Hypoxia-Inducible Factor Activators in Renal Anemia: Current Clinical Experience
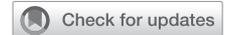
Neil S. Sanghani and Volker H. Haase

Prolyl hydroxylase domain oxygen sensors are dioxygenases that regulate the activity of hypoxia-inducible factor (HIF), which controls renal and hepatic erythropoietin production and coordinates erythropoiesis with iron metabolism. Small molecule inhibitors of prolyl hydroxylase domain dioxygenases (HIF-PHI [prolyl hydroxylase inhibitor]) stimulate the production of endogenous erythropoietin and improve iron metabolism resulting in efficacious anemia management in patients with CKD. Three oral HIF-PHIs—daprodustat, roxadustat, and vadadustat—have now advanced to global phase III clinical development culminating in the recent licensing of roxadustat for oral anemia therapy in China. Here, we survey current clinical experience with HIF-PHIs, discuss potential therapeutic advantages, and deliberate over safety concerns regarding long-term administration in patients with renal anemia.

Key Words: Anemia, Chronic kidney disease, Prolyl hydroxylase domain, Hypoxia-inducible factor, Erythropoietin

Anemia of CKD is a common complication of advanced renal failure and is primarily due to the inability of the diseased kidney to adequately respond to hypoxia and/or anemia with appropriate increases in erythropoietin (EPO) production.[1] Widespread use of EPO replacement therapy consisting of either recombinant human EPO (rhEPO) or re-engineered preparations of recombinant EPO, collectively referred to as erythropoietin stimulating agents (ESA), improved overall quality of life in some studies and reduced anemia-associated cardiovascular morbidity and the need for blood transfusions.[2-5] Despite its clinical success, several large studies have established that liberal administration and supraphysiologic dosing of ESA was associated with increased risk of cardiovascular events, CKD progression, vascular access thrombosis, and overall mortality.[6-11]

Cardiovascular safety concerns and complications from current therapy have provided a strong incentive to develop alternative strategies for the treatment of renal anemia. Although several novel approaches are under investigation in preclinical models and early phase clinical trials, the class of hypoxia-inducible factor-prolyl hydroxylase inhibitors (HIF–PHIs) has advanced to phase III of global clinical development culminating in the recent approval of FibroGen's compound FG-4592 (roxadustat) for marketing in China. HIF-PHIs reversibly inhibit prolyl hydroxylase domain (PHD) dioxygenases, which act as cellular oxygen sensors and control the activity of HIF, a transcription factor that regulates, among other processes, renal and hepatic EPO production and iron metabolism.[12] In this review, we survey current clinical experience with HIF-PHIs, discuss their potential advantages over current anemia therapy, and address potential safety concerns regarding their long-term use in patients with renal anemia.

HIF-PHI THERAPY IN CLINICAL DEVELOPMENT

A classic response to systemic hypoxia is the increased production of red blood cells. This expansion in red blood cell mass follows a pronounced increase in plasma EPO levels and a decrease in plasma hepcidin concentrations.[13,14] Over the last 25 years, tremendous progress has been made toward defining the molecular machinery that controls this response.[15,16] Although the concept of exploiting hypoxia responses for anemia therapy is not novel, as the hypoxia mimic cobalt chloride had been used in hemodialysis (HD) patients for the treatment of refractory anemia,[17,18] the identification of PHD oxygen sensors has provided strong rationale for the development of selective and titratable small molecule inhibitors that are capable of activating HIF responses for the stimulation of erythropoiesis.[19]

Mechanism of Action and Drug Development

HIF transcription factors are essential for cellular survival under hypoxic conditions and regulate a multitude of biological processes that include angiogenesis, cell growth and differentiation, vascular tone, multiple metabolic processes, and erythropoiesis (Fig 1).[22-24] They consist of an oxygen-sensitive α-subunit and a constitutively expressed β-subunit, also known as the aryl hydrocarbon nuclear translocator. Three α-subunits have been identified, HIF-1α, HIF-2α and HIF-3α. Although HIF-1α and HIF-2α, which together with HIF-β form HIF-1 and HIF-2 transcription factors respectively, are well studied, relatively little is known about the biological functions of

HIF-3α and its multiple splice forms.[25] The hypoxic induction of erythropoiesis is predominantly mediated by HIF-2, which increases *EPO* transcription and activates the expression of genes involved in iron metabolism.[26-28]

Although synthesized continuously, HIF-α subunits are immediately degraded under normoxic conditions. Continuous synthesis results in rapid availability of the protein when HIF responses are needed in hypoxia. To dispose of newly synthesized HIF-α, cells use molecular oxygen and 2-oxoglutarate (2-OG, also known as α-ketoglutarate) for the hydroxylation of specific proline residues within HIF-α. Proline hydroxylation is followed by polyubiquitylation with subsequent proteasomal degradation involving the von Hippel-Lindau (VHL) tumor suppressor protein. When proline hydroxylation is reduced, HIF-α degradation is less efficient, resulting in its intracellular accumulation and nuclear translocation. In the nucleus, HIF-α heterodimerizes with HIF-β and activates gene transcription.[15,29] HIF-α hydroxylation is carried out by PHD dioxygenases (Fig 1).[20] A fourth HIF dioxygenase, factor inhibiting HIF (FIH), hydroxylates a C-terminal asparagine residue of HIF-α and fine-tunes HIF transcriptional responses.[15] Although FIH and PHDs utilize 2-OG for hydroxylation, HIF-PHIs are highly selective for PHD1, 2, and 3 over FIH.[21] Because of their biochemical properties and role in HIF regulation, PHD dioxygenases have become prime pharmacologic targets for the development of HIF-activating compounds through structure-based drug discovery programs.[19] Chemical structures of compounds discussed in this review are shown in Figure 1.

HIF-PHIs in Clinical Trials for Renal Anemia: Current Experience

Here we discuss current clinical experience with 3 compounds (daprodustat, roxadustat, and vadadustat) that have advanced to global phase III development in dialysis-dependent (DD) and non-dialysis-dependent (NDD) CKD patients. Bayer Pharmaceuticals has limited their development of molidustat (BAY-85-3934) to smaller phase III studies in Japan and Daiichi Sankyo has discontinued its renal anemia program with compound DS-1093.[1] Other compounds such as enarodustat (JTZ-951; Japan Tobacco/Akros Pharma),[30] desidustat (Zyan1; Cadila Healthcare),[31] and JNJ-42905343 (Janssen)[32] have either completed phase II studies or are in early development. Table 1 provides an overview of compounds currently in phase 3 development.

