



## A Novel Hypoxia-Inducible Factor—Prolyl Hydroxylase Inhibitor (GSK1278863) for Anemia in CKD: A 28-Day, Phase 2A Randomized Trial

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**Background:** Anemia associated with chronic kidney disease (CKD) often requires treatment with recombinant human erythropoietin (EPO). Hypoxia-inducible factor—prolyl hydroxylase inhibitors (PHIs) stimulate endogenous EPO synthesis and induce effective erythropoiesis by non-EPO effects. GSK1278863 is an orally administered small-molecule PHI.

**Study Design:** Multicenter, single-blind, randomized, placebo-controlled, parallel-group study.

**Setting & Participants:** Anemic non-dialysis-dependent patients with CKD stages 3-5 (CKD-3/4/5 group; n = 70) and anemic hemodialysis patients with CKD stage 5D (CKD-5D group; n = 37).

**Interventions:** Patients with CKD-3/4/5 received placebo or GSK1278863 (10, 25, 50, or 100 mg), and patients with CKD-5D received placebo or GSK1278863 (10 or 25 mg) once daily for 28 days.

**Outcomes & Measurements:** Primary pharmacokinetic and pharmacodynamic (increase and response rates in achieving the target hemoglobin [Hb] concentration, plasma EPO concentrations, reticulocyte count, and others) and safety and tolerability end points were obtained.

**Results:** Both CKD-3/4/5 and CKD-5D populations showed a dose-dependent increase in EPO concentrations and consequent increases in reticulocytes and Hb levels. Percentages of GSK1278863 participants with an Hb level increase > 1.0 g/dL (CKD-3/4/5) and >0.5 g/dL (CKD-5D) were 63% to 91% and 71% to 89%, respectively. Per-protocol-defined criteria, high rate of increase in Hb level, or high absolute Hb value was the main cause for withdrawal (CKD-3/4/5, 30%; CKD-5D, 22%). A dose-dependent decrease in hepcidin levels and increase in total and unsaturated iron binding were observed in all GSK1278863-treated patients.

**Limitations:** Sparse pharmacokinetic sampling may have limited covariate characterization. EPO concentrations at the last pharmacodynamic sample (5-6 hours) postdose may not represent peak concentrations, which occurred 8 to 10 hours postdose in previous studies. Patients were not stratified by diabetes status, potentially confounding vascular endothelial growth factor and glucose analyses.

**Conclusions:** GSK1278863 induced an effective EPO response and stimulated non-EPO mechanisms for erythropoiesis in anemic non-dialysis-dependent and dialysis-dependent patients with CKD.

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**INDEX WORDS:** Erythropoietin (EPO); hypoxia-inducible factor (HIF); prolyl hydroxylase inhibitor (PHI); hemoglobin response rate; pharmacokinetics; pharmacodynamics; dosing; erythropoiesis-stimulating agent (ESA); hemoglobin; reticulocyte count; hepcidin; chronic kidney disease (CKD); dialysis; phase II; randomized controlled trial (RCT).

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Chronic kidney disease (CKD) is a major health issue globally and is categorized based on glomerular filtration rate (GFR).<sup>1</sup> The multifactorial cause of anemia of CKD is attributed to, among other conditions, diminished erythropoietin (EPO) production, inflammation, and accompanying nutritional deficiencies, with the resultant inhibition of erythroid progenitor cells due to diminished iron in the bone marrow, with an overall negative influence on EPO response.<sup>2-5</sup> Current strategies to prevent the anemia associated with CKD largely include the use of erythropoiesis-stimulating agents (ESAs)<sup>6</sup> such as recombinant human EPO.

A review by Carrera et al<sup>7</sup> (2007) reported that a longer-acting ESA (darbepoetin alfa) administered every 2 weeks is effective in maintaining hemoglobin (Hb) levels in selected patients with CKD, although a relatively high dose (and consequent EPO plasma concentrations) is required.<sup>8</sup> Sohmiya et al<sup>9</sup> (1998) showed that a more effective improvement in Hb level and reticulocyte count can be achieved by increasing EPO concentrations modestly and consistently by continuous subcutaneous infusion compared with weekly subcutaneous bolus injections. Orally administered inhibitors of hypoxia-inducible factor (HIF) prolyl hydroxylases, referred to as prolyl hydroxylase domain inhibitors (PHIs), have the potential to achieve effective erythropoiesis through similar modest elevations in EPO concentrations.

GSK1278863, a small-molecule oral PHI, stabilizes HIF, which is known to modulate HIF-controlled gene products including EPO.<sup>10-14</sup> Several clinical trials have confirmed the ability of PHIs to induce endogenous EPO production,<sup>14,15</sup> resulting in effective erythropoiesis.<sup>16</sup> In addition, HIF affects iron homeostasis and bioavailability by hepcidin modulation.<sup>17,18</sup> The progression of anemia in non-dialysis-dependent patients with CKD with sufficient iron stores (assessed by ferritin levels) can be predicted by higher hepcidin concentrations.<sup>18,19</sup> A decrease in hepcidin level through prolyl hydroxylase inhibition may increase the bioavailability of oral iron and enhance iron utilization from liver stores,<sup>20</sup> thus improving the iron-restricted erythropoiesis in CKD-associated anemia.<sup>21</sup>

The safety, tolerability, endogenous EPO stimulation, and non-EPO effects of GSK1278863 administration have been evaluated in phase 1 clinical trials.<sup>20,22,23</sup> The dose rationale for this study was primarily based on final pharmacokinetic/pharmacodynamic data from single- and repeat-dose phase 1 studies in healthy individuals ([ClinicalTrials.gov](https://clinicaltrials.gov) study numbers NCT00750256 and NCT00840320)<sup>20,22</sup> and a single-dose phase 1B study in patients with non-dialysis-dependent CKD and hemodialysis-dependent CKD and matched healthy individuals

([ClinicalTrials.gov](https://clinicaltrials.gov) study number NCT00935831).<sup>23</sup> The present short-term efficacy study was primarily designed to determine the recommended GSK1278863 starting dose for use in long-term efficacy and safety studies in patients with CKD-induced anemia.

