Vadadustat, a novel oral HIF stabilizer, provides effective anemia treatment in nondialysis-dependent chronic kidney disease

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Current treatment of anemia in chronic kidney disease (CKD) with erythropoiesis-stimulating agents can lead to substantial hemoglobin oscillations above target range and high levels of circulating erythropoietin. Vadadustat (AKB-6548), a novel, titratable, oral hypoxia-inducible factor prolyl hydroxylase inhibitor induces endogenous erythropoietin synthesis and enhances iron mobilization. In this 20-week, double-blind, randomized, placebo-controlled, phase 2b study, we evaluated the efficacy and safety of once-daily vadadustat in patients with stages 3a to 5 non-dialysis-dependent CKD. The primary endpoint was the percentage of patients who, during the last 2 weeks of treatment, achieved or maintained either a mean hemoglobin level of 11.0 g/dl or more or a mean increase in hemoglobin of 1.2 g/dl or more over the predose average. Significantly, the primary endpoint was met in 54.9% of patients on vadadustat and 10.3% of patients on placebo. Significant increases in both reticulocytes and total iron-binding capacity and significant decreases in both serum hepcidin and ferritin levels were observed in patients on vadadustat compared with placebo. The overall incidence of adverse events was comparable between the 2 groups. Serious adverse events occurred in 23.9% and 15.3% of the vadadustat- and placebo-treated patients, respectively. Three deaths occurred in the vadadustat arm. Thus, this phase 2b study demonstrated that vadadustat raised and maintained hemoglobin levels in a predictable and controlled manner while enhancing iron mobilization in patients with nondialysis-dependent CKD.

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Anemia is a common complication of chronic kidney disease (CKD), driven predominantly by a relative deficiency in renal erythropoietin (EPO) production, concomitant functional and/or absolute iron deficiency, and resistance to EPO signaling.[1,2] As the severity of kidney disease progresses, anemia increases in prevalence and affects nearly all patients with advanced-stage CKD.[3] The presence of anemia in patients with CKD is associated with increased risk for hospitalization, cognitive impairment, reduced quality of life, and major cardiovascular (CV) events, such as myocardial infarction and stroke; furthermore, the severity of anemia is also an independent predictor of mortality.[4–7] The administration of injectable preparations of recombinant EPO coupled with oral or i.v. iron supplementation are the current mainstay of treatment for anemia in CKD.[8,9] Though generally very effective therapeutically, the use of erythropoiesis-stimulating agents (ESAs) has raised significant safety concerns. ESA administration often results in substantial hemoglobin (Hb) oscillations and excursions above target range, which are associated with increased CV risk.[9–12] Furthermore, patients who require very high ESA doses to reach target Hb, or who fail to reach target Hb levels at ESA doses that are normally effective, have increased mortality and hospitalization rates.[13–18] Meanwhile, i.v. iron supplementation may place patients at increased risk of allergic reactions, infections, and CV events.[19,20] Therefore, a novel approach to anemia therapy that is effective without generating supraphysiologic plasma EPO levels and that reduces the need for iron supplementation is highly desirable.

The pharmacologic targeting of the molecular machinery that regulates the hypoxic induction of erythropoiesis has the potential to solve some of the clinical dilemmas associated with conventional ESA therapy. EPO synthesis in the kidney and liver is regulated by hypoxia-inducible factor (HIF)-2, an oxygen-sensitive heterodimeric transcription factor that, together with HIF-1, regulates a multitude of biological processes that help cells and tissues adapt to hypoxia.[2] HIF activity is controlled by iron- and 2-oxoglutarate–dependent prolyl-4-hydroxylase domain (PHD) dioxygenases PHD1, PHD2, and PHD3, which function as oxygen sensors. In the presence of oxygen, PHD enzymes inhibit HIF activity by hydroxylating specific proline residues within the

oxygen-sensitive HIF-α subunit, targeting HIF-α for proteasomal degradation.[21] Under hypoxic conditions, PHD-mediated hydroxylation is reduced and HIF signaling is activated. This, in turn, results in the transcriptional activation of multiple HIF target genes, including *EPO* and iron metabolism genes.[21] HIF prolyl-4-hydroxylase (PH) inhibitors, compounds that reversibly inhibit PHD catalytic activity, represent a promising new class of drugs that activate HIF signaling and increase endogenous EPO production, while also simultaneously stimulating iron metabolism.[2,22]

Vadadustat, also known as AKB-6548, is a novel, titratable, oral HIF-PH inhibitor in development for the treatment of anemia in both nondialysis-dependent (NDD) and dialysis-dependent CKD patients. In early clinical studies, vadadustat was well-tolerated in healthy volunteers and patients with CKD, where it increased reticulocytes, plasma EPO, and Hb levels in a dose-dependent manner.[23,24] The increase in plasma EPO levels seen with vadadustat was comparable in magnitude to that occurring physiologically at moderate altitude and showed a normal diurnal pattern with a return to baseline levels prior to the next dose.[24] Earlier results also showed that vadadustat improved iron homeostasis by decreasing hepcidin and increasing transferrin levels.[23] Taken together, once-daily oral administration of vadadustat, titrated to increase and maintain Hb in the target range, may provide multiple advantages over conventional ESAs. Here we report the results of a phase 2b study evaluating vadadustat in NDD patients with stages 3a to 5 CKD.