Roxadustat (FG-4592). Roxadustat is the first-in-class compound that has received formal marketing authorization by the National Medical Products Administration for the treatment of anemia in HD or peritoneal dialysis patients in China.[47] FibroGen developed roxadustat in partnership with AstraZeneca (United States and China) and Astellas Pharma (Europe, Commonwealth of Independent States, Japan, and Middle East) and has recently completed the *PYRENEES* (NCT02278341), *SIERRAS* (NCT02273726),[48] *HIMALAYAS* (NCT02052310),[48] *ROCKIES* (NCT02174731),[49] *ANDES* (NCT01750190),[48] *ALPS* (NCT01887600), and *OLYMPUS* (NCT02174627)[49] phase III studies, which enrolled more than 9000 participants combined (Table 2). The *OLYMPUS* trial was a large randomized, double-blinded placebo-controlled trial in 2781 NDD-CKD patients, CKD Stages 3, 4, and 5, while the *ROCKIES* trial was a randomized, open-label active-controlled trial in 2133 DD-CKD patients with epoetin alfa as the active comparator. Results from these studies have not yet been published. The *DOLOMITES* (NCT02021318) study is a phase III clinical trial which is currently active with an estimated enrollment of approximately 600 participants (Table 2).

Roxadustat is an orally administered, highly protein-bound small molecule, which targets all 3 HIF-PHDs to a similar extent and is usually dosed three times weekly (TIW).[21] It has a half-life of approximately 12-15 hours (healthy subjects and patients with impaired liver function) and is primarily metabolized by phase I oxidation via cytochrome P_{450} (CYP) 2C8 and phase II conjugation via uridine diphosphate (UDP)-glucuronosyltransferase 1-9.[38,39] Phase II trials have demonstrated that successful anemia management can be achieved with roxadustat in DD-CKD and NDD-CKD patients. The results from these studies are summarized below and in Tables 3 and 4.

Provenzano and colleagues[43] demonstrated dose-dependent effects of roxadustat on erythropoiesis and iron metabolism in American dialysis patients previously maintained on stable rhEPO therapy. The first part of this phase II trial was a 6-week dose finding study in 54 patients treated with either TIW roxadustat or intravenous (IV) epoetin alfa. Patients were given fixed doses of roxadustat ranging from 1 to 2 mg/kg TIW on interdialytic days. After 6 weeks of treatment, a dose-dependent increase in hemoglobin (Hgb) was observed in the roxadustat group compared to epoetin alfa. The second part of the study included 90 patients who either received 6 different doses of roxadustat (1-2 mg/kg TIW) or IV epoetin alfa for a total of 19 weeks. The mean roxadustat dose required for maintenance of Hgb levels of > 11 g/dL was 1.68 mg/kg TIW. Peak plasma EPO levels were found to be 5.4 times lower in patients receiving a mean roxadustat dose of 1.3 mg/kg (130 IU/L) compared

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CLINICAL SUMMARY

- HIF-prolyl hydroxylase inhibitors (HIF-PHIs) are efficacious in correcting and maintaining hemoglobin in patients with renal anemia.

- HIF-PHIs stimulate the production of endogenous erythropoietin and have positive effects on iron metabolism.

- HIF-PHIs have the potential to produce beneficial effects beyond erythropoiesis.

- Clinical studies investigating the long-term safety profile of HIF-PHI therapy in patients with CKD are pending.
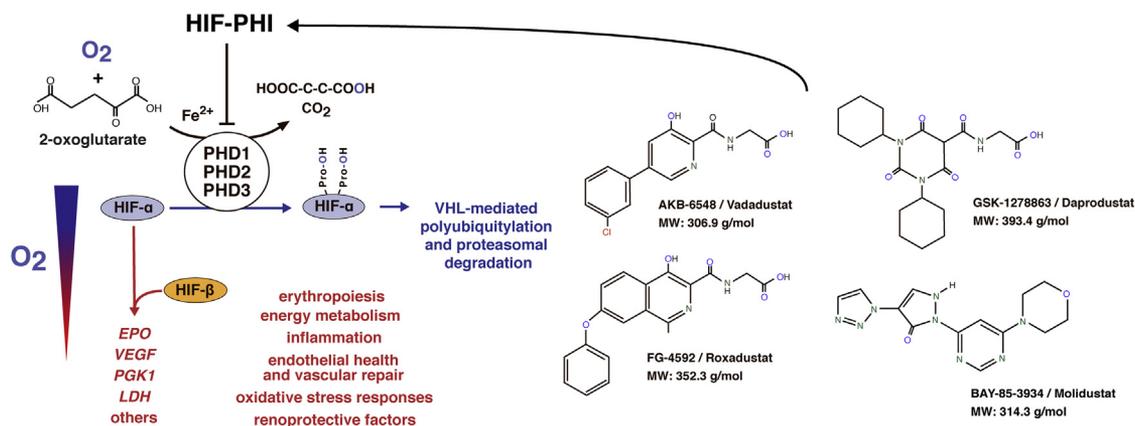

Figure 1. HIF-prolyl hydroxylase inhibitors activate HIF signaling. Overview of HIF activity regulation by PHD dioxygenases. Shown on the right are the chemical structures of HIF-PHIs currently in phase III clinical development. The oxygen-sensitive HIF-α subunit is constitutively synthesized and rapidly degraded under normoxic conditions. Proteasomal degradation of HIF-α is mediated by the VHL-E3-ubiquitin ligase complex and requires prolyl hydroxylation. PHD1, PHD2, and PHD3 are dioxygenases that utilize molecular oxygen (O_2) and 2-oxoglutarate (2-OG, also known as α-ketoglutarate) for HIF-α hydroxylation.[20] PHD2 is the main regulator of HIF activity in most cells.[15] A reduction in PHD catalytic activity, either under hypoxia or as a result of pharmacologic inhibition, results in a shift of the balance between HIF-α synthesis and degradation toward synthesis, intracellular HIF-α accumulation, and nuclear translocation of HIF-α.[15] In the nucleus, HIF-α forms a heterodimer with HIF-β, which increases the transcription of HIF-regulated genes such as *EPO, VEGF, PGK1, LDH,* and others. Also shown are examples of HIF-regulated biological processes. A common feature of HIF-PHIs is the presence of a carbonylglycine side chain, which is structurally analogous to 2-OG (daprodustat, roxadustat, and vadadustat). Molidustat is structurally different and does not contain a carbonylglycine side chain. With regard to specificity, HIF-PHIs appear to selectively target PHDs over FIH and other 2-OG-dependent dioxygenases. Abbreviations: *EPO, erythropoietin*; HIF, hypoxia-inducible factor; *LDH, lactate dehydrogenase*; *PGK1, phosphoglycerate kinase 1*; PHD, prolyl hydroxylase domain; PHI, prolyl hydroxylase inhibitor; *VEGF, vascular endothelial growth factor*; VHL, von Hippel-Lindau. Adapted from Haase.[12]

to those receiving epoetin alfa (700 IU/L). Dose-dependent increases in Hgb were associated with a decrease in plasma hepcidin levels along with decreases in plasma ferritin and increase in total iron binding capacity (TIBC). The decrease in hepcidin was statistically significant in the 2 mg/kg roxadustat cohort (part 1 of study) compared to epoetin alfa, which was associated with a less pronounced decrease in plasma hepcidin. Furthermore, Provenzano and colleagues reported that average weekly roxadustat maintenance dose requirements were not associated with concurrent C-reactive protein (CRP) levels, which suggested that inflammation may not notably impact the efficacy of HIF-PHI therapy. This notion is also supported by a phase III study with roxadustat in China (26 weeks of treatment) and a phase II study with vadadustat.[57,58] In addition to its effects on erythropoiesis and iron metabolism, roxadustat reduced nonfasting total cholesterol levels compared to rhEPO, indicating that systemic HIF-PHI administration has effects beyond erythropoiesis, which are EPO-independent. Observations similar to those made by Provenzano and colleagues were described in 87 prevalent HD patients in China previously treated with epoetin alfa.[53]

