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:
Study Number: PHI116581
Title: A four-week Phase IIa, randomized, double-blind, placebo-controlled, parallel-group, multi-center study to evaluate the safety, efficacy and pharmacokinetics of GSK1278863 in subjects with anemia associated with chronic kidney disease who are not taking recombinant human erythropoietin and are not undergoing dialysis.
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 for correcting anemia in non-dialysis dependant (NDD) subjects with chronic kidney disease (CKD) who were not taking recombinant human erythropoietin (rhEPO). In addition, the study characterized the effect of GSK1278863 on various pharmacokinetic/pharmacodynamic (PK/PD) markers, and investigated the safety and tolerability of GSK1278863.
Phase: IIa
Study Period: 20 May 2012 – 30 May 2013
Study Design: This was a 4-week, randomized, double-blind, placebo-controlled, parallel-group, multi-center study to evaluate the safety, efficacy, and pharmacokinetics of 0.5, 2 or 5 mg GSK1278863 and placebo in subjects with anemia associated with CKD who were not taking rhEPO and who were not undergoing dialysis. The range of Hgb values for study eligibility was 8.5 to 11.0 g/dL, verified by measurements at Week -2, Week -1, and Day 1 (randomization). The study consisted of a screening phase of up to 2 weeks, a 4-week treatment phase, and a 2-week follow-up phase.
Centers: 42 centers in 3 countries: 36 in the United States, 4 in Canada, and 2 in Germany
Indication: Anemia associated with chronic kidney disease
Treatment: Study medication was supplied as film-coated tablets containing 0.5 mg, 2 mg or 5 mg of GSK1278863 or matching placebo. Subjects took 1 tablet orally in the morning of each dosing day with a glass of water (and were to be consistent in taking tablets with or without food), except when subjects were dosed at the clinic on Day 1 and at Week 4 (when blood samples were collected for pre-dose and post-dose PK/PD analyses
Objectives: The primary objective was to estimate the relationship between dose of GSK1278863 and hemoglobin (Hgb) response for correcting anemia in NDD subjects with CKD who were not taking rhEPO.
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 efficacy endpoints were: observed Hgb and change from baseline summaries over time; maximum Hgb changes over 4 weeks; number of subjects who reached protocol defined Hgb stopping criteria (i.e., Hgb drop <8 g/dL, Hgb increase to >=13 g/dL, or Hgb changed >=2 g/dL within one week); change in plasma erythropoietin (EPO); change in markers of iron metabolism and utilization (hepcidin, ferritin, transferrin, transferrin saturation, total iron, TIBC) and inflammation (high-sensitivity C-reactive protein (hsCRP)); changes in hematocrit, RBC concentration, reticulocyte concentration; plasma vascular endothelial growth factor (VEGF) concentration ; 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 modeled 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 of maximum Hgb change over 4 weeks, peak change in serum EPO concentration from baseline over 4 weeks, change from baseline at Week 4 in serum concentrations of hepcidin, ferritin, transferrin, transferrin saturation, total iron, unbound iron binding capacity, TIBC, and hsCRP were analyzed using an analysis of covariance (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, mean corpuscular hemoglobin (MCH), change from baseline at Week 1 and Week 4 for reticulocyte concentration, and change from baseline in peak serum 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 change from baseline in the laboratory, vital sign, and electrocardiogram (ECG) parameters were presented in addition to values outside the normal and clinical concern ranges.

Study Population

Inclusion Criteria: adults >=18 years of age, weighing >=45 kg with CKD stages 3/4/5 defined by estimated global filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) equation; not routinely undergoing dialysis; no current or prior rhEPO use within the past 7 weeks; had a stable Hgb concentration of 8.5 to 11.0 g/dL; vitamin B12 levels above lower limit of the reference range, folate >=2.0 mg/mL, ferritin >=40 ng/mL (absence of microcytic or hypochromic RBCs), and transferrin saturation [TSAT] within the reference range. Male subjects, and female subjects of childbearing potential, agreed to use a protocol approved contraception method from screening to completion of the Follow-up visit. Exclusion criteria included: dialysis or planned to initiate dialysis; 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); hyperparathyroidism (parathyroid hormone >=600 pg/mL); had proliferative retinopathy requiring treatment within the prior 12 months, or macular edema requiring treatment.

Number of Subjects	Placebo	GSK1278863 0.5 mg	GSK1278863 2 mg	GSK1278863 5 mg	Total
Planned, N	17	17	17	17	68
Randomized, N	19	18	18	18	73
Completed, N (%)	15 (79)	11 (61)	16 (89)	17 (94)	59 (81)
Premature Withdrawal, N (%)	4 (21)	7 (39)	2 (11)	1 (6)	14 (19)
Due to Adverse event	1 (5)	1 (6)	0	0	2 (3)
Lack of Efficacy	0	0	0	0	4 (5)
Other reasons	3 (5)	6 (6)	1 (6)	1 (6)	11 (4)
Demographics	**Placebo**	**GSK1278863 0.5 mg**	**GSK1278863 2 mg**	**GSK1278863 5 mg**	**Total**
N (ITT)	19	16	18	18	71
Females: Males	15: 4	11: 5	10: 8	15: 3	51: 20
Mean age, years (SD)	69.5 (10.77)	65.2 (11.79)	66.9 (11.45)	71.9 (11.24	68.5 (11.34)
White, N (%)	12 (63)	10 (63)	13 (67)	14 (78)	49 (68)
Stage of CKD (N %)					
3a	1 (5)	1 (6)	2 (11)	1 (6)	5 (7)
3b	4 (21)	2 (13)	3 (17)	5 (28)	14 (20
4	8 (42)	9 (56)	7(39)	8 (44)	32 (45)
5	6 (32)	4 (25)	6 (33)	4 (22)	20 (28)