## METHODS

### Study Design

This phase 2A, multicenter (Australia, New Zealand, India, and Russia), single-blind, randomized, placebo-controlled, parallel-group study evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of once-daily administration of GSK1278863 (28 days) to anemic patients with moderately to severely decreased kidney function or end-stage renal disease. The study evaluated placebo and GSK1278863 (10, 25, 50, and 100 mg) in anemic patients with non-dialysis-dependent CKD stages 3, 4, or 5 (CKD-3/4/5 group). Anemic patients with hemodialysis-dependent CKD stage 5 (CKD-5D group) were eligible if their estimated GFR (eGFR) was 10 to <15 mL/min/1.73 m<sup>2</sup>; these patients received placebo or GSK1278863 doses (10 and 25 mg). The addition of the lower dose (10 mg) to patients was based on real-time data showing a stronger than anticipated Hb level response at doses  $\geq$  25 mg. Patients were followed up for assessments for 28 days after the treatment period. The study design is summarized in [Item S1](#) (provided as online supplementary material).

The study protocol was approved by institutional review boards and ethics committees and conducted in compliance with ICH/GCP (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use—Good Clinical Practice) guidelines and the Declaration of Helsinki. Written informed consent was obtained from all patients at screening.

The primary objective was to determine the recommended GSK1278863 starting dose for the subsequent long-term efficacy and safety studies in anemic patients with CKD. Secondary objectives were to characterize the repeat-dose pharmacokinetics, dose proportionality, and effect on markers of erythropoiesis (serum EPO concentration, absolute reticulocyte count, hematocrit, and total red blood cell count) and explore other pharmacodynamic end points, which included biomarkers (eg, vascular endothelial growth factor [VEGF] and hepcidin), iron mobilization markers (eg, total iron-binding capacity [TIBC], transferrin saturation [TSAT, percentage], serum iron, and serum ferritin), and other markers (fetal Hb and C-reactive protein).

### Study Population

Eligibility included male and female patients aged 18 to 85 years diagnosed with CKD (CKD-3/4/5 group: eGFR, 15-59 mL/min/1.73 m<sup>2</sup> for stages 3-4 and 10-<15 mL/min/1.73 m<sup>2</sup> for stage 5; CKD-5D group: eGFR, 10-<15 mL/min/1.73 m<sup>2</sup> receiving hemodialysis) based on the NKF-KDOQI (National Kidney Foundation—Kidney Disease Outcomes Quality Initiative) criteria<sup>23</sup> who were ESA-naïve with Hb levels  $\leq$  11.0 g/dL or if ESA treatment was discontinued for 7 or more days or equivalent to the interval between scheduled ESA doses. Details provided in [Item S1](#).

### Interventions

Randomly assigned patients reported to the clinical research unit for assessments and dosing on days 1, 4, 8, 15, and 22 (dosing days) and days 29, 36, and 57. They self-administered the study medication daily between the clinical research unit visits until day 28. They refrained from all food and drinks, with the exception of water, from 2 hours before to 1 hour after dosing. Dosing in any treatment arm could be stopped or adjusted if 5 or more

individuals had severe adverse events (AEs), elevated blood pressure, Hb level > 13.5 g/dL following dosing, and rate of Hb level increase > 1 g/dL over 2 weeks. Dosing in any treatment arm could be stopped or adjusted if the probability of an Hb level increase > 2 g/dL over 4 weeks was  $\geq 75\%$ , based on ongoing observations of the slope of the Hb level change and taking into account the individual sample variation for individuals in that treatment arm receiving GSK1278863.

### Pharmacokinetic and Pharmacodynamic Assessments

Blood for pharmacokinetic and pharmacodynamic analyses was collected predose and at 1 to 2, 3 to 4, and 5 to 6 hours postdose on days 1, 15, and 22. A predose assessment of markers of iron metabolism was performed at screening and days 1 and 15. Samples for all pharmacodynamic evaluations were also collected on days 29 and 57. Hematology and clinical chemistry evaluations were performed at screening; predose on days 1, 4, 8, 15, and 22; and on follow-up days 29, 36, and 57. Further details are provided in [Item S1](#).

### Study End Points

#### Primary End Points

End points included rate of response in patients achieving the target Hb level, rate of Hb level increase, absolute Hb concentrations, maximum change from baseline, and rate of Hb level decrease following stopping of dosing. Safety end points included AEs, clinical safety laboratory tests (hematology, chemistry, and urinalysis, when obtainable), vital signs (blood pressure and heart rate), electrocardiograms, and clinical monitoring/observations.

#### Secondary End Points

Pharmacokinetic end points were population pharmacokinetic parameters estimated from sparse pharmacokinetic samples

collected in a subset of individuals on days 1, 15, and 22. Pharmacodynamic end points included change in endogenous EPO concentration, reticulocyte count, hematocrit, total red blood cell count, VEGF level, hepcidin level, TIBC, TSAT (percentage), serum iron level, serum ferritin level, and fetal Hb level.

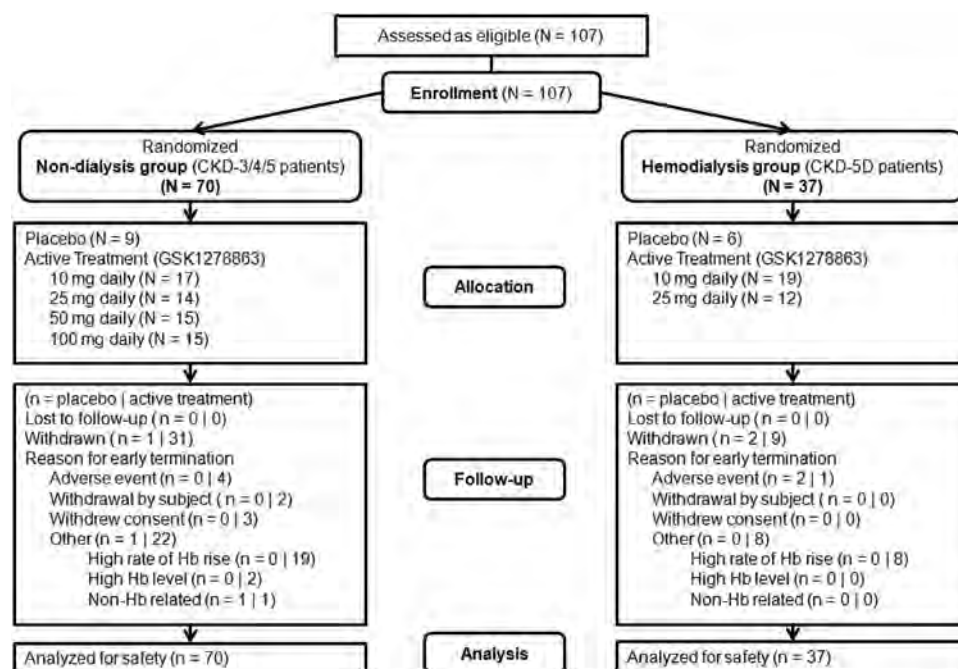
### Statistical Methods

Sample size was based on prior preliminary data in healthy individuals with a within-individual variance of 0.06 to 0.15 and between-individual variance of 0.05 in Hb level response after 14 days of treatment with GSK1278863 (study NCT00840320).<sup>23</sup>