Positive Hgb and iron responses, including increases in plasma transferrin, were also observed in incident rhEPO-naïve peritoneal dialysis or HD patients,[52] who were given a mean weekly dose of 4.3 mg/kg of roxadustat in combination with varying doses of oral and IV iron therapy for 12 weeks. A greater Hgb response was noted in the cohorts receiving supplemental iron. Interestingly, Hgb responses in the oral and IV iron groups were reported as comparable. Consistent with other studies in DD-CKD, patients with elevated baseline CRP levels did not require higher doses of roxadustat. Hypertension necessitating increase or change in medication was the most commonly reported adverse event in 10% of patients.

To evaluate roxadustat in patients not on dialysis, Besarab and colleagues[42] performed a 28-day dose finding and pharmacodynamics study in 116 patients with Stage 3 and 4 CKD. Patients were given roxadustat twice weekly or TIW in doses ranging from 0.7 and 2.0 mg/kg. Oral iron was allowed in this study. Consistent with results from FibroGen's DD-CKD trials, roxadustat increased Hgb levels in a dose-dependent fashion, with faster responses in the TIW compared to twice weekly dosing groups. The increase in endogenous plasma EPO was dose-dependent but independent of dosing frequency (Table 1). Hepcidin levels decreased concomitantly, with significant changes seen at 1.5 and 2.0 mg/kg compared to placebo. This was associated with decreased plasma ferritin levels and increase in TIBC. Hyperkalemia was observed in 4 patients treated with roxadustat but not in the control group.

Similar changes in Hgb and iron parameters were also observed in 2 other NDD-CKD trials published by Provenzano and colleagues and Chen and colleagues.[53,55] The latter study was performed in China. Furthermore, both studies demonstrated that roxadustat decreases total, LDL (low-density lipoprotein), and HDL (high-density lipoprotein)

Table 1. Pharmacologic Profiles of HIF-PHIs in Phase III Development

Compound	Effective Daily Oral Doses in Phase II Trials	Dosing Schedule	Half-Life (h)	Plasma EPO (IU/L)	Metabolism	Rel. Activity, IC50 for PHD2 (μM)
Daprodustat (GSK-1278863)	5-25 mg (50 and 100 mg also examined)	QD	~1-7*	24.7 and 34.4, 82.4†	CYP2C8 with minor CYP3A4	PHD3>PHD1>PHD2, 0.067
Molidustat (BAY 85-3934)	25-150 mg (>75 mg in DD-CKD)	QD	4-10‡	39.8§	n.r.	PHD3>PHD1/PHD2, 0.007
Roxadustat (FG-4592, ASP1517)	0.7-2.5 mg/kg	TIW	12-15‖	113 and 397, 130¶	CYP2C8	PHD1,2,3 equally, 0.027
Vadadustat (AKB-6548, MT-6548)	150-600 mg	QD (TIW)	4.7-9.1#	32**	n.r.	PHD3>PHD1>PHD2, 0.029

Shown are the effective daily dose ranges and most commonly used dosing regimens reported in phase II studies in DD-CKD and NDD-CKD. *ASP1517* and *MT-6548* are alternative drug designations for roxadustat and vadadustat. The right column shows relative activity against the 3 HIF-PHDs obtained with mass spectrometry-based assays (range of differences from 2-fold to 9-fold) and the IC_{50} values for PHD2 (in μM) determined with an antibody-based hydroxylation assay.[21] All 4 compounds stabilize HIF-1α and HIF-2α in cell-based assays but display differences in potency and time course of HIF-α stabilization when the same concentrations of compounds were tested and compared to each other.[21]

Abbreviations: CYP, cytochromeP450; DD-CKD, dialysis-dependent CKD; EPO, erythropoietin; HIF, hypoxia-inducible factor; IC50, half maximal inhibitory concentration; NDD-CKD, non-dialysis-dependent CKD; n.r., not reported/not published; PHD, prolyl hydroxylase domain; PHI, prolyl hydroxylase inhibitor; QD, once daily; TIW, thrice weekly.

*Compound half-life is dose-dependent and shown for a single 10 mg dose in healthy Caucasian and Japanese subjects (~1 h) and CKD patients (~7 h).[33,34]

†Median peak plasma EPO level for daprodustat in the 5 mg dose cohort, 5-6 hours postdose (24.7 IU/L in DD-CKD and 34.4 in NDD-CKD),[35] and in the Japanese 10 mg DD-CKD cohort (82.4 IU/L).[36]

‡Half-life of molidustat in healthy subjects.[37]

§Mean peak plasma EPO level in healthy subjects 12 hours post 50 mg of molidustat.[37]

‖The half-life of roxadustat ranges from 12 h in healthy subjects to 15 h in subjects with moderate hepatic impairment.[38,39] Roxadustat's pharmacokinetic profile does not change when omeprazole, warfarin, or lanthanum carbonate are administered simultaneously.[38,40,41]

¶Median peak plasma EPO level for roxadustat 10 h postdose in NDD-CKD (113 IU/L at 1 mg/kg twice weekly and 397 IU/L at 2 mg/kg)[42] and mean EPO level 12 h postdose in DD-CKD patients (130 IU/L at a mean dose of 1.3 mg/kg).[43]

#The half-life of vadadustat ranges from 4.7 h in healthy subjects to 7.9 h in patients with NDD-CKD, and 9.1 h in DD-CKD.[44] HD does not affect its plasma levels.[45]

**Mean peak plasma EPO levels for vadadustat 8 h post single dose of 500 mg in Stage 3 and 4 CKD; baseline prior to dose was 22 IU/L.[46]

cholesterol in NDD-CKD patients (Table 4). Moreover, Chen and colleagues[53] reported decreases in triglycerides and very-low-density lipoprotein cholesterol in roxadustat-treated CKD patients.

In addition to evaluating roxadustat in patients with renal anemia, FibroGen in collaboration with AstraZeneca is currently enrolling patients to assess efficacy and safety of roxadustat in patients with low-risk myelodysplastic syndrome (NCT03263091 and NCT03303066).