RESULTS

Patient characteristics and disposition

We conducted a 20-week, phase 2b multicenter, randomized, double-blind, placebo-controlled study to assess the ability of oral, once-daily vadadustat to correct anemia in patients with NDD-CKD. Patients with NDD-CKD stages 3a/b, 4, and 5 enrolled from 61 sites were grouped based on ESA treatment status and Hb level at screening (Supplementary Table S1): group 1 were ESA treatment naïve and Hb ≤10.5 g/dl; group 2 were previously treated with ESA and Hb ≤10.5 g/dl; group 3 were actively treated with ESA and Hb ≥9.5 g/dl to ≤12.0 g/dl. Within each group, patients were randomized 2:1 to receive vadadustat or placebo and stratified according to CKD stage and the presence or absence of diabetes mellitus.

The intent-to-treat population included 210 patients who received the study drug (vadadustat, $n = 138$; placebo, $n = 72$) and were included in the safety analyses. The modified intent-to-treat population, used for all efficacy analyses, comprised 208 patients who had a baseline and ≥1 post-baseline Hb and red blood cell measurement (vadadustat, $n = 136$; placebo, $n = 72$). The per-protocol population, pre-specified as the primary population to be used to analyze the primary endpoint, included all patients in the modified intent-to-treat population who also completed the study, had efficacy data through week 20, were ≥80% compliant with study medication, and had no major protocol deviations. There were 160 patients who qualified for the per-protocol population (Supplementary Figure S1). Of the 210 patients who received the study drug, 81% ($n = 112$) in the vadadustat group and 88% ($n = 63$) in the placebo group completed treatment through to week 20 of the study. Treatment groups were matched for demographic and disease-related characteristics at baseline as outlined in Table 1.

Table 1 | Patient demographics and pretreatment baseline characteristics (ITT population)

Characteristic	Vadadustat $n = 138$	Placebo $n = 72$
Sex		
Male	57 (41.3)	38 (52.8)
Female	81 (58.7)	34 (47.2)
Race		
White/Caucasian	83 (60.1)	49 (68.1)
Black/African American	49 (35.5)	19 (26.4)
American Indian	3 (2.2)	1 (1.4)
Asian	2 (1.4)	3 (4.2)
Other	1 (0.7)	0 (0.0)
Age (yr)	66.6 ± 9.97	65.9 ± 12.33
BMI (kg/m^2)	31.9 ± 6.56	30.0 ± 7.27
eGFR (ml/min/1.73 m^2)	25.2 ± 10.41	25.0 ± 11.72
CKD status[a]		
Stage 3a/b	36 (26.1)	18 (25.0)
Stage 4	85 (61.6)	42 (58.3)
Stage 5	17 (12.3)	12 (16.7)
Diabetes mellitus	106 (76.8)	57 (79.2)
Etiology of CKD[b]		
Diabetes	103 (74.6)	51 (70.8)
Hypertension and large vessel disease	78 (56.5)	36 (50.0)
Other	5 (3.6)	7 (9.7)
uACR (mg/g)	1145.5 ± 1620.69	1454.6 ± 2046.51
C-reactive protein (mg/dl)	0.7 ± 0.98	0.5 ± 0.61
Hb (g/dl)	9.9 ± 0.86	10.0 ± 0.79
TSAT (%)	28.8 ± 10.41	28.4 ± 9.42
Ferritin (ng/ml)	284.7 ± 251.32	264.5 ± 203.27
Systolic blood pressure (mm Hg)	139.2 ± 18.84	140.6 ± 19.05
Diastolic blood pressure (mm Hg)	70.1 ± 10.97	71.4 ± 11.15

BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; ITT, intent-to-treat population, i.e. all randomized patients who received ≥1 dose of study medication; TSAT, transferrin saturation; uACR, urine albumin-to-creatinine ratio. Values are *n* (%) or mean ± SD.
[a]G3a/b = eGFR, 30 to 59 ml/min/1.73 m^2; G4 = eGFR, 15 to 29 ml/min/1.73 m^2, G5 = eGFR, <15 ml/min/1.73 m^2.
[b]If a subject had >1 reason checked for etiology of CKD, all reasons were counted.

