The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

GSK Medicine: GSK1278863
Study Number: PHI116582
Title: A four-week, Phase IIa, randomized, active-controlled, parallel-group, multi-center study to evaluate the safety, efficacy and pharmacokinetics of switching subjects from a stable dose of recombinant human erythropoietin to GSK1278863 in hemodialysis-dependent subjects with anemia associated with chronic kidney disease.
Rationale: GSK1278863 is a prolyl hydroxylase inhibitor that stimulates erythropoiesis in a manner similar to the natural response to hypoxia, where EGL-9 homologous proteins (EGLN1, EGLN2, and EGLN3) are inhibited ultimately leading to increased transcription of hypoxia inducible factor (HIF)-responsive genes. This study aimed to estimate the relationship between dose of GSK1278863 and hemoglobin (Hgb) response in hemodialysis-dependent (HDD) subjects with anemia associated with chronic kidney disease (CKD) after switching from a stable maintenance dose of recombinant human erythropoietin (rhEPO). In addition, the study characterized the effect of GSK1278863 on various PK/PD markers, and investigated the safety and tolerability of GSK1278863.
Phase: IIa
Study Period: 06 June 2012 – 17 June 2013
Study Design: This was a 4-week, randomized, active-controlled, parallel-group, multi-center study to evaluate the safety, efficacy, and pharmacokinetics of switching subjects from stable rhEPO to GSK1278863 in hemodialysis-dependent (HDD) subjects with anemia associated with chronic kidney disease (CKD). The range of Hgb values for study eligibility was 9.5 to 12.0 g/dL (verified by measurements at Week -2, Week -1, and Day 1 [randomization]), and subjects must have received the same rhEPO product with total weekly doses that varied by no more than 50% during the 4 weeks prior to the Screening visit (Week -1). The study consisted of a 2-week screening phase, a 4-week treatment phase, and a 2-week follow-up phase. Subject completion was defined as completion of all study phases including the follow-up phase.
Centers: 48 centers in 6 counties: 32 in the United States, 5 in Canada, 4 in Germany, 3 in Denmark, and 2 sites each in Norway and Sweden
Indication: Anemia associated with CKD
Treatment: Subjects randomized to GSK1278863 discontinued their current rhEPO therapy and started therapy with 0.5 mg, 2 mg or 5 mg GSK1278863 (at their next scheduled mid-week dialysis day, which served as the day of randomization, Day 1) taken orally once daily and subjects were to be consistent in taking tablets with or without food. Subjects randomized to rhEPO (open-label due to different route of administration) received their rhEPO in accordance with their usual schedule. rhEPO treatment may have included epoetins or their biosimilars, or darbepoetin, but Mircera and peginesatide were not permitted.
Objectives: The primary objective was to estimate the relationship between dose of GSK1278863 and Hgb response following switching from a stable dose of rhEPO in subjects undergoing hemodialysis.
Primary Outcome/Efficacy Variable: The primary efficacy endpoint was modeled Hgb change from baseline over 4 weeks of treatment
Secondary Outcome/Efficacy Variable(s): Secondary endpoints were: observed Hgb and change from baseline summaries over time, endpoints to describe Hgb variability over 4 weeks (that included: within subject standard deviation [SD]; residual SD [derived from a regression model]; time spent with Hgb within range [where range was defined as ±0.5 g/dL and ±1 g/dL from baseline Hgb]; and Area Under the Hgb Change versus time Curve [AUC] using change from baseline); maximum Hgb change over 4 weeks, number of subjects who reached Hgb stopping criteria (i.e., Hgb drop <=8 g/dL, Hgb increased to >=13 g/dL, or Hgb changed by >=2 g/dL within 1 week); change in plasma erythropoietin (EPO); change in markers of iron metabolism/utilization (hepcidin, ferritin, transferrin, transferrin saturation (TSAT), total iron, total iron binding capacity [TIBC]), and a measure of inflammation (high sensitivity C-Reactive Protein; [hsCRP]); change from baseline in hematocrit, red blood cells (RBC), reticulocytes, and plasma vascular endothelial growth factor (VEGF) concentrations (; and population PK parameters of GSK1278863 and relevant metabolites.
Statistical Methods: The primary endpoint of modeled Hgb change from baseline over 4 weeks was derived using a random coefficient mixed effects linear regression model. The model included fixed effects for baseline Hgb, treatment, and a treatment by day interaction. Random effects were fitted in the intercept and the slope over time. This model was used to estimate individual Hgb modelled change from baseline over 4 weeks to be taken forward into the dose-response analysis. All subjects having a baseline and at least 2 on-treatment Hgb assessments and data up until investigational product discontinuation were included.

Secondary efficacy endpoints to describe Hgb variability were summarized (i.e., within subject SD calculation included baseline values; residual SD was taken for each subject from the proc mixed model; time spent within a specified Hgb range was calculated by the Rosendaal method, 1993; and the AUC for Hgb versus time curve was derived using the "trapezoidal rule" as approximation to integration [Eckardt, 2010]). Secondary endpoints of maximum Hgb change over 4 weeks, peak EPO change from baseline over 4 weeks, change from baseline at Week 4 in hepcidin, ferritin, transferrin, transferrin saturation, total iron, TIBC, and hsCRP were analyzed using an ANCOVA model with terms included for treatment and baseline value. A similar analysis was used to evaluate the change from baseline at Week 4 for hematocrit and RBC count, change from baseline at Week 1 and Week 4 for reticulocytes, and change from baseline in peak VEGF (pre-dose) over 4 weeks.