Daprodustat (GSK-1278863). Daprodustat is a once daily oral HIF-PHI developed by GlaxoSmithKline. It inhibits all 3 PHDs with a preference for PHD1 and PHD3 and stabilizes both HIF-1α and HIF-2α.[21,59] The half-life of daprodustat is ~1 hour in healthy subjects (10 mg),[33] and ~7 hours in CKD patients (10 mg).[34] Daprodustat is highly protein-bound, not significantly cleared by HD and primarily metabolized by CYP2C8. Therefore, coadministration with strong CYP2C8 inhibitors (eg, gemfibrozil) should be avoided.[60] However, daprodustat can be safely coadministered with food, rosuvastatin, trimethoprim, and pioglitazone and does not prolong the corrected QT interval in healthy subjects.[33,60-62] The compound is currently undergoing evaluation in the phase III clinical trials *ASCEND-D* (NCT02879305), *ASCEND-ID* (NCT03029208), *ASCEND-TD* (NCT03400033), *ASCEND-*

ND (NCT02876835), and *ASCEND-NHQ* (NCT03409107), which are expected to have an estimated combined enrollment of more than 8000 participants (Table 2). Six notable phase II studies have been published, which established that daprodustat is efficacious in managing anemia of CKD with added positive effects on iron metabolism (Tables 3 and 4).

Holdstock and colleagues[35] treated 82 DD-CKD patients previously maintained on stable doses of rhEPO with 0.5, 2, or 5 mg of daily daprodustat for 4 weeks. Hgb levels were only maintained in the 5 mg study arm, which was associated with a median peak plasma EPO level of 24.7 IU/L compared to 424 IU/L in the rhEPO arm, a decrease in ferritin and increase in plasma transferrin and TIBC by ~12%. Similar to roxadustat, treatment with daprodustat affected cholesterol metabolism. Total cholesterol, LDL and HDL levels decreased with 5 mg of daprodustat by a mean of 2.9%, 8.1%, and 8.4% respectively with high variability among patients.

Higher doses of daprodustat, 10 and 25 mg, were given to rhEPO-naïve HD patients in a study by Brigandi and colleagues[34] demonstrating a dose-dependent rise in Hgb levels. However, the trial reported a 50% withdrawal rate in the 25 mg group due to a greater than 1 g/dL rise in Hgb over 2 weeks. In contrast to

Table 2. Major Named Phase III Clinical Trials

Compound	Trial Name ClinicalTrials.gov Identifier	n	Patient Population	Comparator	Duration (wk), Status
Daprodustat (GSK-1278863)	*ASCEND-D* NCT02879305	3000 (est.)	Stable DD-CKD	Epoetin alfa, darbepoetin alfa	52 +, active
	ASCEND-ID NCT03029208	300 (est.)	Incident DD-CKD	Darbepoetin alfa	52, active
	ASCEND-TD NCT03400033	402 (est.)	Stable DD-CKD	Epoetin alfa	52, active
	ASCEND-ND NCT02876835	4500 (est.)	NDD-CKD ± rhEPO-naïve	Darbepoetin alfa	52 +, active
	ASCEND-NHQ NCT03409107	600 (est.)	NDD-CKD rhEPO-naïve	Placebo	28, active
Molidustat (BAY 85-3934)	*MIYABI HD-C* NCT03351166	25	DD-CKD rhEPO-naïve	None	24, completed
	MIYABI HD-M NCT03543657	220	Stable DD-CKD	Darbepoetin alfa	52, active
	MIYABI PD NCT03418168	51	DD-CKD (PD)	None	36, active
	MIYABI ND-C NCT03350321	166	NDD-CKD rhEPO-naïve	Darbepoetin alfa	52, active
	MIYABI ND-M NCT03350347	162	NDD-CKD on rhEPO	Darbepoetin alfa	52, active
Roxadustat (FG-4592, *ASP1517*)	*PYRENEES* NCT02278341	838	Stable DD-CKD	Epoetin alfa, darbepoetin alfa	52 +, completed
	ROCKIES NCT02174731	2133	Stable DD-CKD	Epoetin alfa	52 +, completed[49]
	SIERRAS NCT02273726	741	Stable DD-CKD	Epoetin alfa	52 +, completed[48] (average 1.9 y)
	HIMALAYAS NCT02052310	900 (est.)	Incident DD-CKD	Darbepoetin alfa	52 +, completed[48] (average 1.8 y)
	ALPS NCT01887600	597	NDD-CKD	Placebo	52 +, completed
	ANDES NCT01750190	922	NDD-CKD	Placebo	52 +, completed[48] (average 1.7 y)
	OLYMPUS NCT02174627	2781	NDD-CKD	Placebo	52 +, completed[49]
	DOLOMITES NCT02021318	616	NDD-CKD	Darbepoetin alfa	104, active
Vadadustat (AKB-6548, *MT-6548*)	*INNO₂VATE*				
	NCT02865850	300 (est.)	Incident DD-CKD	Darbepoetin alfa	52 +, active
	NCT02892149	3300 (est.)	Stable DD-CKD	Darbepoetin alfa	52 +, active
	PRO₂TECT				
	NCT02680574	1850 (est.)	NDD-CKD on rhEPO	Darbepoetin alfa	52 +, active
	NCT02648347	1850 (est.)	NDD-CKD rhEPO-naïve	Darbepoetin alfa	52 +, active

Listed are major named phase III clinical trials. Detailed information can be obtained at ClinicalTrials.gov. *ASP1517* and *MT-6548* are alternative drug designations for roxadustat and vadadustat.

Abbreviations: +, with extended treatment period, average duration indicated if published; DD-CKD, dialysis-dependent CKD; est., estimated enrollment; n, number of patients enrolled; NDD-CKD, non-dialysis-dependent CKD.

Table 3. Summary of Published Peer-Reviewed Phase II Studies in DD-CKD

Compound	Study	n	Duration (wk)	Comp	Ferritin	TIBC	Hepcidin	VEGF	Cholesterol
Daprodustat (GSK-1278863)	Holdstock et al.[35]	82	4	rhEPO	↓	↑	No chg. (5 mg)	No chg.	↓
	Brigandi et al.[34]	83	4	Placebo	↓	↑	↓ (10 and 25 mg)	Lg. variation	n.r.
	Akizawa et al.[36]	97	4	Placebo	↓	↑	↓	No chg.	↓
	Meadowcroft et al.[50]	216	24	Placebo	↓	↑	↓	No chg.	n.r.
Molidustat (BAY 85-3934)	Macdougall et al.[51]	199	16	rhEPO	No chg.	No chg.	No chg.	n.r.	No chg.
Roxadustat (FG-4592, *ASP1517*)	Provenzano et al.[43]	54 (part 1) and 90	6 or 19*	rhEPO	↓	↑ (part 1†)	↓†	n.r.	↓
	Besarab et al.[52]	60	12	None	↓†	↑†	↓†	n.r.	n.r.
	Chen et al.[53]	87	6	rhEPO	↓	↑†	↓	n.r.	↓†
Vadadustat (AKB-6548, *MT-6548*)	Haase et al.[54]	94	16	None	↓	↑†	↓†	No chg.	No chg.

