90]).

Hb, haemoglobin; PEM, patient-exposure month; MACE, major adverse cardiac event (composite of death, non-fatal myocardial infarction and/or stroke); AVF, arteriovenous fistula; IV, intravenous; ESA, erythropoiesis stimulating agent; TEAE, treatment emergent adverse event; TSAT, transferrin saturation

Table 4. Safety outcomes of different HIF-PHi (data from pooled analyses and meta-analyses)						
	Roxadustat		**Daprodustat**		**Vadadustat**	
	NDD-CKD	**DD-CKD**	**NDD-CKD**	**DD-CKD**	**NDD-CKD**	**DD-CKD**
All-cause mortality	**Roxadustat vs placebo** HR 1.08 (95% CI 0.93-1.26)[59] RR 0.40 (95% CI 0.06-2.84)[111]	**Roxadustat vs ESAs** RR 1.13 (95% CI 0.95-1.34)[94]	**Daprodustat vs placebo** RR 0.54 (95% CI 0.09-3.31)[111] **Daprodustat vs ESAs** RR 1.01 (95% CI 0.87-1.17)[70]	**Daprodustat vs ESAs** RR 0.99 (95% CI 0.86-1.14)[70]	**Vadadustat vs placebo** RR 1.43 (95% CI 0.15-13.27)[111]	
CV event		**Roxadustat vs ESAs** RR 1.00 (95% CI 0.88-1.14)[112]		**Daprodustat vs ESAs** RR 0.96 (95% CI 0.85-1.08)[112]		**Vadadustat vs ESAs** RR 0.94 (95% CI 0.83-1.07)[112]

MACE	**Roxadustat vs placebo** HR 1.10 (95% CI 0.96-1.27)[59]	**Roxadustat vs ESAs** RR 1.09 (95% CI 0.95-1.26)[94]	**Daprodustat vs ESAs** RR 1.05 (95% CI 0.94-1.18)[70]	**Daprodustat vs ESAs** **RR 0.89 (95% CI 0.89-0.98)[70]**		
MACE+	**Roxadustat vs placebo** HR 1.07 (95% CI 0.94-1.21)[59]	**Roxadustat vs ESAs** RR 0.98 (95% CI 0.86-1.11)[94]				
MI	**Roxadustat vs placebo** HR 1.29 (95% CI 0.90-1.85)[59]	**Roxadustat vs ESAs** RR 0.59 (95% CI 0.29-1.21)[113] RR 1.05 (95% CI 0.81-1.35)[94]	**Daprodustat vs ESAs** RR 1.08 (95% CI 0.84-1.38)[70]	**Daprodustat vs ESAs** **RR 0.74 (95% CI 0.59-0.92)[70]**		
Stroke	**Roxadustat vs placebo**	**Roxadustat vs ESAs**	**Daprodustat vs ESAs**	**Daprodustat vs ESAs**		

	HR 1.25 (95% CI 0.82-1.90)[59]	RR 1.01 (95% CI 0.69-1.50)[94]	RR 1.41 (95% CI 0.86-2.29)[70]	RR 0.78 (95% CI 0.50-1.20)[70]		
Hospitalisation for heart failure	**Roxadustat vs placebo** HR 0.93 (95% CI 0.75-1.16)[59]	**Roxadustat vs ESAs** **RR 0.39 (95% CI 0.17-0.89)[113]** RR 0.91 (95% CI 0.73-1.14)[94]	**Daprodustat vs ESAs** RR 1.02 (95% CI 0.36-2.87)[70]	**Daprodustat vs ESAs** RR 1.01 (95% CI 0.82-1.25)[70]		
Cancer-related death or tumor progression or recurrence		**Roxadustat vs ESAs** RR 0.25 (95% CI 0.03-2.24)[112]		**Daprodustat vs ESAs** RR 0.86 (95% CI 0.60-1.24)[112]		**Vadadustat vs ESAs** RR 0.77 (95% CI 0.29-2.03)[112]
AVF thrombosis	**Roxadustat vs placebo** 0.7 vs 0.2 per 100 PY[59]	**Roxadustat vs ESAs** **RR 1.43 (95% CI 1.09-**		**Daprodustat vs ESAs** **RR 0.78 (95% CI 0.66-**		**Vadadustat vs ESAs** RR 0.98 (95% CI 0.83-