A population PK model was used to characterize the plasma PK of GSK1278863 and 6 metabolites. This analysis combined the dosing and concentration-time data from 1 Phase 1 (PHI114703; healthy subjects) and 3 Phase 2A studies (PHI112844, PHI116581, and PHI116582; subjects with CKD).

Adverse events and changes from baseline in laboratory, vital signs, and electrocardiogram (ECG) parameters were presented in addition to values outside the normal and clinical concern ranges.

Study Population

Eligible subjects were: adults >=18 years of age, weighing >=45 kg, on three times weekly hemodialysis for at least 8 weeks, had a single-pool Kt/Vurea of >=1.2 within the prior month or if Kt/Vurea was not available, then an average of the last 2 values of urea reduction ratio (URR) of at least 65%; were using the same rhEPO with total weekly doses that varied by no more than 50% during the prior 4 weeks; had a stable Hgb concentration of 9.5 to 12.0 g/dL; had vitamin B12 levels above the lower limit of the reference range, folate >=2.0 mg/mL, ferritin >=40 ng/mL (with the absence of microcytic or hypochromic red blood cells [RBCs]), and TSAT within the reference range.

Subjects were excluded who were: on peritoneal dialysis OR planned change in dialysis modality within the study time period; were receiving an epoetin dose of >=360 IU/kg/week intravenous (IV) or darbepoetin dose of >=1.8 µg/kg/week IV within the prior 8 weeks; had or planned to have a renal transplant within the study time; had prior CV or thrombotic events within the last 6 months, NYHA Class III-IV heart failure, known pulmonary hypertension, hematologic disease affecting platelets, coagulation or red blood cells other than CKD, clinically significant liver disease, or chronic inflammatory disease; had creatine phosphokinase >5 x upper limit of normal (ULN); had major surgery within prior 12 weeks or planned major surgery; had a blood transfusion within prior 12 weeks of screening; had recent peptic, duodenal, esophageal ulcers or gastrointestinal (GI) bleeding; had a malignancy within 5 years of screening (with the exception of squamous cell or basal cell carcinoma of the skin); had proliferative retinopathy requiring treatment within the prior 12 months, or macular edema requiring treatment.

Number of Subjects	GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=21)	GSK1278863 5 mg (N=21)	rhEPO (N=20)	Total (N=83)
Planned, N	17	17	17	17	68
Randomized, N	21	21	21	20	83
Completed, N (%)	17 (81)	17 (81)	17 (81)	19 (95)	70 (84)
Premature Withdrawn, N (%)	4 (19)	4 (19)	4 (19)	1 (6)	13 (16)
Due to Adverse event, N (%)	0	2 (10)	0	0	2 (2)
Met protocol-defined Hgb stopping criteria, N (%)	2 (10)	0	1 (5)	0	3 (4)
Withdrew for other reasons, N (%)	2 (10)	2 (10)	3 (14)	1 (5)	8 (38)
Demographics	**GSK1278863 0.5 mg (N=21)**	**GSK1278863 2 mg (N=21)**	**GSK1278863 5 mg (N=21)**	**rhEPO (N=20)**	**Total (N=83)**
N (ITT)	21	20	19	20	80
Females: Males	3 :18	7 : 13	8 : 11	4 : 16	22 : 58
Mean Age, years (SD)	56.4 (16.80)	54.7 (18.78)	55.9 (18.37)	64.2 (12.77)	57.8 (16.92)
White, n (%)	14 (67)	14 (70)	12 (63)	14 (70)	54 (68)

Primary Efficacy Results:

Hemoglobin (g/dL) Change from Baseline (CFB) at Week 4

	GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline Hgb Mean (SD)	10.66 g/dL (0.7)	10.75 g/dL (0.6)	10.80 g/dL(0.6)	10.89 g/dL (0.5)

Modeled Hgb CFB at Week 4 Mean (SD)		-1.13 g/dL (0.7)	-1.07 g/dL (0.8)	0.21 g/dL (0.8)	-0.27 g/dL(0.6)