Published phase II studies which have shown efficacy in the correction and maintenance of hemoglobin in patients with dialysis-dependent CKD. *ASP1517* and *MT-6548* are alternative drug designations for roxadustat and vadadustat.
Abbreviations: comp, comparator group; DD-CKD, dialysis-dependent CKD; Lg. variat., large variation; n, number of patients; no chg., no change; n.r., not reported/not published; rhEPO, recombinant human erythropoietin.
*Two-part study: first part was a 6-week dose ranging study and second part was a 19-week treatment study with various starting doses and titration adjustments.
†Denotes statistically significant values reported for the end of treatment in one or several dose cohorts or for the combined analysis of all dosing groups. Changes at earlier time points or in individual dose cohorts may not have reached statistical significance and are not indicated in the table.

the 5 mg group studied by Holdstock and colleagues, plasma hepcidin levels decreased in the 10 and 25 mg groups more notably.

To assess for potential differences in drug metabolism, Akizawa and colleagues[36] defined efficacious dose ranges for daprodustat in Japanese DD-CKD patients previously maintained on rhEPO (4-week study). Daprodustat increased Hgb levels in Japanese dialysis patients when transitioned to 8 or 10 mg and maintained Hgb levels in the 4 and 6 mg cohorts.

Table 4. Summary of Published Peer-Reviewed Phase II Studies in NDD-CKD

Compound	Study	n	Duration (wk)	Comp	Ferritin	TIBC	Hepcidin	VEGF	Cholesterol
Daprodustat (GSK-1278863)	Holdstock et al.[35]	72	4	Placebo	↓	↑	↓	No chg.	↓
	Brigandi et al.[34]	70	4	Placebo	↓	↑	↓	Lg. variat.	n.r.
Enarodustat (JTZ-951)	Akizawa et al.[30]	94 (correct.) 107 (conv.)	30	Placebo (first 6 wk)	↓*	↑*	↓*	No chg.	n.r.
Molidustat (BAY 85-3934)	Macdougall et al.[51]	121†	16	Placebo	↓	No chg.	↓	n.r.	No chg.
	Macdougall et al.[51]	124‡	16	Darbepoetin alfa	↓	No chg.	↓	n.r.	No chg.
Roxadustat (FG-4592, *ASP1517*)	Besarab et al.[42]	116	4	Placebo	↓	↑*	↓*	n.r.	n.r.
	Provenzano et al.[55]	145	16-24	None	↓*	↑*	↓*	n.r.	↓*
	Chen et al.[53]	91	6	Placebo	↓*	↑*	↓*	n.r.	↓*
Vadadustat (AKB-6548, *MT-6548*)	Pergola et al.[56]	210	20	Placebo	↓*	↑*	↓*	No chg.	No chg.
	Martin et al.[45]	93	6	Placebo	↓*	↑*	↓*	No chg.	No chg.

Published phase II studies which have shown efficacy in the correction and maintenance of hemoglobin in patients with NDD-CKD. *ASP1517* and *MT-6548* are alternative drug designations for roxadustat and vadadustat.
Abbreviations: comp, active comparator group; conv., conversion from ESA; correct., correction (EPO-naïve patients); EPO, erythropoietin; ESA, ESA, erythropoiesis stimulating agent; Lg. variat., large variation; n, number of patients; NDD-CKD, non-dialysis-dependent CKD; no chg., no change; n.r., not reported/not published.
*Denotes statistically significant values reported for the end of treatment in one or several dose cohorts or for the combined analysis of all dosing groups. Changes at earlier time points or in individual dose cohorts may not have reached statistical significance and are not indicated here.
†DIALOGUE 1 was a placebo-controlled fixed-dose study.
‡DIALOGUE 2 was an open-label variable dose study with darbepoetin alfa as the active comparator.

Meadowcroft and colleagues[50] performed a large open-label randomized controlled 24-week trial in 216 HD patients previously maintained on stable doses of rhEPO. Patients were randomized to receive fixed starting doses between 4 and 12 mg of daprodustat once daily or placebo for 4 weeks followed by dose adjustments and rhEPO administration as needed. Hgb targets were reached with a median average daily dose of 6 mg. This was associated with a decrease in hepcidin, ferritin, and transferrin saturation. Significant changes in plasma vascular endothelial growth factor (VEGF) levels were not observed. Eight patients in the daprodustat but not control group developed hyperkalemia. Interestingly, the investigators reported a trend of increased systolic blood pressure in the daprodustat arm with 12% of patients receiving an increase in the number of antihypertensive medications. Serious adverse events in the daprodustat arm included 3 patients with fatal and nonfatal myocardial infarction and 5 patients who were hospitalized for heart failure exacerbations. Five patients in the daprodustat arm died during the study.

Daprodustat is also efficacious in NDD-CKD as shown in 72 rhEPO-naïve patients.[35] Patients received daily doses of 0.5, 2, or 5 mg of daprodustat or placebo. However, only patients in the 5 mg cohort achieved a mean increase in Hgb, which was associated with a decrease in plasma hepcidin concentrations and ferritin and increases in plasma transferrin and TIBC. Total cholesterol, LDL and HDL levels were decreased (-7.4%, -13.9%, and -15.6%, respectively). Similar to observations made in DD-CKD trials, larger doses of daprodustat (25 mg and above) were associated with a high rate of study discontinuation mostly due to adverse events, rapid increase in Hgb, or high absolute Hgb levels.[34] The most commonly observed side effect was nausea in the 50 and 100 mg dose groups.

Vadadustat (AKB-6548). Vadadustat is an orally administered HIF-PHI developed by Akebia Therapeutics. Akebia has partnered with Mitsubishi Tanabe Pharma and Otsuka to expand development and future commercialization in Asia, Europe, Australia, and the Middle East. Vadadustat inhibits all 3 PHDs with a preference for PHD3 and stabilizes both HIF-1α and HIF-2α.[21] Vadadustat is currently undergoing evaluation in several phase III clinical trials with more than 7000 participants, most notably the 2 large global efficacy and safety studies INNO$_2$VATE in DD-CKD (NCT02865850, NCT02892149) and PRO$_2$TECT in NDD-CKD (NCT02680574, NCT02648347), as well as smaller studies in Japan (Table 2). Three phase II studies have been published thus far, 2 in NDD-CKD and 1 in DD-CKD patients, which demonstrate its efficacy in anemia management.

Pergola and colleagues[56] published the first placebo-controlled study in 210 NDD-CKD patients. Patients were given a starting dose of 450 mg daily of vadadustat titrated to final doses ranging from 150 to 600 mg and compared to placebo over a period of 20 weeks. About 54.9% of patients treated with vadadustat reached the primary endpoint of achieving a Hgb level of >11 g/dL or an increase in Hgb of >1.2 g/dL over the predose average, compared to 10% of patients receiving placebo. Hgb levels greater than 13 g/dL were found in 4.3% of patients in the treatment group. The mean dose of vadadustat was 450 mg daily at the end of the study period, with 89% of patients requiring 2 or fewer dose adjustments during the trial. Vadadustat decreased hepcidin and ferritin levels while increasing TIBC. Changes in cholesterol or triglycerides, plasma VEGF, or blood pressure were not reported in this and a second NDD-CKD study.[45] The percentage of patients with adverse events was comparable between vadadustat and placebo groups. The most commonly reported side effects in this study were gastrointestinal (diarrhea and nausea). Interestingly, 7 patients in the vadadustat group developed hyperkalemia vs none in the control cohort. The significance of this finding is unclear.