In the CKD-3/4/5 group, response was defined as  $\geq 1$ -g/dL Hb level increase over baseline after 4 weeks of treatment. The estimated probability of response, at the individual level, was used to estimate the mean population response rate through averaging across individuals. A target response rate of achieving a response ( $\geq 1$ -g/dL Hb level increase over baseline) was set at 55% of the population as a mean.

This mean population target response rate (55%) has been modeled and achieves power > 80% if the true mean shift in Hb level is >1.09 g/dL for a given arm. The mean population response rate achieves power > 90% if the true mean shift in Hb level is >1.12 g/dL for 25 individuals in a given arm. A sample size of 5 was considered adequate to determine the target response rate with >90% power if the actual mean change from baseline Hb level is  $\geq 1.20$  g/dL.

Similarly, in the CKD-5D group, response was defined as  $\geq 0.5$ -g/dL Hb level increase over baseline after 4 weeks of treatment, and a 55% response rate was set as the target population mean rate. In a given arm, an Hb level increase would meet the target if the mean response rate exceeds 55% using a response cutoff of a 0.5-g/dL Hb level increase over baseline. A sample size of 25 was considered adequate to determine the target response rate (55%) with >80% power if the actual mean Hb level increase was  $\geq 0.54$  g/dL above



**Figure 1.** CONSORT flow chart. Multiple individuals were discontinued due to a high hemoglobin (Hb) level response (these were not participants who: [1] met criteria for early termination on account of adverse events, [2] withdrew themselves, or [3] withdrew consent). Based on the large number of discontinued individuals, the primary short-term efficacy end point included both individuals who received all 28 days of dosing and those who discontinued between days 22 and 28. Individuals who discontinued prior to day 22, who by definition had an increase > 1.0 g/dL, were not included in the analysis. Had these individuals continued dosing, they would have contributed to a positive outcome for the primary end point analysis. Abbreviations: CKD-3/4/5, chronic kidney disease stages 3, 4, or 5; CKD-5D, dialysis-dependent chronic kidney disease stage 5.

baseline and with a power of >90% achieved if the actual mean Hb level increase was  $\geq 0.56$  g/dL. A sample size of 5 was considered adequate to determine the target increase of 0.5 g/dL with >90% power if the actual mean Hb level increase was  $\geq 0.60$  g/dL. There was no formal interim analysis planned. However, during the course of this study, ongoing planned Bayesian analysis of the primary end point of Hb level increase was assessed after the first 5 individuals completed each active dose cohort and then for each completed individual at every 2-week cutoff thereafter.

Population GSK1278863 pharmacokinetic methods and results are presented in [Item S1](#).

## RESULTS

### Demographic Characteristics

There were 70 patients with CKD-3/4/5 and 37 patients with CKD-5D enrolled and randomly assigned. Demographics and patient disposition for both groups are presented in [Fig 1](#) and [Item S1](#). A total of 22 patients with CKD-3/4/5 and 28 patients with CKD-5D in the pharmacokinetic substudy provided evaluable data for pharmacokinetic modeling. However, 32 patients with

CKD-3/4/5 and 11 patients with CKD-5D were withdrawn from the study, as discussed next.

### Safety

AEs, regardless of causality, were reported by 35 of 61 (57%) patients with CKD-3/4/5 and 15 of 31 (48%) patients with CKD-5D receiving GSK1278863. Overall, the frequency of AE reports was similar in the placebo arms in both groups. The most common AE in the CKD-3/4/5 group was nausea ( $n = 9$  [13%]; 3 [21%] with 25 mg and 6 [40%] with 100 mg). In the CKD-3/4/5 group, 16 of 70 (23%) patients had investigator-assessed drug-related AEs, of which nausea was the most common (reported by 6 of 70 [9%] of patients; [Table 1](#)). In the CKD-5D group, the most commonly reported AEs were anemia and hypotension, each occurring in 2 (5%) patients. In this population, a total of 2 patients reported investigator-assessed drug-related AEs of abdominal

**Table 1.** Summary of Drug-Related Adverse Events

System Organ Class Preferred Term	Total	Placebo	GSK1278863 Dose			
			10 mg	25 mg	50 mg	100 mg
<b><u>Non – Dialysis-Dependent Population: CKD-3/4/5 Group</u></b>						
No. of patients	70	9	17	14	15	15
Any drug-related AE	16 (23%)	1 (11%)	1 (6%)	2 (14%)	3 (20%)	9 (60%)
Nausea	6 (9%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)	5 (33%)
Dyspepsia	3 (4%)	1 (11%)	1 (6%)	0 (0%)	0 (0%)	1 (7%)
Vomiting	3 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (20%)
Hypotension	3 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	2 (13%)
Abdominal pain upper	2 (3%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)	1 (7%)
Dizziness	2 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	1 (7%)
Insomnia	2 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (13%)
Idiopathic thrombocytopenic purpura	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Acute coronary syndrome	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Abdominal discomfort	1 (1%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)	0 (0%)
Diarrhea	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Pancreatitis acute	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Chest pain	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)
Malaise	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Carbon dioxide abnormal	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Anorexia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Dehydration	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Hyperuricemia	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Arthritis	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)
Headache	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)
Lethargy	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Acute kidney injury	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
Reduced kidney function	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)
<b><u>Hemodialysis Population: CKD-5D Group</u></b>						
No. of patients	37	6	19	12	0	0
Any drug-related AE	2 (5%)	1 (17%)	1 (5%)	0 (0%)		
Abdominal pain	1 (3%)	0 (0%)	1 (5%)	0 (0%)		
Nausea	1 (3%)	1 (17%)	0 (0%)	0 (0%)		
Decreased appetite	1 (3%)	1 (17%)	0 (0%)	0 (0%)		

*Note:* Values are given as number (percentage). Percentages are based on total number of people in the safety population in each treatment. For “Any drug-related AE,” an individual is counted once if the individual reported 1 or more event. AE terms are coded using MedDRA (Medical Dictionary for Regulatory Activities), version 12.0.