Secondary Efficacy Results:					
Observed Hgb CFB at Week 4 Mean (SD)		-1.06 g/dL(0.8)	-0.93 g/dL (0.8)	-0.08 g/dL(0.6)	-0.25 g/dL (0.8)
Hgb Variability Endpoints		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Within subject SD	n	20	20	18	19
	Mean (SD)	0.53 (0.27)	0.55 (0.33)	0.40 (0.36)	0.35 (0.19)
	Median	0.51	0.55	0.31	0.36
	Min : Max	0.1 : 1.0	0.1 : 1.1	0.1 : 1.7	0.1 : 0.8
Residual SD	Mean (SD)	0.24 (0.11)	0.26 (0.12)	0.26 (0.31)	0.20 (0.11)
	Median	0.23	0.25	0.20	0.19
	Min : Max	0.1 : 0.6	0.1 : 0.5	0.1 : 1.4	0.1 : 0.5
Hgb AUC	Mean (SD)	16.67 (9.64)	18.76 (12.75)	11.89 (8.06)	10.89 (8.69)
	Median	14.89	16.39	8.69	8.64
	Min : Max	4.3 : 37.8	3.6 : 45.3	2.9 : 32.4	1.1 : 32.0
Number of Days within ± 0.5 g/dL from Baseline					
	n	20	20	18	19
	Mean (SD)	14.57 (8.24)	15.38 (9.95)	19.27 (9.37)	19.84 (8.91)
	Median	12.82	14.34	24.41	21.15
	Min : Max	4.0 : 28.0	2.8 : 29.0	4.6 : 30.0	3.9 : 31.0
Percentage of Days within ± 0.5 g/dL from Baseline					
	Mean (SD)	51.98 (29.50)	55.04 (35.80)	68.42 (33.03)	71.24 (31.56)
	Median	45.77	51.20	87.16	88.89
	Min : Max	14.2 : 100.0	10.1 : 100.0	16.3 : 100.0	13.9 : 100.0
Number of Days within ± 1 g/dL from Baseline					
	Mean (SD)	23.58 (6.04)	20.16 (8.16)	25.54 (5.20)	25.65 (5.32)
	Median	27.71	20.79	28.00	28.00
	Min : Max	10.5 : 28.0	5.7 : 29.0	9.1 : 30.0	9.7 : 31.0
Percentage of Days within ± 1 g/dL from Baseline					
	Mean (SD)	83.95 (21.61)	71.94 (29.28)	90.83 (18.27)	91.99 (17.96)
	Median	98.96	74.23	100.00	100.00
	Min : Max	37.5 : 100.0	20.3 : 100.0	32.6 : 100.0	34.5 : 100.0
Summary and Analysis of Maximum Hgb (g/dL) Change over 4 weeks					
		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline	n	21	20	19	20
	Mean (SE)	10.66 (0.14)	10.75 (0.13)	10.80 (0.14)	10.89 (0.12)
	Median	10.70	10.93	10.60	10.85
	Min : Max	9.47 : 11.90	9.60 : 11.70	9.90 :11.97	10.03 :11.87
	95% CI	(10.36, 10.96)	(10.47, 11.03)	(10.50, 11.09)	(10.64, 11.13)
Maximum CFB Over 4 Weeks	n	21	20	19	20
	Mean (SE)	-0.15 (0.10)	-0.20 (0.13)	0.31 (0.14)	0.17 (0.12)
	Median	-0.27	-0.17	0.233	0.117
	Min : Max	-0.73: 0.77	-1.23 :0.67	-0.60 :2.00	-0.73 :1.20
	95% CI	(-0.36, 0.05)	(-0.46,0.06)	(0.03,0.60)	(-0.08,0.42)
Modeled Adjusted Maximum CFB Over 4 Weeks	n	21	20	19	20
	Adjusted Mean (SE)	-0.17 (0.12)	-0.20 (0.12)	0.32 (0.12)	0.18 (0.12)
	95% CI	(-0.40, 0.06)	(-0.44, 0.04)	(0.07, 0.56)	(-0.05, 0.42)
Maximum Hgb (g/dL) Change at Any Time During the Study					

		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Subjects achieving:					
Decrease of >0.5 g/dL	n (%) 95% CI	17 (81) (58.1, 94.6)	14 (70) (45.7, 88.1)	8 (42) (20.3, 66.5)	8 (40) (19.1, 63.9)
Decrease of 0.5 to increase of <0.5 g/dL	n (%) 95% CI	2 (10) 1.2, 30.4)	5 (25) (8.7, 49.1)	7 (37) (16.3, 61.6)	7 (35) (15.4, 59.2)
Increase of ≥0.5 to 1.0 g/dL	n (%) 95% CI	2 (10) (1.2, 30.4)	1 (5%) (0.1, 24.9)	1 (5) (0.1, 26.0)	4 (20) (5.7, 43.7)
Increase of ≥1.0 to <1.5 g/dL	n (%) 95% CI	0 (0.0, 16.1)	0 (0.0, 16.8)	2 (11) (1.3, 33.1)	1 (5) (0.1, 24.9)
Increase ≥1.5 g/dL	n (%) 95% CI	0 (0.0, 16.1)	0 (0.0, 16.8)	1 (5%) (0.1, 26.0)	0 (0.0, 16.8)