The only phase II study published in DD-CKD included 94 HD patients previously maintained on epoetin alfa.[54] Patients were randomized to receive vadadustat 300 mg daily, 450 mg daily, or 450 mg TIW for 16 weeks, with permissible dose increases of up to 600 mg starting at week 8. The study found that mean Hgb levels were maintained in all 3 cohorts with no significant differences reported between groups. Mean plasma hepcidin and ferritin levels decreased in a dose-dependent manner (for hepcidin statistically significant in the 450 mg daily group) and were associated with a statistically significant increase in TIBC in all 3 dosing cohorts. The most frequently reported side effects were nausea, vomiting, and diarrhea. Changes in blood pressure parameters, plasma VEGF, or cholesterol levels were not reported.

ADVANTAGES OF HIF-PHI THERAPY

Current renal anemia therapy poses several clinical challenges and raises multiple patient safety concerns. These include an increase in cardiovascular risk that is associated with supraphysiologic ESA plasma levels, EPO-resistance caused by inflammation, hypertension, and the need for frequent IV iron administration due to the high prevalence of absolute and functional iron deficiency in CKD patients.[1,10,63-67] All published phase II trials indicate that HIF-PHI therapy is at least as efficacious as conventional ESA therapy in managing Hgb levels in both NDD-CKD and DD-CKD patients. Phase III cardiovascular safety data pending, this raises obvious questions regarding potential advantages of HIF-prolyl hydroxylase inhibition over current ESA therapy and why renal medicine practitioners should switch their patients from well-established standards of care to a new oral therapy for which long-term clinical data are not yet available. This is especially relevant to patients who are doing well on current ESA therapy as clinical benefits of HIF-PHIs that extend beyond erythropoiesis have not been clearly established and safety concerns have not been completely addressed (Table 5).

A potentially beneficial feature of HIF-PHI therapy is that Hgb targets were achieved with lower plasma EPO levels compared to ESA therapy. Approximately 5- to 17-fold lower plasma EPO levels were measured in CKD

Table 5. Benefits, Potential Disadvantages, and Safety Concerns

Clinical Benefits	Potential Disadvantages and Safety Concerns
Correction and/or maintenance of Hgb is associated with lower plasma EPO levels compared to ESA	Potential pro-tumorigenic effects
Lowering of hepcidin levels and beneficial effects on iron metabolism	Neuroendocrine tumor development
	Pulmonary hypertension
Potential anti-inflammatory effects	Pro-angiogenic effects negatively impacting retinal diseases or cancer development
Potential benefits in ESA-resistant patients	Thromboembolic complications
Potential protection from ischemic events	CKD progression (the role of HIF in renal fibrogenesis is controversial, cell type- and context-dependent), renal and liver cyst progression in PKD
Potential blood pressure lowering effects	Effects on autoimmune diseases are not clear
	Effects on underlying infectious processes is unclear
	Adverse metabolic effects such as hyperglycemia and hyperuricemia
	Adverse effects on blood pressure
	Hyperkalemia (reported in phase II studies)
	Adverse effects in patients with chronic hepatitis

Listed are potential clinical benefits and major disadvantages or safety concerns of HIF-PHI therapy that need further clinical evaluation.
Abbreviations: EPO, erythropoietin; ESA, erythropoiesis stimulating agent; Hgb, hemoglobin; PKD, polycystic kidney disease.

patients who were successfully treated with HIF-PHIs compared to those receiving epoetin alfa.[35,43] Because increased cardiovascular morbidity and mortality in ESA-treated patients has been associated with supraphysiologic EPO dosing and plasma EPO levels,[65,67] HIF-PHI therapy has the potential to improve cardiovascular outcomes in CKD. However, safety data are not yet available to support this notion. Table 1 provides an overview of reported plasma EPO concentrations in CKD patients receiving HIF-PHIs.

Another major advantage of HIF-PHI therapy would be the suppression of hepatic hepcidin production and its negative effects on iron mobilization. Hepcidin plays a central role in the pathogenesis of functional iron deficiency as it inhibits gastrointestinal iron uptake and iron release from internal stores by down-regulating the surface expression of ferroportin, the only known cellular iron exporter (Fig 2). Clinical data from phase II studies have consistently shown "positive" effects on iron metabolism as manifested by a reduction in plasma ferritin and hepcidin and simultaneous increase in plasma transferrin and TIBC (Tables 3 and 4; plasma transferrin levels were reported in several phase II studies[35,36,52,53]). These results are consistent with experimental data from animal and cell culture studies, which demonstrated that the PHD/HIF axis coordinates iron metabolism with erythropoiesis via transcriptional regulation of genes involved in iron uptake, iron release, and transport (Fig 2).[70] The observed effects on plasma hepcidin levels in CKD patients receiving HIF-PHIs are most likely indirect, as hepcidin is not a direct transcriptional target of HIF.[71,72] Transcriptional suppression of *hepcidin* in the context of HIF activation requires erythropoietic activity and is mediated by bone marrow-derived factors such as erythroferrone.[68,73] It is unclear, however, whether the effects of oral HIF-PHI therapy on iron metabolism are primarily mediated via the hepcidin-ferroportin axis (increase in erythropoietic activity with subsequent suppression of hepcidin and increased ferroportin-mediated iron release) or through direct transcriptional

regulation of iron metabolism gene expression. Although several iron metabolism genes, such as *divalent metal transporter 1* (*DMT1*) or *duodenal cytochrome b* (*DCYTB*), are bona fide HIF-regulated genes and can be upregulated by oral prolyl hydroxylase inhibition,[32,74] it has not been examined whether HIF-PHI doses currently used in clinical trials are sufficient enough to induce the expression of these genes in CKD patients. Nevertheless, the added HIF-PHI effect on iron mobilization has the potential to reduce the need for IV iron supplementation in patients with renal anemia as suggested by Besarab and colleagues.[52]

Daprodustat and roxadustat alter lipid metabolism, as lower total cholesterol and triglyceride levels (the latter reported for roxadustat) were found in both DD-CKD and NDD-CKD patients. This appears to be a drug class effect, as HIF activation increases lipoprotein uptake and has been shown to promote the degradation of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase reducing cholesterol synthesis.[75,76] It is unclear, however, to what degree HIF-PHI therapy will impact the treatment of dyslipidemias, which are highly prevalent in CKD patients and have been associated with an increased risk of cardiovascular events.[77] In contrast to daprodustat and roxadustat, cholesterol- or triglyceride-lowering effects were not reported for molidustat and vadadustat (Tables 3 and 4). Whether this is due to differences in pharmacokinetics, tissue distribution, or dosing is not known.

HIF-PHI therapy has the potential to lower blood pressure as demonstrated in a rodent model of CKD treated with molidustat.[78] However, a blood pressure lowering effect could not be established in phase II trials, and results from phase III investigations will likely provide additional information regarding this potential benefit.