Abbreviations: AE, adverse event; CKD, chronic kidney disease.



**Table 2.** Participant Disposition, Withdrawals, and Discontinuations Due to Hemoglobin Concentrations

	Non-Dialysis-Dependent: CKD-3/4/5 Group						Hemodialysis: CKD-5D Group			
	Total (n = 70)	Placebo (n = 9)	10 mg <sup>a</sup> (n = 17)	25 mg <sup>a</sup> (n = 14)	50 mg <sup>a</sup> (n = 15)	100 mg <sup>a</sup> (n = 15)	Total (n = 37)	Placebo (n = 6)	10 mg <sup>a</sup> (n = 19)	25 mg <sup>a</sup> (n = 12)
Completed study	38 (54%)	8 (89%)	13 (77%)	5 (36%)	6 (40%)	6 (40%)	26 (70%)	4 (67%)	17 (90%)	5 (42%)
Withdrawn	32 (46%)	1 (11%)	4 (27%)	9 (64%)	9 (60%)	9 (60%)	11 (30%)	2 (33%)	2 (11%)	7 (58%)
Withdrawal reason										
Adverse event	6 (9%)	1 (11%)	—	2 (14%)	1 (7%)	2 (13%)	3 (8%)	2 (33%)	—	1 (8%)
Withdrawal by participant	2 (3%)	—	—	—	1 (7%)	1 (7%)	—	—	—	—
Withdrew consent	3 (4%)	—	—	—	1 (7%)	2 (13%)	—	—	—	—
Other <sup>b</sup>	21 (30%)	—	4 (24%)	7 (50%)	6 (40%)	4 (27%)	8 (22%)	—	2 (11%)	6 (50%)
“Other” reason <sup>b</sup>										
High rate of Hb increase: >1 g/dL in 2-wk period	19 (27%)	—	4 (24%)	7 (50%)	4 (27%)	4 (27%)	8 (22%)	—	2 (11%)	6 (50%)
High Hb level: >13.5 g/dL	2 (3%)	—	—	—	2 (13%)	—	—	—	—	—

Note: Values are given as number (percentage).

Abbreviations: CKD-3/4/5, chronic kidney disease stages 3, 4, or 5; CKD-5D, chronic kidney disease stage 5D; Hb, hemoglobin.

<sup>a</sup>Of GSK1278863.

<sup>b</sup>“Other” was an option for capturing withdrawal for reasons other than withdrawal by participant or consent. Explanations are described in lower part of table.

pain in 1 patient (10-mg dose) and nausea and decreased appetite, both in 1 patient receiving placebo (Table 1).

Early termination from the study due to AEs was reported by 6 (9%) and 3 (8%) patients in the CKD-3/4/5 and CKD-5D groups, respectively (Table 2), and none was considered drug-related by the investigator. In the CKD-3/4/5 group, serious AEs were reported for 7 individuals (Table 3). Only 2 patients, both in the 100-mg group, had possibly related serious AEs.

In the CKD-5D group, 3 individuals had serious AEs (Table 3). No deaths were reported during the study.

There were no clinically significant changes in clinical laboratory values, vital signs, or electrocardiograms during this study in any group.

### Pharmacodynamic End Points

#### Erythropoietin

There was a dose-dependent increase in EPO concentrations in all GSK1278863-treated patients

**Table 3.** Listing of Serious Adverse Events, Safety Population

Participant Dose	Preferred Term	Time Since Most Recent Dose	Intensity	Relation to Study Drug
<b>Non-Dialysis-Dependent Population: CKD-3/4/5 Group</b>				
Placebo	Impaired liver functions	34 d 14 h 30 min	Moderate	Not related
25 mg GSK1278863	Sciatica	5 d 13 h 27 min	Severe	Not related
25 mg GSK1278863	Pyrexia	10 d 3 h 50 min	Moderate	Not related
50 mg GSK1278863	Peripheral arterial occlusive disease	3 d 5 h 59 min	Moderate	Not related
100 mg GSK1278863	Acute coronary syndrome	3 d 11 h 55 min	Severe	Possibly related
	Acute kidney injury	3 d 11 h 55 min	Severe	Not related
	Diabetic ketoacidosis	3 d 11 h 55 min	Severe	Not related
	Hyperglycemia	3 d 11 h 55 min	Severe	Not related
	Hypotension	3 d 11 h 55 min	Severe	Possibly related
	Lower respiratory tract infection	3 d 11 h 55 min	Severe	Not related
100 mg GSK1278863	Acute kidney injury	4 d 7 h 0 min	Moderate	Possibly related
	Dehydration	4 d 7 h 0 min	Moderate	Possibly related
100 mg GSK1278863	Respiratory failure	1 d 14 h 0 min	Severe	Not related
	Pneumonia	1 d 14 h 0 min	Severe	Not related
<b>Hemodialysis Population: CKD-5D Group</b>				
10 mg GSK1278863	Atrial fibrillation	20 d 15 h 40 min	Moderate	Not related
10 mg GSK1278863	Hepatitis acute	37 d 5 h 50 min	Severe	Not related
25 mg GSK1278863	Peripheral arterial occlusive disease	1 d 23 h 50 min	Severe	Not related

Abbreviation: CKD, chronic kidney disease.

(both groups), with the highest EPO concentrations in those in the CKD-3/4/5 group given 100 mg. EPO concentrations generally achieved maximum observed concentrations 5 to 6 hours postdose (last collection time point) on days 1, 15, and 22 in both populations (Fig 2). For the 10- and 25-mg dose arms, mean EPO concentrations returned to baseline in the predose samples on days 15 and 22 (generally within 2-fold of the day-1 predose concentration), but were elevated 15- to 150-fold in higher dose arms, demonstrating accumulation of EPO after repeat dosing at these dose levels.