Analysis of Peak EPO (U/L) Change from Baseline (Pre-Dose)					
		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline	n Mean (SD) Median Min : Max	18 13.03 (8.938) 11.12 2.50 : 37.74	18 10.56 (6.596) 8.93 2.50 : 26.26	16 11.24 (10.017) 8.14 2.50 : 39.92	19 13.42 (12.683) 9.59 2.50 : 54.10
Peak[a,b] EPO	n Mean (SD) Median Min : Max	19 16.23 (17.901) 13.86 3.49 : 86.27	18 15.01 (11.519) 12.65 4.96 : 57.13	17 183.90 (452.723) 24.66 6.64 : 1786.50	19 405.57 (416.080) 424.89 9.77 : 1371.20
Peak[a,b] EPO CFB	n Mean (SD) Median Min : Max	18 3.66 (14.085) 2.10 -19.88 : 48.53	18 4.44 (10.801) 2.28 -11.61 : 42.48	16 182.61 (465.265) 14.07 -7.05 : 1775.62	19 392.16 (416.836) 418.81 -17.79 : 1339.42
Modeled Adjusted Peak[a,b] EPO CFB (Pre-Dose)	n Adjusted Mean (SE) 95% CI	18 4.37 (73.349) -142.077 , 150.813	18 3.26 (73.502) -143.489, 150.015	16 181.95 (77.776) 26.662, 337.233	19 393.16 (71.486) 250.434, 535.885

a. Peak refers to the highest observed mean EPO concentration, but it is possible this did not represent the true peak EPO response. EPO = Erythropoietin; Baseline is the last pre-dose value

b. Includes EPO outlier values

Markers of Iron Metabolism and Utilization Summary of Change from Baseline in Hepcidin (mcg/L) by Visit					
		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline Pre-dose	n Mean (SD) Median Min : Max	21 523.8 (359.35) 412.7 119.8 - 1567.0	20 485.9 (338.86) 351.5 51.9 : 1238.3	19 489.5 (311.38) 483.1 93.5 : 1241.8	20 355.5 (220.92) 286.3 61.5 : 893.7
Week 2 4-8 hrs Post-dose CFB	n Mean (SD) Median Min : Max	19 180.8 (215.48) 171.0 -132.2 : 745.5	18 144.3 (340.71) 41.1 -681.8 : 833.1	16 -23.8 (142.65) -19.1 -258.8 : 244.5	15 -51.1 (111.02) -36.8 -211.2 : 172.6
Week 4 Pre-Dose CFB	n Mean (SD) Median Min : Max	18 203.2 (296.85) 154.0 -141.9 : 866.6	17 146.5 (295.48) 103.7 -656.0 : 463.4	17 10.7 (261.09) -0.50 -379.4 : 706.7	18 -34.8 (148.91) -41.0 -299.5 : 266.6

Summary of Change from Baseline in Ferritin (UG/L) by Visit					
		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline	n Mean (SD) Median Min : Max	21 741.6 (455.65) 582.0 174 :1650	20 686.6 (483.78) 679.5 122 : 2042	19 734.9 (386.76) 738.0 126 : 1650	20 441.7 (252.37) 458.5 16 : 928
Week 2 CFB	n Mean (SD) Median Min : Max	20 59.3 (115.52) 37.5 -224 : 276	20 43.7 (122.85) 5.5 -151 : 305	19 -46.6 (122.19) -26.0 -344 : 204	19 17.5 (112.90) -13.0 -237 : 228
Week 4 CFB	n Mean (SD) Median Min : Max	19 74.2 (173.97) 81.0 -263 : 396	18 -5.8 (178.67) -38.5 -219 : 413	17 -80.8 (95.89) -74.0 -265 : 48	19 -27.9 (165.95) -52.0 -266 : 406
Week 6 Follow-up CFB	n Mean (SD) Median Min : Max	17 42.1 (302.57) 124.0 -917 : 446	19 4.1 (177.76) -6.0 -266 : 333	18 -50.8 (124.30) -36.0 -308 : 243	19 -88.5 (107.36) -114.0 -260 : 262
Summary of Change from Baseline in Transferrin (g/L) by Visit					
		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline	n Mean (SD) Median Min : Max	21 1.7 (0.40) 1.7 1.0 : 2.6	20 1.6 (0.26) 1.7 1.2 : 2.2	19 1.7 (0.45) 1.7 1.0 : 3.0	20 1.9 (0.44) 1.9 1.1 : 3.1
Week 2 CFB	n Mean (SD) Median Min : Max	20 0.0 (0.47) 0.0 -0.6 : 1.8	20 0.1 (0.36) 0.1 -1.1 : 0.7	19 0.1 (0.36) 0.1 -1.0 : 0.4	19 0.1 (0.16) 0.0 -0.1 : 0.4
Week 4 CFB	n Mean (SD) Median Min : Max	19 0.1 (0.49) 0.0 -0.3 : 2.0	18 0.2 (0.17) 0.2 -0.1 : 0.4	17 0.2 (0.25) 0.2 -0.5 : 0.6	19 0.0 (0.26) 0.1 -0.4 : 0.4
Week 6 Follow-up CFB	n Mean (SD) Median Min : Max	17 0.1 (0.46) 0.0 -0.5 : 1.6	19 -0.1 (0.52) 0.0 -1.7 : 0.5	18 0.1 (0.23) 0.1 -0.4 : 0.4	18 -0.1 (0.35) -0.1 -0.9 : 0.5
Summary of Change from Baseline in Total Iron Binding Capacity (UMOL/L) by Visit					
		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline	n Mean (SD) Median Min : Max	21 41.4 (8.78) 42.0 26 : 60	20 39.3 (5.54) 39.0 28 : 51	19 41.1 (8.93) 40.0 26 : 66	20 44.6 (8.50) 43.5 30 : 66
Week 2 CFB	n Mean (SD) Median Min : Max	17 1.4 (5.16) 2.0 -4 : 17	19 1.9 (3.37) 1.0 -4 : 10	19 3.9 (4.06) 4.0 -6 : 11	19 0.4 (4.49) 1.0 -10 : 11
Week 4 CFB	n Mean (SD) Median Min : Max	18 3.3 (6.27) 3.0 -8 : 18	18 3.9 (3.42) 4.0 -2 : 11	17 5.2 (3.17) 5.0 1 : 10	19 1.0 (4.56) 2.0 -8 : 6
Week 6 Follow-	n	16	19	18	19