A large body of literature demonstrates that HIF regulates both innate and humoral immunity and suppresses inflammation, for example, in preclinical models of inflammatory bowel disease.[79-81] Currently it
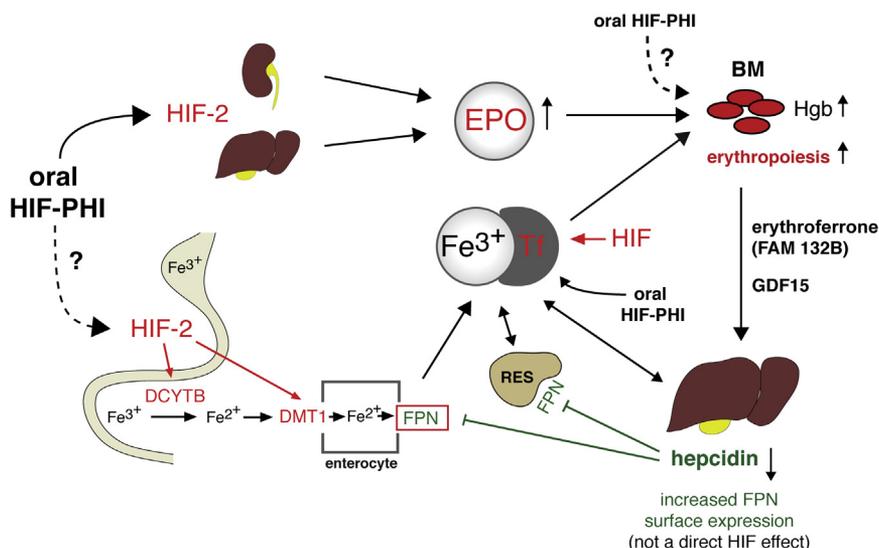
Figure 2. HIF-prolyl hydroxylase inhibitors coordinate erythropoiesis with iron metabolism. Simplified overview of the role of HIF in the regulation of iron metabolism. HIF-2 induces renal and hepatic EPO synthesis in response to hypoxia or administration of HIF-PHD inhibitors (HIF–PHI), which stimulate erythropoiesis. An adjustment in iron mobilization is needed to match increased iron demand in erythroid precursor cells in the BM. In the duodenum, DCYTB reduces ferric iron (Fe^{3+}) to its ferrous form (Fe^{2+}), which is then transported into the cytosol of enterocytes by DMT1. DCYTB and DMT1 are HIF-2-regulated. Absorbed iron is released into the circulation by FPN (HIF-2-regulated), the only known cellular iron exporter and then transported in complex with TF to the liver, RES cells, BM, and other organs. TF is HIF regulated and hypoxia increases its serum levels. Low serum iron and increased "erythropoietic drive" inhibit hepcidin synthesis in the liver resulting in increased FPN cell surface expression, as hepcidin promotes FPN degradation and lowers its cell surface expression. Erythroferrone (FAM132B) is produced by erythroblasts and suppresses hepatic *hepcidin* transcription when erythropoiesis is stimulated.[68] GDF15 is another factor with *hepcidin*-suppressing properties; however, its role in vivo is not clear.[69] As a result of *hepcidin* suppression more iron is released from enterocytes, hepatocytes, and RES cells. Whether HIF–PHI effects on iron mobilization are mediated through the hepcidin/FPN axis or reflect a direct transcriptional activation of iron metabolism gene expression is unclear (dashed lines). Phase II studies reported consistent increases in TIBC suggesting a direct effect on TF synthesis. Plasma TF was measured in some of the studies and found to be increased.[35,36,52,53] It is unclear whether HIF-PHIs affect the BM directly as HIF has been shown to be involved in erythroid maturation and hemoglobin synthesis. Abbreviations: BM, bone marrow; DCYTB, duodenal cytochrome *b*; DMT-1, divalent metal transporter-1; EPO, erythropoietin; FPN, ferroportin; GDF15, growth differentiation factor 15; HIF, hypoxia-inducible factor; PHD, prolyl hydroxylase domain; PHI, prolyl hydroxylase inhibitor; RES, reticuloendothelial system; TF, transferrin; TIBC, total iron binding capacity.

is not clear whether HIF-PHI therapy produces anti-inflammatory effects in patients with CKD. Suppressive effects on inflammation would be particularly beneficial for patients with renal anemia, who do not adequately respond to ESA therapy and are considered EPO-resistant. Several phase II studies have indicated that biomarkers of inflammation such as CRP and hepcidin do not correlate with HIF-PHI dose requirements, suggesting that systemic HIF activation may overcome some of the suppressive effects of inflammation on erythropoiesis.[52,55,57,58] Whether this occurs through direct or indirect effects on the immune system is unclear and warrants further investigation. Cizman and colleagues[82] included 15 EPO-resistant HD patients in a single arm study to determine if Hgb target levels could be maintained with daprodustat starting at 12 mg daily. However, solid conclusions could not be drawn from this trial due the very low number of patients being able to complete the study.

Additional benefits afforded by HIF-PHI therapy may include cytoprotection and improvements in cardiovascular health. Preclinical studies have consistently shown that pre-ischemic HIF activation protects multiple organs from acute ischemia-reperfusion injury, including the kidneys, heart, brain, and liver.[83] This is of particular importance for patients with CKD who are at increased risk for cardiovascular events, including myocardial infarction and stroke.[84,85] In support of the notion that systemic HIF activation could induce a certain level of protection from ischemic events are epidemiologic data indicating that life at high altitude reduces cardiovascular risk in dialysis patients.[86,87] In addition, HIF-PHI therapy may ameliorate the effects of acute renal injury on CKD progression.[83]

PATIENT SAFETY CONCERNS

Because HIF-1 and HIF-2 control a multitude of biological processes, systemic PHD inhibition has the potential to produce undesirable on-target effects ranging from changes in glucose, fat, and mitochondrial metabolism, to alterations in cellular differentiation, inflammation, vascular tone, and cell growth. Notwithstanding these

Table 6. Summary of Serious Adverse Events

NDD-CKD Studies	DD-CKD Studies
Worsening CHF	Worsening CHF
Acute myocardial infarction	Acute myocardial infarction
Increased transaminase levels	Increased transaminase levels
Worsening hypertension	Worsening hypertension
Acute pancreatitis	Acute pancreatitis
Pulmonary embolus	CVA
Increased edema	AVF thrombosis
Dizziness	
Insomnia	
Worsening CKD	

Shown are SAEs reported in patients enrolled in phase II clinical studies. SAEs were thought to be within expected range or deemed not related to study medication.
Abbreviations: AVF, arteriovenous fistula; CHF, congestive heart failure; CVA, cerebrovascular accident; DD-CKD, dialysis-dependent CKD; NDD-CKD, non-dialysis-dependent CKD; SAE, serious adverse event.

concerns, phase III investigation in Chinese dialysis patients previously treated with ESA did not produce significant safety signals, resulting in the recent licensing of roxadustat in China. However, this study was not major adverse cardiovascular event-driven and lasted only 27 weeks, which included a 26-week treatment period (NCT02652806).[57] Major adverse events reported in phase II studies were deemed not to be drug related and to fall within the range of expected event frequencies in CKD patients (Table 6). Nevertheless, patient safety concerns regarding the long-term use of HIF-PHIs remain and need to be carefully addressed in extended clinical studies and/or postmarketing investigations. Long-term safety concerns relate to a theoretical oncogenic risk, certain cardiovascular risks such as predisposition to pulmonary arterial hypertension and thromboembolic disease, increased angiogenesis potentially facilitating the progression of diabetic retinopathy, the potential for metabolic alterations, and potentially negative effects on CKD and renal cyst progression (Table 5).