		1.87)[113] **RR 1.15 (95% CI 1.04-1.27)[112]** 5.7 vs 3.9 per 100 PY[94]		**0.92)[112]**		1.16)[112]
Hypertension	**Roxadustat vs placebo** **RR 1.45 (95% CI 1.12-1.87)[113]** 9.0 vs 6.6 per 100 PY[59]	**Roxadustat vs ESAs** RR 1.13 (95% CI 0.93-1.37)[113] RR 1.00 (95% CI 0.88-1.13)[112] MD 1.00 (95% CI 0.81-1.24)[114]		**Daprodustat vs ESAs** RR 1.00 (95% CI 0.85-1.16)[112] MD 0.95 (95% CI 0.82-1.10)[114]		**Vadadustat vs ESAs** **RR 0.81 (95% CI 0.69-0.96)[112]** **MD 0.74 (95% CI 0.60-0.91)[114]**

		8.3 vs 6.9 per 100 PY[94]				
Hyperkalaemia	**Roxadustat vs placebo RR 1.41 (95% CI 1.08-1.85)[113]** 7.0 vs 5.7 per 100 PY[59]	**Roxadustat vs ESAs** RR 1.03 (95% CI 0.80-1.33)[113] RR 1.03 (95% CI 0.78-1.37)[112]		**Daprodustat vs ESAs** RR 0.91 (95% CI 0.63-1.33)[112]		**Vadadustat vs ESAs** RR 0.84 (95% CI 0.60-1.17)[112]

HR, hazard ratio; RR, relative risk; MD, mean difference; ESA, erythropoiesis stimulating agent; MACE, major adverse cardiac event (composite of death, non-fatal myocardial infarction and/or stroke); MACE+, expanded major adverse cardiac event (MACE plus hospitalisation for either heart failure or unstable angina or MACE plus hospitalisation for either heart failure or a thromboembolic event)

Table 5. Suggestions for clinical practice
Consider use of HIF-PHi
NDD-CKD or PD patients • Patient preference for oral treatment (accessibility, convenience, ease of administration, no storage requirements) • Challenges to starting or receiving ESAs (needle-phobia, unable to self-administer ESAs) • Challenges to administering iron therapy or when increased iron availability is desired • ESA hyporesponsiveness or intolerance • Chronic inflammatory states (CRP ≥3 mg/L)
Haemodialysis patients • Patient preference for oral treatment • Home haemodialysis • Hypersensitivity or unavailability of IV iron • ESA hyporesponsiveness or intolerance • Chronic inflammatory states (CRP ≥3 mg/L)
Use with caution
• Vascular access with a high risk of thrombotic complication • Retinal disorders[1] • Autoimmune diseases[2] • History of cured malignancy or without recurrence for at least 5 years • Kidney transplant recipients[3]
Avoid or use with extreme caution

- Patient with a CV or thrombotic event in the previous 3 months
- History of malignancy in the last 5 years
- Polycystic kidney disease
- Untreated proliferative diabetic retinopathy, macular degeneration, and retinal vein occlusion
- Idiopathic pulmonary arterial hypertension

Administration key points

- Ensure adequate iron stores prior to initiating treatment (ferritin >100 µg/L, TSAT >20%)[4]
- Individualise dose to achieve and maintain target Hb levels of 10-12 g/dL

Monitoring key points

- Avoid rapid rises in Hb e.g. >2 g/dL over four weeks, or very high Hb levels (>12 g/dL)[5]; in the case of Hb overcorrection, consider treatment discontinuation for Hb levels >13 g/dL and dose decreases for Hb levels between 12 and 13 g/dL
- Monitor Hb levels at least monthly until the target Hb level of 10-12 g/dL is achieved and stabilised, thereafter as clinically indicated
- Monitor potassium and liver function tests[6]