up CFB	Mean (SD) Median Min : Max	2.4 (7.14) 2.5 -8 : 17	2.4 (5.31) 2.0 -7 : 17	1.9 (5.42) 2.5 -11 : 15	0.7 (6.16) 1.0 -12 : 15
Summary of Change from Baseline in Transferrin Saturation (%) by Visit					
		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=21)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline	n Mean (SD) Median Min : Max	21 30.0 (10.95) 29.0 14 : 52	20 33.0 (14.35) 31.0 11 : 55	19 32.6 (11.95) 28.0 19 : 61	20 28.4 (12.30) 26.5 12 : 54
Week 2 CFB	n Mean (SD) Median Min : Max	17 9.5 (14.48) 9.0 -9 : 50	19 8.7 (13.23) 8.0 -12 : 37	19 -0.2 (11.95) 1.0 -21 : 20	19 -0.3 (9.56) 1.0 -23 : 14
Week 4 CFB	n Mean (SD) Median Min : Max	18 7.7 (20.13) 2.0 -21 : 43	18 10.1 (15.38) 7.5 -12 : 49	17 0.3 (11.82) 2.0 -22 : 21	19 1.2 (13.04) 4.0 -27 : 26
Week 6 Follow-up CFB	n Mean (SD) Median Min : Max	16 14.0 (19.22) 5.0 -4 : 52	19 4.1 (19.97) 2.0 -23 : 39	18 4.4 (16.10) 2.5 -27 : 45	19 -0.5 (9.02) 2.0 -24 : 10
Summary of Change from Baseline in Serum Iron (UMOL/L) by Visit					
		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline	n Mean (SD) Median Min : Max	21 12.1 (4.41) 11.0 6 : 21	20 12.9 (5.62) 13.0 4 : 22	19 12.8 (3.39) 13.0 7 : 19	20 12.5 (5.53) 10.5 6 : 24
Week 2 CFB	n Mean (SD) Median Min : Max	19 5.9 (7.91) 5.0 -3 : 26	20 4.5 (5.61) 3.5 -6 : 16	19 1.2 (5.29) 1.0 -8 : 9	19 -0.4 (3.99) 1.0 -10 : 4
Week 4 CFB	n Mean (SD) Median Min : Max	19 5.0 (9.53) 1.0 -8 : 26	18 5.7 (6.85) 4.0 -5 : 23	17 2.2 (4.69) 2.0 -6 : 9	19 0.4 (5.65) 1.0 -14 : 9
Week 6 Follow-up CFB	n Mean (SD) Median Min : Max	17 6.9 (7.49) 4.0 -2 : 21	19 2.3 (8.18) 2.0 -9 : 21	18 2.7 (5.62) 1.5 -7 : 16	19 -0.3 (4.27) 0.0 -11 : 6
Summary of Change from Baseline in hsCRP (mg/L) by Visit					
		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline	n Mean (SD) Median Min : Max	21 9.50 (11.695) 3.80 0.2 : 43.7	20 11.21 (21.420) 4.30 0.4 : 93.9	19 7.47 (8.548) 4.20 0.5 : 30.2	20 7.75 (16.497) 2.90 0.7 : 75.5
Week 2 CFB	n Mean (SD) Median Min : Max	20 3.39 (14.648) 0.55 -27.5 : 42.2	20 -0.23 (26.171) -0.50 -88.5 : 64.8	19 5.86 (20.410) 0.10 -17.7 : 71.1	19 -3.22 (16.081) -0.20 -65.9 : 18.8
Week 4 CFB	n Mean (SD)	19 -0.67 (7.018)	18 -5.62 (19.752)	17 -0.95 (5.438)	19 -2.30 (18.737)

	Median Min : Max	-0.40 -17.0 : 17.8	-0.55 -83.1 : 8.7	-0.10 -14.9 : 11.9	0.10 -71.0 : 33.2
Week 6 Follow-up CFB	n Mean (SD) Median Min : Max	17 -0.46 (11.941) -0.50 -25.5 : 37.1	19 0.56 (26.607) 0.10 -87.4 : 57.0	18 -0.92 (5.890) -0.20 -16.0 : 11.8	19 -3.32 (16.424) 0.40 -70.2 : 7.2