Primary endpoint

The primary endpoint of the study was the percentage of patients who, during the last 2 weeks of treatment, achieved or maintained a mean Hb level of ≥11.0 g/dl or an increase in Hb of ≥1.2 g/dl over the predose average (average of the 2 Hb values obtained before dosing at screening and baseline). Patients who received ESA or transfusion as rescue therapy were counted as treatment failures. Patients who received transfusion for nonrescue reasons were excluded from the primary analysis.

Treatment with vadadustat raised and maintained Hb levels in patients with anemia secondary to CKD (Table 2). In the per-protocol population, 54.9% of patients treated with

Table 2 | Percentage of Patients achieving the primary endpoint (PP population)

Outcome	Vadadustat $n = 102$	Placebo $n = 58$	*P*-value
Primary endpoint: successful Hb response[a]	56 (54.9%)	6 (10.3%)	<0.0001[b]
OR estimates for successful Hb response at EOT[c]	11.47 (95% CI: 3.35–39.29)		0.0001[d]

CI, confidence interval; CKD, chronic kidney disease; EOT, end of treatment; Hb, hemoglobin; OR, odds ratio; PP, per protocol.
[a]Success: Hb average of weeks 19 and 20 ≥11.0 g/dl or Hb average of weeks 19 and 20 ≥1.2 g/dl higher than predose mean. If a value was missing, the remaining value was used.
[b]Fisher exact test.
[c]Vadadustat versus placebo.
[d]*P*-value for vadadustat versus placebo is from a logistic regression analysis, with treatment, erythropoiesis-stimulating agent study group, CKD status, treatment-by-CKD status interaction, and diabetes mellitus as covariates.

vadadustat achieved the primary endpoint compared with 10.3% of placebo-treated patients ($P < 0.0001$). Based on estimated odds ratio, patients treated with vadadustat were approximately 11.5 times more likely than patients treated with placebo to achieve a successful Hb response ($P = 0.0001$) (Table 2).

Secondary and additional endpoints

Hemoglobin. Vadadustat increased and maintained Hb levels in patients throughout the 20-week study (Figure 1). By week 2, mean Hb levels in the vadadustat group had increased significantly from baseline; Hb levels plateaued by weeks 6 to 8 and were sustained throughout the 20 weeks of treatment (Figure 1). Hb response versus time in each of the 3 study groups based on ESA treatment status is displayed in Supplementary Figure S2. Hb excursions ≥13 g/dl occurred in only 4.3% (6 of 138) of patients in the vadadustat group. A *post hoc* analysis showed that from weeks 8 to 20, 71.2% of all Hb measurements in the vadadustat group and 42.7% in the placebo group were between 10 and <12 g/dl; 8.9% of Hb measurements in the vadadustat group were between 12.0 and 12.9 g/dl and 1% was ≥13.0 g/dl and none in the placebo group were ≥12.0 g/dl.

ESA and transfusion rescue. Fewer patients in the vadadustat group (4.4%) than in the placebo group (16.7%) received ESA rescue therapy during the study. Of the 6 vadadustat-treated patients who received ESA during the study, 4 patients did not meet the protocol-specified criteria for ESA rescue; of the other 2, 1 was in the previously treated group, and 1 in the actively treated group. Of the 12 placebo patients who received ESA rescue, 2 patients did not meet the protocol-specified criteria; of the remaining 10, 1 was in the treatment naïve group, 3 were in the previously treated group, and 6 were in the actively treated group. None of the vadadustat-treated patients and 1 placebo-treated patient received transfusion rescue during the trial.

Absolute reticulocyte count. An increase from baseline in mean absolute reticulocyte count was observed in the vadadustat group at week 2 ($+0.022 \times 10^6$/μl) versus a slight decrease in the placebo group (-0.005×10^6/μl; $P = 0.0001$). The mean reticulocyte count in the vadadustat group gradually declined and plateaued by weeks 6 to 8 at a level significantly higher than that of the placebo group, reflecting the new Hb baseline (Figure 2).

Iron parameters. Significant decreases in hepcidin and ferritin, and a significant increase in total iron-binding capacity were observed in the vadadustat group compared with the placebo group at each postbaseline assessment (Figure 3a to c). Serum iron and transferrin saturation were similar in the 2 treatment groups throughout the study.

At baseline, 47.1% of patients in the vadadustat group and 45.8% in the placebo group were receiving iron supplementation. At the end of the 20-week trial, 59.6% of patients in the vadadustat group and 52.8% in the placebo group were receiving iron supplementation. During the study, 2.9% of patients (4 of 136) in the vadadustat group and none of the patients in the placebo group received i.v. iron.

Dosage and compliance. The starting dose of vadadustat at study entry was 450 mg once daily; the mean dose of vadadustat at week 19 was 450 mg once daily. The majority of patients (89%, 120 of 135) in the vadadustat group achieved and maintained a stable Hb level with ≤2 dose adjustments throughout the 20-week treatment period; 24% of patients (33 of 135) required no dose adjustment. The proportion of patients who were >80% compliant with treatment was 92.8% (128 of 138) in the vadadustat group and 94.4% (68 of 72) in the placebo group.