[1]Consider close ophthalmology follow-up

[2]Patients with a known chronic inflammatory disease that could impact erythropoiesis (e.g., systemic lupus erythematosus, rheumatoid arthritis, celiac disease), even if it was in remission were excluded in some of the trials

[3]Not enrolled in clinical trials, no information on potential interaction with immunosuppressive drugs, unknown effects on the immune system

[4]For haemodialysis patients the pro-active high-dose intravenous iron (PIVOTAL) regime if ferritin <700 µg/L and TSAT ≤40% can be used (at least in patients with a relatively short dialysis duration and no signs of severe inflammation)

[5]These can be associated with an increased risk of thrombotic complications

[6]Reports of hyperkalaemia and liver injury (uncommon) in clinical trials

Figure 1. HIF pathway in the presence of normal oxygen levels, under hypoxic conditions and after pharmacological inhibition of the prolyl hydroxylases. In conditions of normal oxygen tension, HIF-α is hydroxylated by the oxygen-sensitive HIF-prolyl hydroxylases (HIF-PH) and undergoes rapid proteasomal degradation. Factor inhibiting HIF (FIH) is an asparaginyl (Asn) hydroxylase enzyme that regulates the transcriptional activity of HIF. Under hypoxic conditions, HIF-PH is inactive and cannot hydroxylate HIF-α, which then accumulates, translocates to the nucleus and forms heterodimers with the HIF-β resulting in an active HIF complex. The HIF complex activates transcription of multiple genes promoting erythropoiesis via stimulation of endogenous erythropoietin production and regulators of iron metabolism.