Other Pharmacodynamic Markers					
Summary of Change from Baseline in Hematocrit (%) by Visit					
		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline	n Mean (SD) Median Min : Max	21 32.15 (2.451) 32.00 27.2 : 36.6	20 32.27 (2.541) 32.65 27.9 : 37.8	19 33.05 (2.400) 33.10 28.4 : 37.9	20 32.47 (1.588) 32.55 29.6 : 34.7
Week 1 1 CFB	n Mean (SD) Median Min : Max	19 -0.59 (1.609) -0.90 -3.7 : 2.6	20 -0.16 (1.823) -0.15 -3.8 : 2.7	19 -0.75 (1.735) -0.40 -5.7 : 2.3	18 0.20 (1.738) 0.25 -3.9 : 3.6
Week 2 CFB	n Mean (SD) Median Min : Max	19 -1.33 (2.122) -1.50 -5.1 : 2.0	20 -1.56 (2.296) -1.95 -5.5 : 2.9	17 -0.75 (1.960) -1.10 -4.6 : 3.6	19 2.02 (8.248) 0.00 -2.7 : 35.4
Week 3 CFB	n Mean (SD) Median Min : Max	16 -2.32 (2.634) -1.80 -8.1 : 0.8	17 -2.22 (2.712) -1.70 -6.7 : 2.4	17 -0.65 (2.277) -0.60 -4.7 : 2.5	18 0.24 (2.507) 0.55 -6.5 : 3.8
Week 4 CFB	n Mean (SD) Median Min : Max	18 -3.22 (2.731) -3.10 -7.9 : 1.3	18 -2.63 (3.006) -3.05 -7.7 : 1.4	15 -0.33 (2.044) 0.40 -5.8 : 2.3	19 -0.22 (2.874) -0.60 -7.1 : 5.2
Week 6 Follow-up CFB	n Mean (SD) Median Min : Max	17 -4.24 (3.802) -4.00 -10.0 : 3.2	19 -3.63 (4.151) -3.90 -10.5 : 5.0	18 -1.59 (2.691) -0.90 -8.9 : 1.8	19 -0.51 (3.795) -0.40 -7.5 : 6.5
Summary of Change from Baseline in Red Blood Cell Count (10^{12}/L) by Visit					
		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline	n Mean (SD) Median Min : Max	21 3.25 (0.273) 3.20 2.8 : 3.7	20 3.35 (0.461) 3.30 2.7 : 4.9	19 3.36 (0.306) 3.40 2.8 : 4.1	20 3.38 (0.317) 3.30 2.9 : 4.4
Week 1 CFB	n Mean (SD) Median Min : Max	19 -0.04 (0.157) -0.10 -0.3 : 0.3	20 -0.03 (0.189) 0.00 -0.4 : 0.3	19 -0.06 (0.184) 0.00 -0.6 : 0.2	18 0.02 (0.177) 0.00 -0.4 : 0.3
Week 2 CFB	n Mean (SD) Median Min : Max	19 -0.13 (0.191) -0.10 -0.5 : 0.2	20 -0.14 (0.243) -0.15 -0.5 : 0.3	17 -0.05 (0.210) -0.10 -0.4 : 0.5	19 0.18 (0.771) 0.00 -0.3 : 3.3
Week 3 CFB	n Mean (SD) Median Min : Max	16 -0.22 (0.248) -0.15 -0.7 : 0.1	17 -0.19 (0.305) -0.10 -0.7 : 0.3	17 -0.05 (0.229) 0.00 -0.4 : 0.3	18 0.01 (0.256) 0.00 -0.7 : 0.4
Week 4	n	18	18	15	19