Safety

The percentage of patients who experienced ≥1 adverse event (AE) was comparable between the vadadustat and placebo groups (74.6% vs. 73.6%) (Table 3). Occurrence of ≥1 drug-related AE was reported in 25.4% of vadadustat-treated patients (35 of 138) and 11.1% of placebo-treated patients (8 of 72). AEs in both treatment groups were primarily mild or moderate in severity. Most commonly reported drug-related AEs in the vadadustat group included diarrhea (4.3%) and nausea (4.3%), whereas diarrhea (2.8%) was the most commonly reported drug-related AE in the placebo group. Ten vadadustat-treated patients (7.2%) and 3 placebo-treated patients (4.2%) discontinued the study because of AEs.

There were no observed trends (either increases or decreases) in systolic (or diastolic) blood pressure values over time and the distribution of systolic blood pressure values in patients treated with vadadustat was similar to that of patients treated with placebo. Hypertension was reported as an AE in 8.0% of vadadustat-treated patients (11 of 138) and 2.8% of those treated with placebo (2 of 72); all of the patients had a preexisting history of hypertension. Of the 11 patients on vadadustat who had an AE of hypertension during the study, 1 subject had furosemide discontinued approximately 1 month prior to the event. Otherwise, no subject had an interruption or decrease in the dose of antihypertensive agents prior to the onset of the AE of hypertension and no subject discontinued vadadustat treatment because of hypertension.

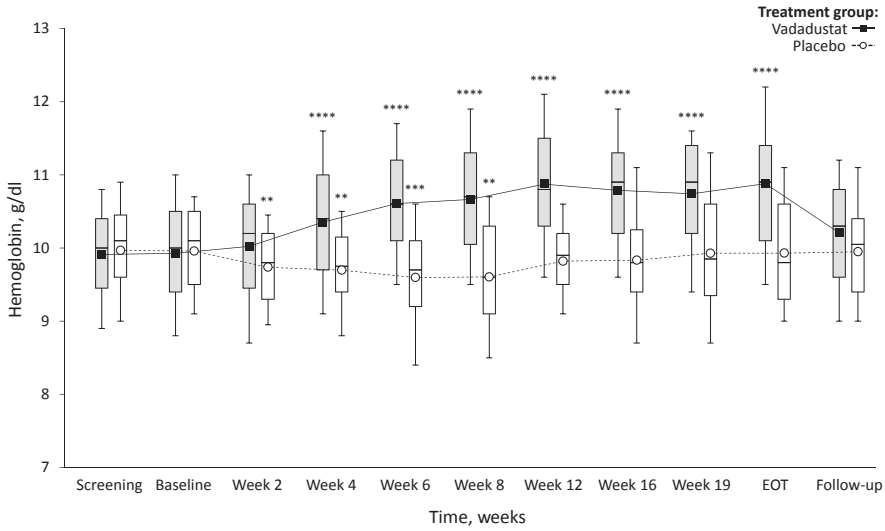

Figure 1 | Mean hemoglobin level over time (modified intent-to-treat population). Box-and-whiskers plot represents 10th, 25th, 75th, and 90th percentiles. The medians are indicated by the line within the boxes, and the means are indicated by the symbol within the boxes. Comparison of baseline to weekly and end of treatment (EOT) means for vadadustat or placebo groups was performed with a 2-sided Student *t*-test at $\alpha = 0.05$: $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$.

A total of 33 vadadustat-treated patients (23.9%) reported ≥1 serious adverse event (SAE), as did 11 placebo-treated patients (15.3%); the higher incidence of SAEs was primarily due to a higher incidence of renal-related SAEs in the vadadustat group (10.1%) compared with the placebo group (2.8%). The requirement for initiation of dialysis, an objective measure of the severity of renal SAEs, was evenly balanced between the vadadustat (11 of 138, 8.0%) and placebo (7 of 72, 9.7%) groups. No serious renal-related events were attributed to the study medication based on the investigators' decision.

Between-group analyses revealed no statistically significant differences between the vadadustat and placebo groups in the mean change from baseline in vascular endothelial growth factor (VEGF) levels at week 12 or end of treatment (Figure 3d). Mean decreases from baseline in cystatin C levels were observed in the vadadustat group at week 12 and end of treatment (nonsignificant), whereas significant mean increases from baseline in cystatin C were observed in the placebo group. Analysis between the 2 treatment groups showed that the mean change from baseline to end of treatment in cystatin C levels was significantly less in the vadadustat group (34.9 ng/ml) than in the placebo group (298.2 ng/ml; $P = 0.0063$). No changes from baseline were reported in vital signs or hematological tests. There were no reported effects of vadadustat on electrocardiogram measurements. With the exception of 1 patient in the vadadustat group who had an increase in liver function test, deemed possibly related to study medication, no other changes in liver function tests (serum alkaline phosphatase, alanine transaminase, aspartate transaminase, lactate dehydrogenase, total bilirubin, albumin, or total protein), renal function tests (serum creatinine, blood urea nitrogen, or cystatin C), serum electrolytes, serum lipids (serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides), serum bicarbonate, or serum creatine kinase were reported in either treatment group during the study.