Many of the undesirable responses to systemic HIF-PHI administration are predicted from genetic studies in animals or from clinical observations in patients with genetic defects that lead to activation of the HIF pathway, for example, Chuvash polycythemia, which is caused by specific nontumorigenic mutations in the *VHL* gene.[88-91] However, it is difficult to make clinical predictions from these genetic conditions, as HIF-PHI administration does not result in persistent and irreversible HIF activation, but rather produces limited low-level bursts of reversible HIF-α stabilization and HIF target gene activation.

The occurrence of undesirable HIF responses in CKD patients is likely to depend on the degree, duration, and tissue distribution of cellular HIF-α stabilization, that is, pharmacokinetics and dosing of PHIs. For example, statistically significant increases in plasma VEGF levels were detected when relatively high doses of daprodustat (50-100 mg) were given to healthy subjects,[33] but were not observed with lower doses that were sufficient to maintain Hgb in CKD patients. Similarly, increases in

blood glucose levels (although statistically not significant) were reported with higher doses of daprodustat (50-100 mg) in NDD-CKD patients.[34] Thus, HIF-PHI therapy may achieve desirable pro-erythropoietic effects at doses that are not sufficient to elicit a broader spectrum of HIF responses in CKD patients.

There are theoretical concerns that activation of HIF signaling may be pro-oncogenic, promote tumor growth, or facilitate metastasis. These concerns are largely based on clinical and experimental studies demonstrating that many cancers show evidence of HIF activation. These findings are not surprising, as tumors experience hypoxia and utilize the HIF pathway for metabolic adaptation and angiogenesis.[92] There is currently little evidence that HIF transcription factors by themselves are pro-oncogenic in a normal genetic background. This, for example, is illustrated in renal cancer cells where HIF-α is permanently stabilized due to VHL function loss.[93] Although VHL function loss and constitutive activation of HIF signaling represent an early and frequent event in renal tumorigenesis, additional mutations are required before renal cancers develop.[94,95] Notwithstanding the need for additional mutations in renal cancer pathogenesis, HIF-2 antagonists are currently under investigation for the treatment of advanced renal cancer.[96-98] Certain neuroendocrine tumors, such as pheochromocytomas, paragangliomas, and duodenal somatostatinomas, carry mutations in *HIF2A* and less frequently in the *PHD2* gene.[99-102] However, a relatively high and continuous dose of HIF-2α appears to be required for disease development, which is unlikely to occur in the setting of HIF-PHI therapy.[103,104] To examine the effects of long-term HIF-PHI administration on tumor development and progression, experimental studies were performed in animal models.[105,106] These studies have not demonstrated tumor-initiating or tumor-promoting effects. This notwithstanding, patients on HIF-PHI therapy will need to be carefully monitored, as long-term studies are not available to address concerns relating to the oncogenic potential of HIF-PHIs.

Similarly, long-term clinical data concerning potential adverse effects of HIF activation on CKD progression,[107] cystogenesis,[108] and the progression of diabetic retinopathy or other retinal diseases are pending.[109] Furthermore, it is not clear whether HIF-PHI therapy may be harmful in CKD patients with certain comorbidities, such as a history of previous stroke or autoimmune diseases, for example, systemic lupus erythematosus.

Whether HIF-PHI therapy affects pulmonary vascular tone in CKD patients, who are more likely to develop pulmonary arterial hypertension,[110] is also unclear and will have to be carefully examined. HIF-2 plays a key role in the regulation of pulmonary vascular tone and development of pulmonary arterial hypertension following exposure to chronic hypoxia. Furthermore, mutations in the *HIF2A* gene have been associated with a predisposition to the development of pulmonary arterial hypertension in humans and animals.[111-115]
Several phase II studies reported hyperkalemia in a total of 19 HIF-PHI-treated NDD-CKD and DD-CKD patients

but not in the corresponding control groups.[42,50,56] The significance of these findings is unclear. Phase III data will address this potential safety concern in a larger patient population. Another safety concern relates to the effects of HIF-PHI therapy on liver metabolism and function. This is of particular interest due to the high prevalence of hepatitis C in the dialysis patient population.[116] Compound FG-2216, which is structurally related to roxadustat, was permanently taken out of clinical development in 2008 due to one case of fatal hepatic failure. Although the Food and Drug Administration did not attribute the patient's death to the study medication,[117] CKD patients receiving HIF-PHIs are carefully monitored for abnormalities in liver function in ongoing clinical trials. Persistent negative effects on liver function have not been reported thus far.

SUMMARY AND FUTURE OUTLOOK

Roxadustat is the first-in-class HIF-PHI that has been licensed for the treatment of renal anemia. Although currently limited to the Chinese market, it is expected that licensing of roxadustat and other HIF-PHIs will follow soon in other countries. Clinical data from long-term observations are not available but will be needed to address remaining patient safety concerns.

Daprodustat, roxadustat, and vadadustat are potent inhibitors of PHD dioxygenases and capable of stimulating erythropoiesis in patients with advanced CKD. They act mechanistically similar but display differences in their effects on cells. These differences will likely be reflected in their nonerythropoietic actions, which are still ill-defined in CKD patients.

It will be important to identify those CKD patients who would clearly benefit from PHI therapy and those who should not be treated, as the presence of certain comorbidities may preclude the use of HIF-PHIs in some patients. Although efficacious and not inferior to ESA therapy, phase III patient safety results pending, renal practitioners are not likely to switch patients who are stable on ESA therapy to HIF-PHIs, unless additional clinical trials clearly establish that HIF-PHI therapy has benefits that go beyond erythropoiesis.

An important question for the renal practitioner will be how to choose among different HIF-PHIs once approved for marketing. Although clinical data are currently incomplete to provide guidance in this regard, dosing regimen and patient compliance (eg, TIW vs daily administration), therapeutic window, pharmacokinetic and pharmacodynamic profile, potential drug interaction, ease of switching from ESA therapy, potential differences in metabolic profile, effects on blood pressure and other clinical parameters will have to be taken into consideration by the prescribing physician. Because preclinical studies suggest that HIF-PHIs have indications beyond renal anemia therapy, clinical trials outside this domain are warranted to explore additional therapeutic avenues. These include cytoprotection, inflammation, wound healing, sarcopenia of aging (NCT03371134), and inflammatory bowel disease (NCT02914262).

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