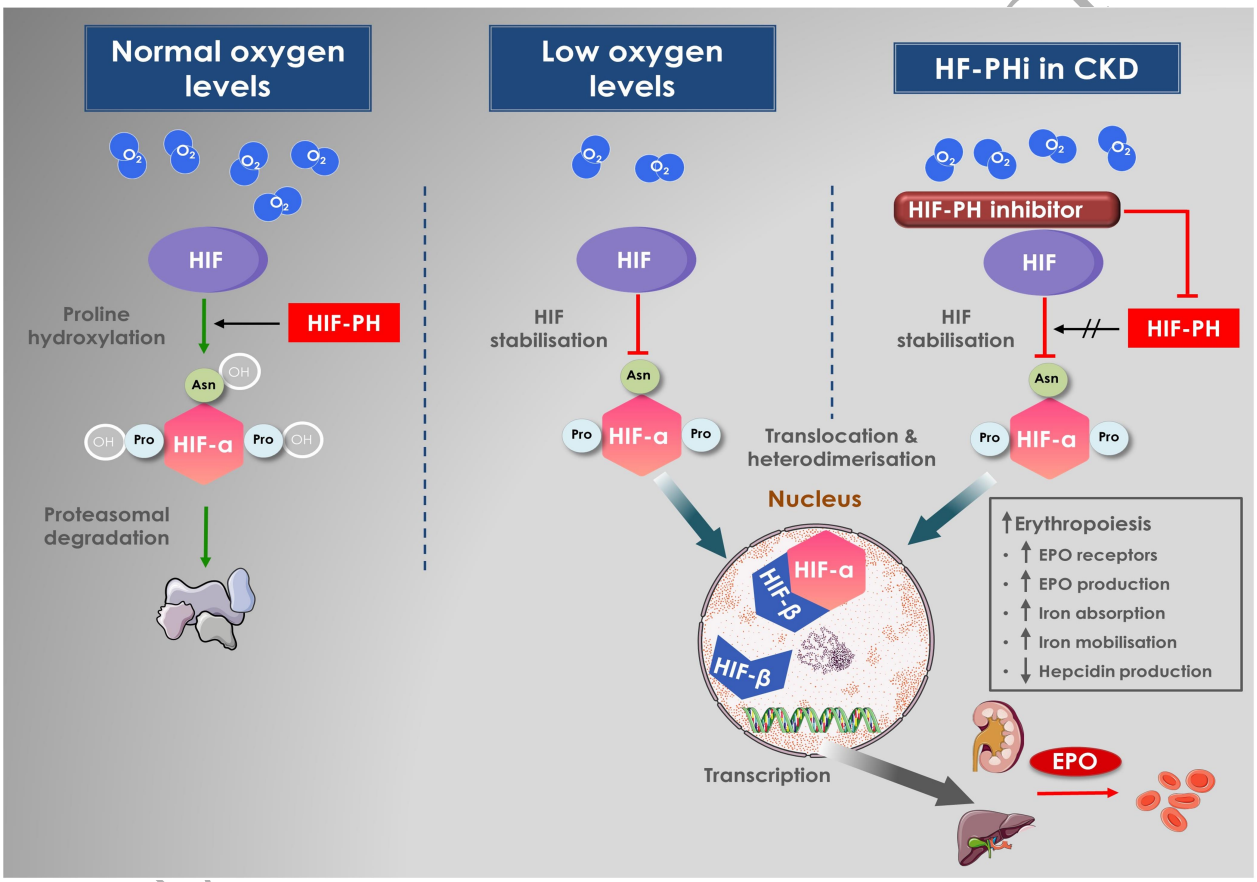

Figure 2. Effects of different HIF-PHi and ESA in parameters of iron homeostasis and hepcidin

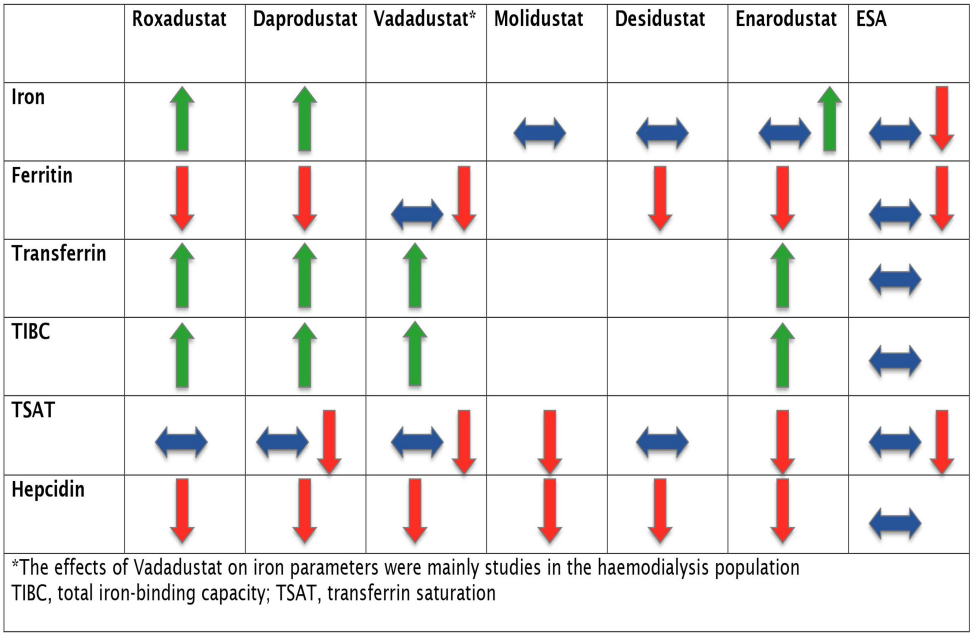

Figure 3. Potential advantages of HIF-PHi compared to ESA therapy in different CKD populations

	NDD-CKD	Haemodialysis	Peritoneal dialysis	Kidney transplant
Convenience of oral treatment	✓	✗	✓	✓
Needle-phobia or unable to self-administer ESA	✓	✗	✓	✓
ESA hyporesponsiveness or intolerance	✓	✓	✓	✓
Chronic inflammatory states	✓	✓	✓	✓
Hypersensitivity or unavailability of iron therapy	✓	✓	✓	✓
Exposure to lower circulating levels of erythropoietin	✓	✓	✓	✓
Clinical trial data on efficacy and safety	✓	✓	✓	✗

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