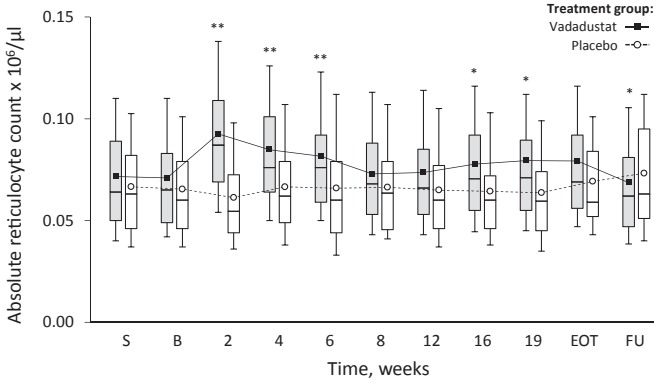

Figure 2 | Absolute reticulocyte count (modified intent-to-treat population). Box-and-whiskers plot represents 10th, 25th, 75th, and 90th percentiles. The medians are the line within the boxes, and the means are the symbol within the boxes. Comparison of vadadustat with placebo at each postbaseline visit was performed with a 2-sided Student *t*-test at $\alpha = 0.05$: $^{*}P < 0.05$; $^{**}P < 0.01$. B, baseline; EOT, end of treatment; FU, follow-up; S, screening.

Three deaths were reported among the 138 subjects who were treated with vadadustat, for an overall mortality rate of 2.2%. The causes of death were sudden cardiac death, cardiac arrest, and myocardial ischemia. A 71-year-old patient with type 2 diabetes, hypertension, congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease, pulmonary hypertension, and sleep apnea receiving continuous oxygen died of a sudden cardiac arrest 2 days posttreatment. A 54-year-old patient with hypertension and severe peripheral artery disease presented to the hospital with a 4-day history of worsening leg pain and was admitted to intensive care for sepsis and an ischemic foot leading to an above-the-knee amputation. During the hospitalization, the subject experienced further