CFB	Mean (SD) Median Min : Max	-0.29 (0.259) -0.30 -0.7 : 0.1	-0.25 (0.337) -0.20 -0.8 : 0.2	-0.03 (0.198) 0.00 -0.6 : 0.2	-0.03 (0.262) 0.00 -0.7 : 0.4
Week 6 Follow-up CFB	n Mean (SD) Median Min : Max	17 -0.37 (0.392) -0.40 -1.0 : 0.6	19 -0.35 (0.421) -0.30 -1.1 : 0.4	18 -0.12 (0.277) -0.10 -0.9 : 0.4	19 -0.04 (0.350) 0.00 -0.7 : 0.6
Summary of Change from Baseline in Reticulocytes (%) by Visit					
		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline	n Mean (SD) Median Min : Max	21 1.60 (0.765) 1.50 0.3 : 3.7	20 1.67 (0.620) 1.60 0.6 : 3.2	19 1.75 (0.649) 1.70 0.6 : 2.7	20 1.96 (0.706) 2.20 0.5 : 3.0
Week 1 CFB	n Mean (SD) Median Min : Max	19 -0.42% (0.966) -0.30 -2.7 : 1.0	20 -0.56% (0.751) -0.70 -1.6 : 1.4	19 0.03% (0.681) 0.00 -1.4 : 1.4	16 -0.08% (0.837) -0.15 -1.5 : 1.7
Week 2 CFB	n Mean (SD) Median Min : Max	19 -0.45% (1.072) -0.20 -3.1 : 1.5	20 -0.49% (0.613) -0.55 -1.8 : 0.6	17 -0.08% (0.656) 0.10 -1.5 : 1.0	19 -0.14% (0.737) -0.20 -1.6 : 1.7
Week 3 CFB	n Mean (SD) Median Min : Max	16 -0.34% (1.114) 0.05 -3.3 : 0.8	17 -0.27% (0.757) -0.50 -1.4 : 1.1	17 -0.06% (0.634) 0.10 -1.4 : 0.7	18 -0.35% (0.782) -0.20 -1.8 : 1.7
Week 4 CFB	n Mean (SD) Median Min : Max	18 -0.36% (1.030) -0.30 -3.3 : 1.1	18 -0.26% (0.533) -0.30 -1.1 : 0.6	15 -0.03% (0.703) -0.20 -1.0 : 1.1	19 -0.29% (0.686) -0.30 -1.4 : 0.8
Week 6 Follow-up CFB	n Mean (SD) Median Min : Max	17 -0.12% (1.128) 0.00 -2.9 : 1.9	19 -0.12% (0.536) 0.00 -1.0 : 0.9	17 -0.29% (0.664) -0.10 -1.5 : 1.4	19 -0.18% (0.696) -0.20 -1.2 : 1.1
Summary of Change from Baseline in Reticulocytes (10^{12}/L) by Visit					
		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline	n Mean (SD) Median Min : Max	21 0.051 (0.0232) 0.053 0.011 :0.109	20 0.055 (0.0193) 0.052 0.021 :0.097	19 0.058 (0.200) 0.060 0.020 : 0.095	20 0.066 (0.0244) 0.070 0.016 :0.120
Week 1 CFB	n Mean (SD) Median Min : Max	19 -0.013 (0.0302) -0.008 -0.078 : 0.034	20 -0.019 (0.0271) -0.026 -0.061 : 0.052	19 0.000 (0.0235) -0.003 -0.050 : 0.049	16 -0.003 (0.0274) -0.002 -0.056 : 0.052
Week 2 CFB	n Mean (SD) Median Min : Max	19 -0.015 (0.0331) -0.007 -0.089 : 0.042	20 -0.018 (0.0208) -0.018 -0.057 : 0.021	17 -0.004 (0.0212) 0.002 -0.055 : 0.029	19 -0.003 (0.0237) -0.002 -0.054 : 0.053
Week 3 CFB	n Mean (SD) Median Min : Max	16 -0.013 (0.0339) 0.001 -0.098 :0.020	17 -0.011 (0.0255) -0.013 -0.051 :0.038	17 -0.003 (0.0219) -0.003 -0.052 : 0.024	18 -0.011 (0.0252) -0.010 -0.068 : 0.051
Week 4 CFB	n Mean (SD)	18 -0.014 (0.0329)	18 -0.011 (0.0196)	15 -0.002 (0.0230)	19 -0.009 (0.0223)

	Median Min : Max	-0.009 -0.098 :0.035	-0.014 -0.045 : 0.020	-0.004 -0.031 : 0.035	-0.009 -0.047 : 0.028
Week 6 Follow-up CFB	n Mean (SD) Median Min : Max	17 -0.008 (0.0344) -0.003 -0.091 : 0.052	19 -0.009 (0.0171) -0.005 -0.039 : 0.021	17 -0.012 (0.0234) -0.006 -0.055 : 0.047	19 -0.007 (0.0238) -0.012 -0.043 : 0.036

Summary of Change from Baseline in VEGF (NG/L) by Visit and Sampling Time					
		GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=20)	GSK1278863 5 mg (N=19)	rhEPO (N=20)
Baseline	n Mean (SD) Median Min : Max	21 124.7 (55.38) 100.4 67.2 : 272.0	20 113.7 (67.30) 91.6 28.8 : 269.6	19 116.7 (82.58) 98.0 23.5 : 336.2	19 87.5 (46.71) 85.4 20.1 : 158.7
Week 2 4 to -8 hrs Post-Dose CFB	n Mean (SD) Median Min : Max	19 -3.0 (48.61) -6.8 -130.4 : 104.5	18 -21.1 (77.07) -4.3 -223.1 : 58.9	17 0.4 (33.05) 9.0 -72.5 : 42.1	15 -15.3 (37.77) 1.0 -83.8 : 36.0
5 to 9 Hrs Post-Dose CFB	n Mean (SD) Median Min : Max	19 -47.1 (32.45) -42.5 -122.7 : 8.7	17 -58.2 (63.22) -57.5 -216.7 : 16.2	17 -6.0 (36.51) -8.6 -62.2 : 110.0	14 -9.6 (34.35) -5.8 -65.7 : 31.5
7 to 11 hours Post-Dose CFB	n Mean (SD) Median Min : Max	19 -28.5 (45.65) -21.4 -127.3 : 79.1	18 -37.3 (64.20) -29.7 -216.5 : 54.9	17 -6.2 (36.40) -0.7 -79.4 : 41.7	14 4.7 (36.40) 11.5 -58.5 : 72.2
Week 4 Pre-Dose CFB	n Mean (SD) Median Min : Max	18 2.1 (41.39) 4.3 -118.1 : 73.4	17 2.7 (81.31) 9.3 -226.8 : 104.1	17 34.4 (44.98) 23.8 -34.1 : 123.7	17 4.5 (26.15) 3.5 -39.8 : 57.5
3 hours Post-Dose CFB	n Mean (SD) Median Min : Max	17 -21.4 (50.12) -12.6 -106.0 : 73.2	17 -4.6 (60.75) -6.2 -127.3 : 94.6	17 19.9 (79.57) 13.9 -83.1 : 297.0	16 1.2 (40.34) -0.30 -57.6 : 68.2