#### Absolute Reticulocyte Count

For all GSK1278863 doses in both groups, the initial peak increase in absolute reticulocyte count was observed between days 8 and 15 and remained elevated on days 22 and 29. In contrast, absolute reticulocyte counts in patients receiving placebo remained at or below baseline in both groups (Fig 3).

#### Hemoglobin

Across both treatment groups, there was a robust Hb level response. Due to such a strong response, a

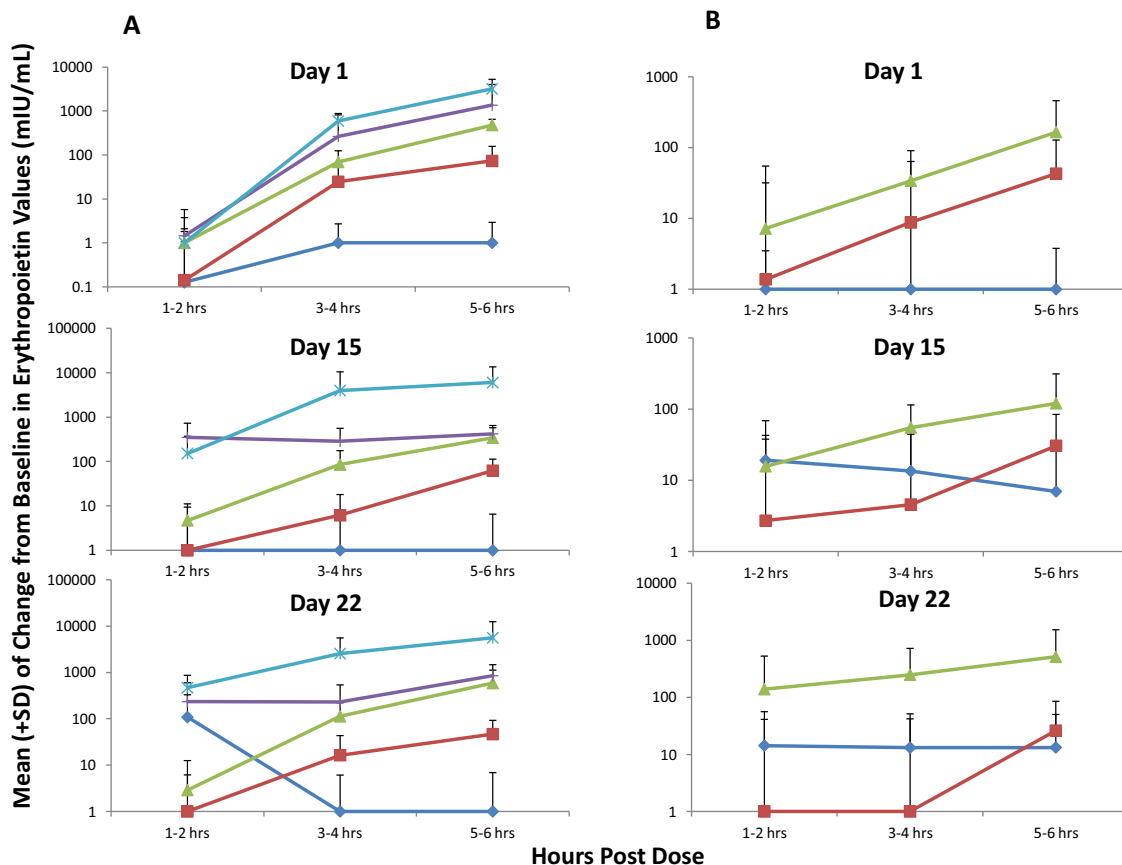
high rate of increase in Hb level or a high absolute Hb concentration was the main cause for early study discontinuation (CKD-3/4/5, 30%; CKD-5D, 22%), based on prespecified protocol criteria (Item S1).

Although all doses  $\geq 25$  mg achieved high Hb level responses (Fig 4), only the 25-mg dose reached the target statistical probability. The 25-mg dose in both groups achieved a probability density  $> 55\%$  (target response rate,  $> 0.55$ ) after 28 doses, such that a 1.0- and 0.5-g/dL Hb level increase (response) occurred in the CKD-3/4/5 and CKD-5D groups, respectively.

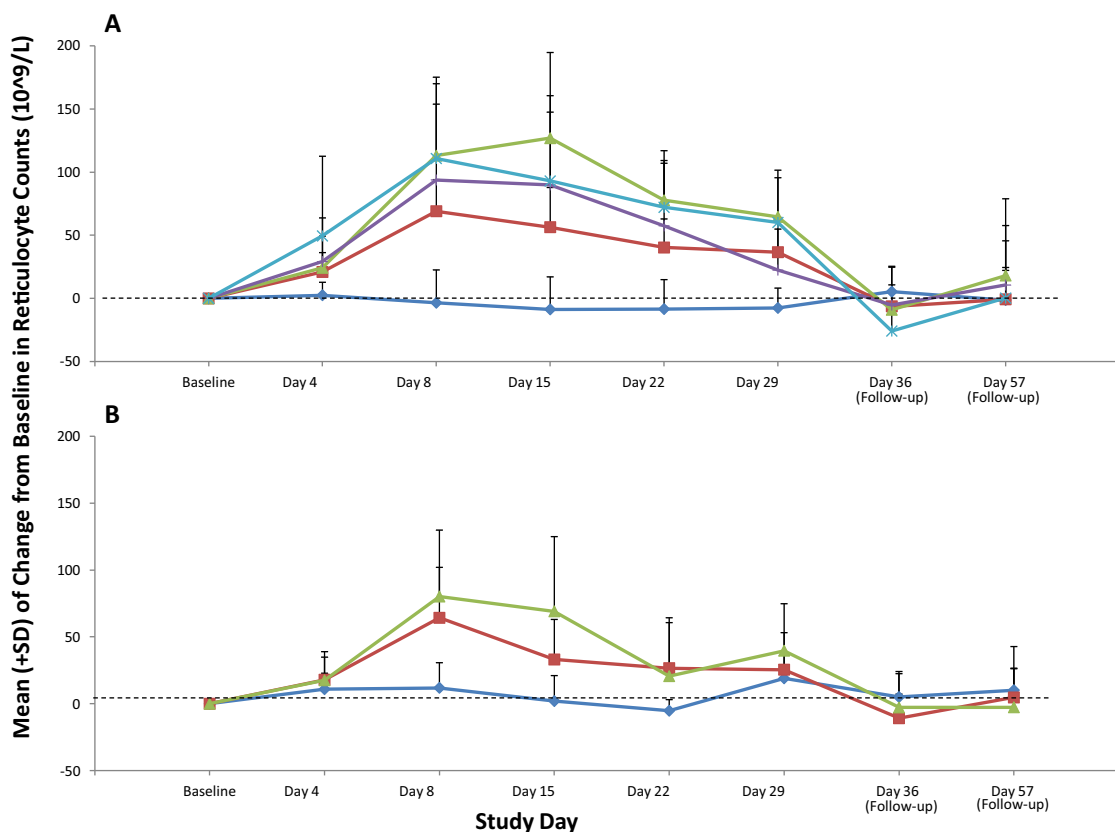
Doses  $> 25$  mg in the CKD-3/4/5 group did not achieve this probability density, potentially due to early discontinuation from either an excessive increase in Hb level or high absolute Hb level (Item S1).