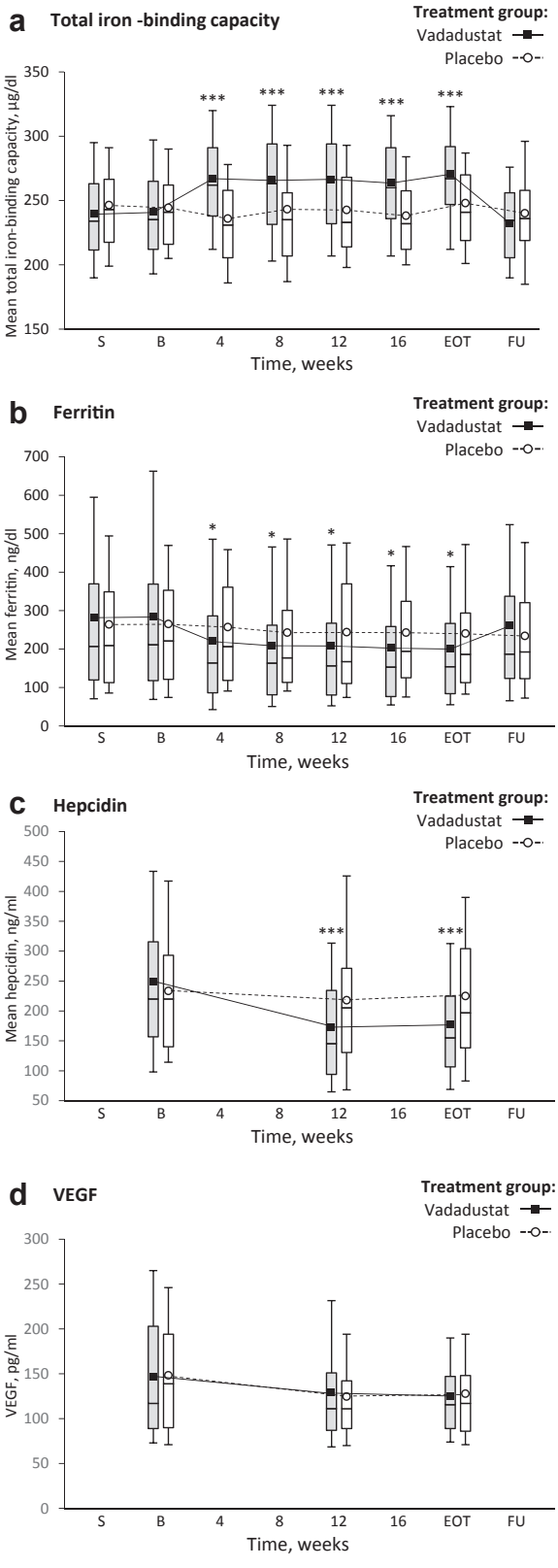

Figure 3 | (a) Total iron-binding capacity, (b) ferritin, (c) hepcidin, and (d) vascular endothelial growth factor (VEGF) over time (modified intent-to-treat [MITT] population). Box-and-whisker plots represent the 10th, 25th, 75th, and 90th percentiles. The medians are represented by a line within the boxes, and the means are the symbol within the boxes. Comparison of vadadustat with placebo at each postbaseline visit was performed with a 2-sided Student *t*-test at $\alpha = 0.05$: *$P < 0.05$; ***$P < 0.0001$. B, baseline; EOT, end of treatment; FU, follow-up; S, screening.

complications including right frontal lobe stroke, acute renal failure, and 2 cardiac arrests. Life support was withheld following the second cardiac arrest. The deaths in these 2 subjects were considered to be unrelated to the study medication. The third death was attributed to myocardial ischemia in a 65-year-old patient with type 2 diabetes, hypertension, and obesity. This death was considered to have a possible relationship to the study medication as the subject died at home, and no autopsy was performed documenting the cause of death. No deaths were reported among the 72-placebo-treated patients.

DISCUSSION

Here we report the results from a 20-week placebo-controlled phase 2b study in patients with NDD-CKD treated with the oral once-daily HIF-PH inhibitor vadadustat. Vadadustat raised and maintained Hb levels in a predictable manner, while minimizing Hb excursions >13 g/dl and increasing iron mobilization.

Targeting the HIF oxygen-sensing pathway has the potential to provide a more physiologic approach to treating anemia than conventional ESA therapy,[2,22] which relies on the administration of high doses of recombinant EPO agents and can result in worsening hypertension and increased CV risk.[13–18,25] Although the underlying pathogenic mechanisms are unclear, out-of-target-range Hb oscillations and supraphysiologic plasma EPO levels are likely to play a causal role in the pathogenesis of adverse CV events associated with high-dose recombinant EPO therapy.[15,26,27]

Patients treated with vadadustat were approximately 11.5 times more likely than patients treated with placebo to achieve the primary endpoint. The protocol-specified algorithm resulted in a controlled rise in Hb and maintenance of Hb levels within the clinically desired range, while the reticulocyte profile mimicked the predicted response to altitude-associated hypoxia.[28] Very few patients on vadadustat experienced Hb excursions ≥13.0 g/dl, which have been associated with an increased risk of hypertension and adverse CV outcomes.[10,11,29–31] The majority of patients required ≤2 dose adjustments during the 20-week treatment period.

An improvement in parameters of iron metabolism was also observed with vadadustat. Indeed, significant reduction of hepcidin and ferritin levels, and increase in total iron-binding capacity indicated enhanced iron utilization in patients treated with vadadustat, which may reduce the need for iron supplementation compared with conventional ESA therapies. This will be further evaluated in the phase 3 program. Recent genetic studies in mice have shown that HIF regulates erythropoiesis by coordinating the transcriptional induction of *EPO* with the enhanced expression of multiple genes involved in regulating iron metabolism.[2] In particular, HIF-2 appears to play a key role in iron absorption under

Table 3 | AEs and SAEs in the ITT population

Category	Number of patients, *n* (%)	
	Vadadustat *n* = 138	Placebo *n* = 72
Patients with ≥1AE[a]	103 (74.6)	53 (73.6)
Diarrhea	14 (10.1)	3 (4.2)
Nausea	14 (10.1)	3 (4.2)
Constipation	5 (3.6)	4 (5.6)
Gastrointestinal hemorrhage	0 (0.0)	4 (5.6)
Fatigue	12 (8.7)	5 (6.9)
Edema peripheral	10 (7.2)	7 (9.7)
Urinary tract infection	9 (6.5)	6 (8.3)
Upper respiratory tract infection	2 (1.4)	5 (6.9)
Hyperkalemia	7 (5.1)	0 (0.0)
Headache	8 (5.8)	2 (2.8)
Dizziness	7 (5.1)	3 (4.2)
Renal failure acute	10 (7.2)	4 (5.6)
Renal failure chronic	7 (5.1)	3 (4.2)
Dyspnea	6 (4.3)	4 (5.6)
Hypertension	11 (8.0)	2 (2.8)
Hypotension	6 (4.3)	4 (5.6)
Patients with ≥1 SAE	33 (23.9)	11 (15.3)
Patients with ≥1 drug-related SAE	3 (2.2)	0 (0.0)
Patients with any renal- and/or dialysis-related AE	18 (13.0)	9 (12.5)
Patients with any renal-related SAE	13 (9.4)[b]	2 (2.8)
Patients with events that required dialysis	11 (8.0)	7 (9.7)
Patients with AEs leading to study withdrawal	10 (7.2)	3 (4.2)
Deaths	3 (2.2)	0 (0.0)