Pharmacokinetics Summary of Individual Steady-state Plasma GSK1278863 and Metabolite PK Parameter Estimates [Geometric mean (CV%)]						
Analyte	C_{max} (ng/mL)			AUC_{τ} (ng.hr/mL)		
	GSK1278863 0.5 mg (N=19)	GSK1278863 2 mg (N=17)	GSK1278863 5 mg (N=17)	GSK1278863 0.5 mg (N=19)	GSK1278863 2 mg (N=17)	GSK1278863 5 mg (N=17)
GSK1278863	2.82 (142)	8.43 (172)	21.4 (149)	10.7 (174)	37.7 (161)	91.8 (185)
M2	1.10 (37.8)	3.66 (71.6)	10.7 (41.4)	15.5 (43.7)	46.7 (45.8)	142 (47.8)
M3	1.38 (38.0)	4.20 (50.9)	12.6 (32.8)	23.7 (49.4)	70.2 (65.8)	202 (42.9)
M4	0.832 (36.8)	2.72 (67.7)	8.57 (62.3)	7.04 (58.4)	21.9 (51.5)	69.8 (59.4)
M5	0.358 (47.5)	1.09 (60.2)	3.09 (30.4)	6.43 (61.5)	19.1 (77.2)	55.3 (44.6)
M6	0.489 (36.3)	1.73 (66.8)	4.70 (37.0)	5.91 (55.4)	19.8 (45.3)	59.9 (41.5)
M13	0.960 (58.5)	2.59 (69.4)	9.13 (65.6)	16.2 (68.3)	45.8 (93.8)	139 (59.7)

Safety Results:				
Most Frequent Adverse Events – On-Therapy Safety Population	GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=21)	GSK1278863 5 mg (N=20)	rhEPO (N=20)

Subjects with any AE(s), n (%)	10 (48)	8 (38)	1 (5)	6 (30)
Anemia	3 (14)	1 (5)	0	0
Hemoglobin decreased	1 (5)	2 (10)	0	0
Abdominal pain	0	1 (5)	0	0
Atrial fibrillation	0	0	0	1 (5)
Blood creatine phosphokinase increased	0	1 (5)	0	0
Blood glucose decreased	0	1 (5)	0	0
Constipation	0	1 (5)	0	0
Device connection issue	1 (5)	0	0	0
Dialysis related complication	0	1 (5)	0	0
Dizziness	0	1 (5)	0	0
Dyspepsia	0	1 (5)	0	0
Electrocardiogram QT prolonged	0	0	0	1 (5)
Erysipelas	0	1 (5)	0	0
Eye pruritus	0	0	1 (5)	0
Fatigue	0	1 (5)	0	0
Gastrointestinal hemorrhage	0	1 (5)	0	0
Gastrooesophageal reflux disease	0	0	0	1 (5)
Generalized edema	1 (5)	0	0	0
Headache	0	1 (5)	0	0
Hyperkalemia	0	0	0	1 (5)
Hypertension	1 (5)	0	0	0
Hypotension	0	0	0	1 (5)
Increased appetite	1 (5)	0	0	0
Large intestine polyp	1 (5)	0	0	0
Liver function test abnormal	1 (5)	0	0	0
Muscle spasms	0	1 (5)	0	0
Nasopharyngitis	0	1 (5)	0	0
Nausea	0	1 (5)	0	0
Nightmare	1 (5)	0	0	0
Oropharyngeal pain	0	1 (5)	0	0
Panic attack	0	1 (5)	0	0
Post procedural hemorrhage	1 (5)	0	0	0
Procedural hypotension	0	0	0	1 (5)
Pulmonary edema	0	0	0	1 (5)
Seasonal allergy	0	1 (5)	0	0
Subcutaneous abscess	1 (5)	0	0	0
Urinary tract infection	1 (5)	0	0	0
Vomiting	0	1 (5)	0	0
Weight increased	1 (5)	0	0	0
Serious Adverse Events On-Therapy n (%) [n considered treatment-related] Safety Population	GSK1278863 0.5 mg (N=21)	GSK1278863 2 mg (N=21)	GSK1278863 5 mg (N=20)	rhEPO (N=20)
Gastrointestinal hemorrhage	0	1 (5)	0	0
Constipation	0	1 (5)	0	0
Pulmonary edema	0	0	0	1 (5)
Hyperkalemia	0	0	0	1 (5)
Subjects with fatal SAEs, n (%)	0	0	0	0
Subjects with Post-Therapy SAEs, n (%)				
Liver Function test abnormal	1 (5)	0	0	0
Acute respiratory failure	1 (5)	0	0	0

Conclusion:

These data inform the dose-response of GSK1278863 on Hgb and other pharmacodynamic markers in anemic HDD subjects after being switched from a stable dose of rhEPO. Switching from rhEPO to 5 mg GSK1278863 was effective in maintaining Hgb and reticulocyte production over 4 weeks; 0.5 and 2 mg resulted in mean decreases in these parameters over 4 weeks. GSK1278863 was generally well tolerated at the doses administered in the study. The most common AEs of anemia and decreased Hgb were reported for the lower GSK1278863 doses (0.5 mg and 2 mg), which were less effective at maintaining Hgb.