#### Hepcidin

For all GSK1278863 doses in both groups, hepcidin concentrations markedly decreased in a dose-dependent manner and returned to baseline or near baseline levels by follow-up. All placebo-treated patients showed a slight increase in hepcidin concentrations during the study (Fig 5).



**Figure 2.** Mean (+ standard deviation [SD]) value for change from baseline in erythropoietin (mIU/mL) versus hours postdose on days 1, 15, and 22 in the (A) non-dialysis-dependent chronic kidney disease stages 3, 4, or 5 (CKD-3/4/5) group and (B) hemodialysis-dependent CKD stage 5 (CKD-5D) group. (◆) Placebo; GSK1278863 treatment: [■] 10 mg, [▲] 25 mg, [+] 50 mg, and [×] 100 mg.



**Figure 3.** Mean ( $\pm$  standard deviation [SD]) value for change from baseline in reticulocyte count ( $10^9/L$ ) versus study day in the (A) non-dialysis-dependent chronic kidney disease stages 3, 4, or 5 (CKD-3/4/5) group and (B) hemodialysis-dependent CKD stage 5 (CKD-5D) group. ( $\blacklozenge$ ) Placebo; GSK1278863 treatment: ( $\blacksquare$ ) 10 mg, ( $\blacktriangle$ ) 25 mg, ( $+$ ) 50 mg, and ( $\times$ ) 100 mg.

### Other Pharmacodynamic Markers

In both CKD groups, mean change from baseline in TIBC and unsaturated iron-binding capacity for all GSK1278863 doses administered increased during the study through day 29 and decreased at follow-up. Mean increases were larger for higher doses. Corresponding values in placebo-treated patients remained close to baseline values (Figs *a* and *b* of Item S2). Mean changes from baseline in serum iron concentrations were variable for all patients in the study. Despite the variability, a trend for dose-dependent decreases was observed in the CKD-3/4/5 group.

In the CKD-3/4/5 group, mean TSATs decreased during the study with GSK1278863 at all doses, in contrast to placebo (Figs *a* and *b* of Item S3). However, changes in TSATs were inconsistent in the CKD-5D group.

In both CKD groups, mean change from baseline in ferritin concentrations for all GSK1278863 doses decreased during the study but was not dose dependent, with no changes from baseline in placebo patients (Figs *a* and *b* of Item S4).

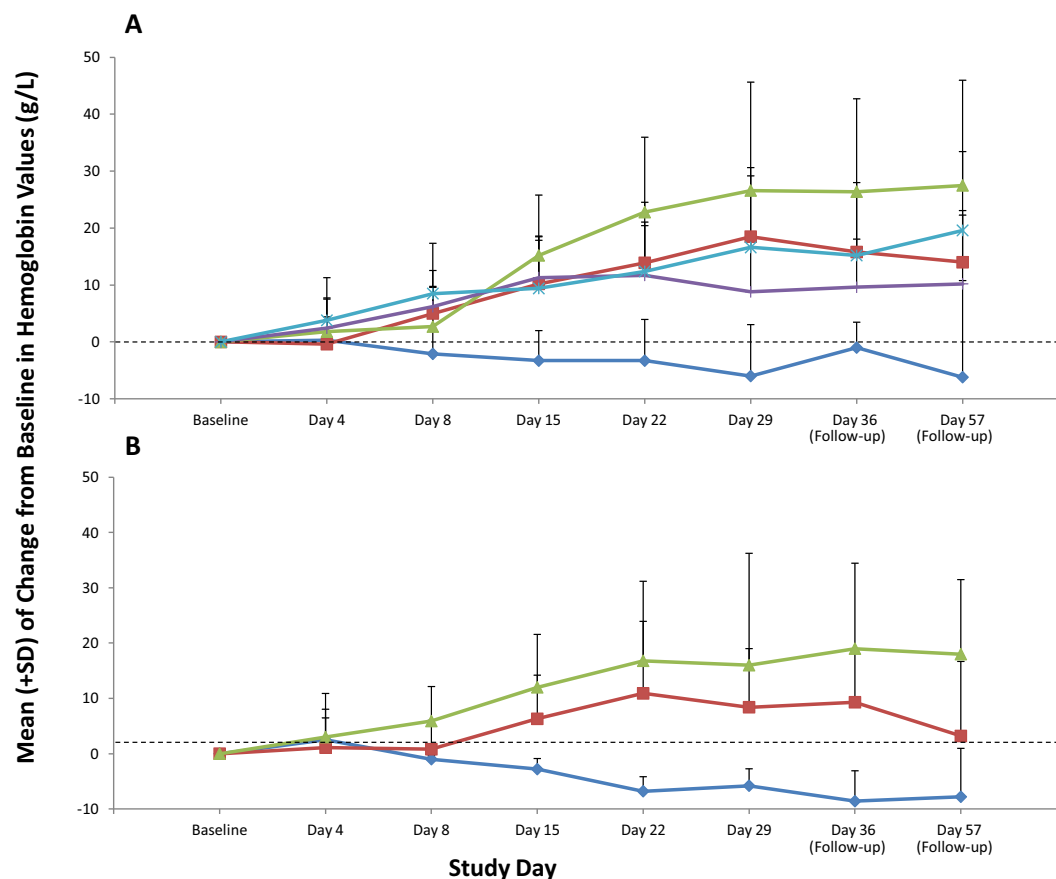
In the CKD-3/4/5 group, patients at the higher doses (50 and 100 mg) showed a trend for increased glucose levels from baseline, with maximal changes

on day 15. In the CKD-5D group, changes in glucose levels were minimal and similar at both active doses and placebo. Patients were not stratified by preexisting diabetes or glucose concentration; hence, the real impact of the drug on glucose metabolism could not be assessed (Figs *a* and *b* of Item S5).