AE, adverse event; ITT, intent-to-treat; SAE, serious adverse event.
[a]Listed are AEs that were reported in ≥5% of the patients.
[b]One of the 14 vadadustat-treated patients who was reported to have a renal-related SAE is not included in this table. This subject (Subject 1490001, previously treated study group) was admitted to the hospital for worsening Goodpasture syndrome after receiving 1 dose of study medication (no other renal-related events were reported).

hypoxic conditions, suggesting a potential mechanism by which vadadustat directly enhances iron metabolism.[32–34] The effects of vadadustat on hepcidin levels are most likely indirect, as previous studies have shown that increased erythropoietic activity is required for hepcidin suppression in the context of systemic HIF activation.[35–37]

Because HIF is a very pleiotropic transcription factor that regulates a multitude of physiologic hypoxia responses, HIF-PH inhibitors have the potential to significantly impact normal physiology and metabolic homeostasis in CKD patients. In particular, the effects of controlled, repeated systemic HIF activation on the CV system, glucose and fat metabolism, and the progression of CKD are not known. In our phase 2b trial, vadadustat was well tolerated by patients and its AE profile was generally similar to that of placebo, which is consistent with previous studies, and typical of the CKD population.[23,24] The observed number of deaths in this study was consistent with that expected (2–4 on vadadustat, 1–2 on placebo) based on the severity of disease, natural mortality rate, and 2:1 randomization of patients.[38] There was an imbalance in SAEs reported during the study period, primarily related to renal events and likely due to inconsistencies in the reporting of severity for renal-associated AEs leading to dialysis, as well as whether investigators reported AEs that led to dialysis with a renal or nonrenal term. The requirement for initiation of dialysis, an objective measure of the severity of renal AEs, was evenly balanced between the vadadustat and placebo groups. Additionally, the number of patients who discontinued from the study because of worsening CKD that required dialysis was comparable between the vadadustat (4.3%) and placebo (5.6%) groups.

Preclinical studies in animal models have predicted that systemic HIF activation has the potential to alter glucose and fat and mitochondrial metabolism.[39–41] Indeed, other HIF-PH inhibitors, which are currently undergoing evaluation in clinical anemia trials, have been shown to decrease serum cholesterol levels;[42] however, the molecular mechanisms that underlie these effects are not well understood. In contrast, no effect on serum lipid levels was associated with vadadustat treatment.

A major safety concern of targeting the HIF pathway is the potential for increased production of VEGF. VEGF is a HIF-regulated angiogenic growth factor and increasing its expression has been shown to disrupt vascular homeostasis, to promote vasculopathies, and to enhance tumor progression and metastatic potential.[43,44] Plasma VEGF levels were not increased with vadadustat treatment in this phase 2b trial, which is consistent with previous studies.[23,24] Ongoing phase 3 studies will continue to monitor plasma VEGF levels in vadadustat-treated subjects.

HIF is involved in the regulation of vascular tone and blood pressure and is also known to contribute to the development of pulmonary hypertension.[22,45,46] Although hypertension was reported more frequently as an AE in the vadadustat group, all of the subjects for whom hypertension was reported as an AE had an established history of hypertension and no general pattern of change in blood pressure values or pulse rate was observed during the study. Phase 3 trials comparing vadadustat with ESA therapy will help elucidate any differences between these therapies on blood pressure.

In summary, we report the results of the first phase 2b study of vadadustat, a novel HIF-PH inhibitor that provides an effective and well-tolerated, titratable, once-daily oral therapy for correcting anemia in patients with CKD. Vadadustat offers several advantages over existing ESA therapy as it generates a more physiologic profile of plasma EPO that maintains Hb levels with minimal fluctuations and improves iron absorption and mobilization. Our study results provide justification for conducting phase 3 clinical investigations to further evaluate the safety and efficacy of vadadustat.

MATERIALS AND METHODS

Ethical approval

The study (ClinicalTrials.gov number NCT01906489) was conducted in compliance with the Declaration of Helsinki and other applicable regulatory requirements, and the protocol was approved by the Institutional Review Board of each participating institution.