Mean changes from baseline in predose VEGF concentrations in patients treated with placebo or GSK1278863 showed inconsistent patterns with large variability in both groups, in contrast to the findings related to changes in EPO concentrations (Figs *a* and *b* of Item S6).

### DISCUSSION

This phase 2A, 28-day, repeat-dose study evaluated the pharmacokinetics, pharmacodynamics, safety, and tolerability of GSK1278863 in patients with CKD-3/4/5 and CKD-5D. Overall, results of this study showed that GSK1278863 administration for 28 days was well tolerated and induced an effective EPO response for erythropoiesis in this patient population. The study results will help determine the starting dose for treatment algorithms to be used in long-term efficacy and safety studies.



**Figure 4.** Mean (+ standard deviation [SD]) value for change from baseline in hemoglobin concentration (g/L) versus study day in the (A) non-dialysis-dependent chronic kidney disease stages 3, 4, or 5 (CKD-3/4/5) group and (B) hemodialysis-dependent CKD stage 5 (CKD-5D) group. (◆) Placebo; GSK1278863 treatment: [■] 10 mg, [▲] 25 mg, [+] 50 mg, and [×] 100 mg.

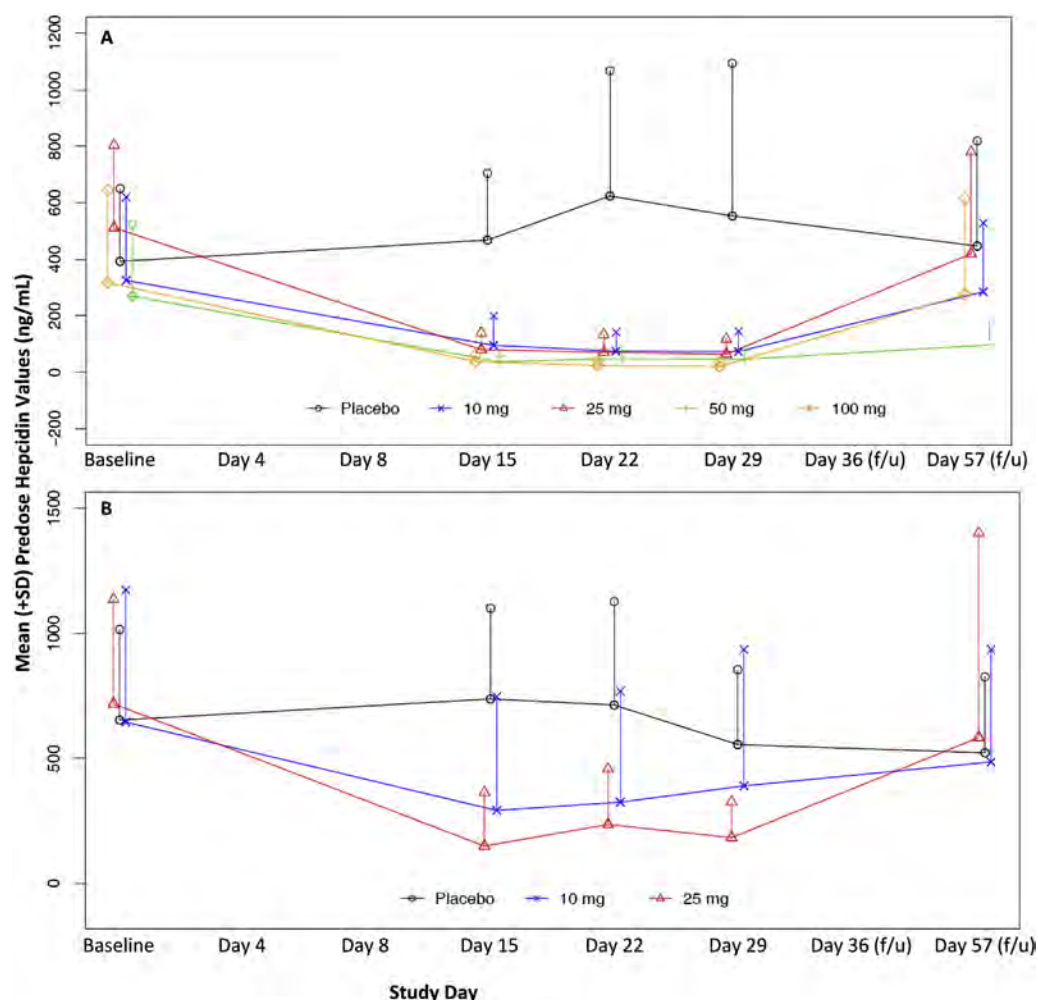
Multiple factors influence the response to ESAs in hemodialysis patients.<sup>20</sup> In our study, the erythropoietic response, on a dose-by-dose basis, was generally not as strong in the CKD-5D group as that in the CKD-3/4/5 group. However, as noted, this could relate to many factors, including acute illness, nutritional changes, and more severe CKD independent of the dialysis process itself.

The prespecified safety criteria related to rate of increase ( $>1$  g/dL in any 2-week period) and extent ( $>13.5$  g/dL) of Hb level response in this study led to the discontinuation of 30% and 22% of patients with CKD-3/4/5 and CKD-5D, respectively, indicating a robust pharmacodynamic response. There was a dose-dependent increase in EPO production; however, response rate (days 22-36) was highest for the lower doses (10 and 25 mg) in both groups as they completed the study, unlike the 50- and 100-mg dose participants in the CKD-3/4/5 group, in which extensive discontinuation rates were observed. Consequently, increases in other pharmacodynamic parameters, such as reticulocyte count, were also observed at the lower doses (10 and 25 mg). Interpretation of the response at higher doses (50 and 100 mg) is problematic because

very few patients receiving these doses completed the study due to a high Hb level response or AEs leading to discontinuation. These early withdrawals at 50 and 100 mg may affect the ability to interpret the response rate and make the high doses appear to have a paradoxically lower response than the lower doses despite a very strong EPO production dose response.