Study design, dosing algorithm, and study conduct

Eligible patients were men and women aged 18 years or older with a diagnosis of CKD stages 3a to 5 who were not expected to initiate maintenance dialysis during the course of the study. Additional inclusion criteria included anemia secondary to CKD with an ESA status and screening Hb level that met 1 of the 3 study groups criteria; a ferritin level ≥50 ng/ml with a transferrin saturation ≥18%, or a ferritin level ≥100 ng/ml, regardless of transferrin saturation. A comprehensive list of eligibility criteria is provided in the Supplementary Information.

Once-daily vadadustat was initiated at 450 mg, and titrated by 1 tablet (150 mg) according to Hb response (maximum of 600 mg and minimum of 150 mg). Dose adjustment was permitted per the protocol-specified dosing algorithm, and suspended if Hb ≥13.0 g/dl. Oral iron supplementation was permitted throughout the study to maintain ferritin levels between 50 and 300 ng/ml; i.v. iron was only allowed for patients who were intolerant of oral iron. Rescue therapy with ESA was permitted (but not mandated) if Hb was ≤9 g/dl in groups 1 and 2, or if Hb was ≤9.4 g/dl in group 3; the higher threshold for initiation of rescue for group 3 was selected assuming the investigators' reluctance to permit Hb levels to decrease substantially in a previously treated population.

Clinical assessments, including Hb and other hematologic parameters, iron indices, and safety assessments were conducted at screening, baseline (day 1), during the treatment period (weeks 2, 4, 6, 8, 12, 16, and 19), at the end-of-treatment visit (week 20 or early withdrawal), and at the posttreatment follow-up visit that was conducted 4 weeks after the last dose of study medication. Blood samples for determination of hepcidin and other biomarkers were assessed at baseline, week 12, and the end-of-treatment visits. Safety assessments included vital signs, electrocardiograms, AEs, complete blood counts with differential, serum chemistries, cystatin C, lipid profiles, VEGF, and pregnancy tests.

Statistical analysis

Sample size and power were calculated using the likelihood ratio chi-square test. Using a randomization ratio of 2:1 for vadadustat to placebo, with a total of 160 evaluable patients for the primary analysis, we expected 87% power to detect the difference in the predicted success rates between vadadustat (60%) and placebo (20%) across the 3 study groups, at the $\alpha = 0.05$ level. Assuming 20% of randomized patients would be lost due to attrition, the target sample size of 200 patients was selected in order to yield 160 evaluable patients for the primary analysis.

Efficacy analyses conducted for the primary and secondary endpoints used Fisher exact test to compare percentage of success of vadadustat to placebo. Odds ratio estimates and 95% confidence intervals were calculated for treatment comparison by adjusting explanatory variables.

During safety analyses, treatment-emergent AEs were coded into Medical Dictionary for Regulatory Activities (MedDRA), version 16.0, System Organ Classes and Preferred Terms and displayed in a frequency table by treatment group. Frequency tables were produced to display all AEs by severity, relationship to study medication, SAEs, and AEs that resulted in discontinuation of study medication.

DISCLOSURE

This study was sponsored by Akebia Therapeutics. PEP is supported by honoraria and lecture fees from Akebia Therapeutics, Keryx, Relypsa, Vifor/Fresenius Pharma, and ZS Pharma. BS is supported by honoraria and lecture fees from Akebia Therapeutics, Hospira, Vifor/Fresenius Pharma, and ZS Pharma. CSH was employed by Akebia Therapeutics. BM is employed by Akebia Therapeutics. VHH is supported by the Krick-Brooks chair in Nephrology and serves on the scientific advisory board of Akebia Therapeutics.

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SUPPLEMENTARY MATERIAL

Supplemental Text.

Figure S1. Patient disposition (all patients). One patient in the placebo group received treatment with placebo but was not randomized to treatment. This was considered a major protocol deviation and the patient was withdrawn from the study.

Figure S2. Mean hemoglobin level over time by erythropoiesis-stimulating agent study group (modified intent-to-treat population). Box-and-whiskers plot represents 10th, 25th, 75th, and 90th percentiles. The median is the line within the box, and the mean is the symbol within the box. Comparison of vadadustat with placebo at each postbaseline visit was performed with a 2-sided Student *t*-test at $\alpha = 0.05$: $^{*}P < 0.05$; $^{**}P < 0.01$. B, baseline; EOT, end of treatment; FU, follow-up; S, screening.

Table S1. Groups of Patients with NDD-CKD Stage 3, 4, or 5 Included in the Study. ESA, erythropoiesis-stimulating agent; Hb, hemoglobin. [a]Patients who had never received an ESA. [b]Patients who had previously received ≥1 dose of an ESA but had not received ESA therapy for ≥11 weeks at the time of screening. [c]Patients who had been treated with an ESA for ≥4 months prior to screening, had received ≥2 doses within the last 4 months, and had received their last dose within 6 weeks before screening.

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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