The modest daily increase in endogenous EPO produced by 10- and 25-mg oral doses of GSK1278863 returned to baseline values each day, without the significant fluctuations observed with ESAs, and consequently helped achieve the targeted Hb level response rate in the CKD-3/4/5 and CKD-5D groups. Even at these doses, the EPO produced and Hb level responses were toward the higher end of the target increase. Therefore, GSK1278863 doses  $< 10$  mg daily may lead to a low daily EPO production, which may help achieve adequate Hb level response in a similar fashion. Future clinical studies will address this question. Hemodialysis did not significantly affect the pharmacodynamic response of the lower doses; however, there was a trend toward lower pharmacodynamic responses in patients with CKD-5D





**Figure 5.** Mean (+ standard deviation [SD]) predose hepcidin values (ng/mL) versus study day in the (A) non-dialysis-dependent chronic kidney disease stages 3, 4, or 5 (CKD-3/4/5) group and (B) hemodialysis-dependent CKD stage 5 (CKD-5D) group. (●) Placebo; GSK1278863 treatment: [×] 10 mg, [▲] 25 mg, [+] 50 mg, and [◆] 100 mg. Follow-up visit includes day 57 assessment or last assessment if the individual withdrew early.

receiving the 10-mg dose compared with patients with CKD-3/4/5 receiving the same dose.

At the higher doses (50 and 100 mg), GSK1278863 produced an excessive EPO response. Consequently, the Hb level response was also too high, leading to discontinuation or AEs. A limitation to the EPO analysis was that the final collection time was at 5 to 6 hours postdose (due to practical limitations). Prior studies in healthy individuals and patients with kidney disease indicated that the peak EPO response to GSK1278863 is at approximately 8 to 10 hours postdose.<sup>20,22</sup> However, peak EPO levels in the current study are expected to be less than 2-fold higher than those observed at the latest postdose time point.

Other PHI agents are being evaluated for increased production of endogenous EPO and subsequent increases in Hb level. Those studies in addition to ours have shown that a PHI-induced increase in endogenous EPO is able to stimulate erythropoiesis in

patients with CKD-3/4/5<sup>24,25</sup> without intravenous iron supplementation.<sup>10</sup> Additionally, this increase in EPO may be partly due to EPO production from extrarenal tissues.<sup>13,26,27</sup>

Hepcidin concentrations were highly suppressed with GSK1278863 in contrast to levels in placebo patients. These data are consistent with PHI stabilization of HIF modulating hepcidin expression. Alternately, the effect could be indirect through an increase in endogenous EPO concentrations. Markers of iron metabolism such as TIBC and unsaturated iron-binding capacity showed an increase through day 29. Although TSAT percentage in the CKD-3/4/5 group decreased over time, an inconsistent pattern was seen in the CKD-5D group. These data, along with hepcidin suppression, indicate significant iron mobilization. Other exploratory pharmacodynamic parameters showed an inconsistent pattern for all doses in both groups during the study period.

Because the current study used a sparse sampling approach, there was limited information to characterize the pharmacokinetics of GSK1278863, which may have affected the ability of the model to identify and estimate covariates of GSK1278863 pharmacokinetic parameters (see [Item S1](#)). The limited pharmacokinetic sampling may have also affected the estimation of terminal half-life, which was estimated to be ~7 hours, longer than previous estimates from phase 1 studies (up to 4 hours).<sup>22</sup> The covariate analysis estimated a reduction in central volume of distribution in patients with CKD-3/4/5 compared with healthy individuals and a slight increase in central volume in patients with CKD-5D, both of which are unlikely to be clinically important because this parameter does not affect total exposure (area under the curve) of GSK1278863. GSK1278863 is highly protein bound, and the reduction in central volume in patients with CKD-3/4/5 may be reflective of differences in albumin concentrations or fluid retention between populations. In this study, the pharmacokinetic profile of GSK1278863 in patients with CKD-3/4/5 and CKD-5D was similar to that observed in healthy individuals.

In conclusion, the target Hb concentration attained helped with selection of the GSK1278863 dose for subsequent studies that followed ([ClinicalTrials.gov](#) study numbers NCT01587898, NCT01587924, NCT01977482, NCT01977573, and NCT02019719). The 10- and 25-mg doses produced effective erythropoiesis with modest daily EPO production, although these doses also resulted in high Hb level increases in some individuals, leading to early discontinuation from the study. The same high Hb level increases also occurred at the 50- and 100-mg doses for the CKD-3/4/5 group and, along with other non-Hb tolerability-related AEs, led to early discontinuation and withdrawals. These data indicate that oral GSK1278863 was able to induce an effective EPO response resulting in increased Hb concentrations in patients with CKD with anemia and suggest that GSK1278863 doses < 10 mg daily may be a suitable dose range to be explored in future long-term clinical trials.

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**Contributions:** Study design, review of analyzed data: all authors; study investigators: MW, GO, JdZ, SDR, MS, NC, LM, VG, EAS, NS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. RAB takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

**Peer Review:** Evaluated by 2 external peer reviewers, a Statistical Editor, a Co-Editor, and the Editor-in-Chief.

## SUPPLEMENTARY MATERIAL

Item S1: Additional study design, inclusion/exclusion, PK assessment, and Hb responder rate information.

Item S2: Change from baseline in TIBC values vs study time for both groups, pharmacodynamic population.

Item S3: Change from baseline in TSAT values vs study day by treatment for both groups, pharmacodynamic population.

Item S4: Change from baseline in ferritin values vs study day by treatment for both groups, pharmacodynamic population.

Item S5: Change from baseline in glucose values vs study time for both groups, pharmacodynamic population.

Item S6: Change from baseline in VEGF values vs study time in both groups, pharmacodynamic population.

Note: The supplementary material accompanying this article (<http://dx.doi.org/10.1053/j.ajkd.2015.11.021>) is available at [www.ajkd.org](http://www.ajkd.org)

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