Primary Efficacy Results:

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

	Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Baseline Hgb (g/dL) Mean (SD)	9.91 g/dL (0.6)	9.98 g/dL (0.6)	9.74 g/dL (0.7)	10.08 g/dL (0.7)
Modeled CFB for Hgb (g/dL) at Week 4. Mean (SD)	-0.15 g/dL(0.2)	0.13 g/dL (0.2)	0.46 g/dL (0.2)	1.01 g/dL (0.3)

Secondary Outcome Results:

		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Observed CFB for Hgb (g/dL) at Week 4' Mean (SD)		-0.23 g/dL (0.5)	-0.12 g/dL(0.5)	0.32 g/dL (0.9)	0.95 g/dL(0.7)
Max Hgb Change Over 4 weeks					
Baseline	N	19	16	18	18
	Mean (SE)	9.91 (0.13)	9.98 (0.14)	9.74 (0.16)	10.08 (0.17)

	Median Min – Max 95% CI	10.10 8.67 – 10.70 (9.63, 10.18)	9.95 8.67 – 10.87 (9.67, 10.28)	9.78 8.67- 10.90 (9.39, 10.08)9	10.18 8.23 - 10.97 (9.72, 10.43)
Max Change Over 4 Weeks	n Mean (SE) Median Min – Max 95% CI	19 0.15 (0.103) 0.10 -0.87 - 1.40 (-0.06, 0.37)	16 0.13 (0.13) 0.13 -0.80 - 1.00 (-0.14, 0.40)	18 0.49 (0.20) 0.33 -0.97 - 3.30 (0.05, 0.93)	18 1.05 (0.15) 0.97 -0.13 - 2.07 (0.74, 1.37)
Model Adjusted Max. Change Over 4 Weeks[a]	n Adjusted Mean (SE) 95% CI	19 0.15 (0.15) (-0.14, 0.45)	16 0.14 (0.16) (-0.18, 0.46)	18 0.47 (0.15) (0.17, 0.78)	18 1.07 (0.15) (0.76, 1.37)

Maximum Hgb (g/dL) Change at Any Time During the Study					
Hgb Response (g/dL)		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Decrease/increase <0.5	n (%) 95% CI	16 (84) (60.4, 96.6)	12 (75) (47.6, 92.7)	11 (61) (35.7, 82.7)	4 (22) (6.4, 47.6)
Increase ≥0.5	n (%) 95% CI	3 (16) (3.4, 39.6)	4 (25) (7.3, 52.4)	7 (39) (17.3, 64.3)	14 (78) (52.4, 93.6)
Increase ≥1.0	n (%) 95% CI	1 (5) (0.1, 26.0)	1 (6) (0.2, 30.2)	3 (17) (3.6, 41.4)	9 (50) (26.0, 74.0)
Increase ≥1.5	n (%) 95% CI	0 (0.0, 17.6)	0 (0.0, 20.6)	1 (6) (0.1, 27.3)	5 (28) (9.7, 53.5)
Increase ≥2.0	n (%) 95% CI	0 (0.0, 17.6)	0 (0.0, 20.6)	1 (6) (0.1, 27.3)	1 (6) (0.1, 27.3)

Analysis of Peak EPO Change from Baseline (U/L)					
		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Baseline	n Mean (SD) Median Min – Max	18 14.63 (7.213) 12.36 6.42 - 35.55	13 13.24 (6.003) 13.76 2.84 - 21.82	16 14.63 (11.346) 9.865 3.11 - 37.21	18 14.27 (7.977) 11.215 3.91 - 28.43
Peak EPO	n Mean (SD) Median Min – Max	18 22.70 (17.466) 16.61 9.66 - 8.55	13 15.95 (6.223) 15.59 5.92 - 26.66	17 22.66 (12.811) 22.35 10.48 - 63.50	18 36.85 (18.708) 34.35 5.34 - 69.04
Peak EPO CFB (Pre-Dose)	n Mean (SD) Median Min – Max	18 8.07 (16.448) 3.68 -2.74 - 69.68	13 2.71 (4.163) 2.56 -4.33 - 10.92	16 8.60 (12.865) 7.52 -9.27 - 41.08	18 22.57 (18.287) 18.26 -1.13 - 60.16
Model Adjusted Peak EPO CFB (Pre-Dose)	n Adjusted Mean (SE) 95% CI	18 8.21 (3.389) (1.43, 14.98)	13 2.34 (3.993) (-5.65, 10.33)	16 8.74 (3.594) (1.55, 15.93)	18 22.58 (3.39) (15.80, 29.36)

Markers of Iron Metabolism and Utilization					
Summary of Change from baseline in Hepcidin (mcg/L) by Visit					
		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)

Baseline	n Mean (SD) Median Min – Max	15 354.91 (228.049) 295.40 140.5 - 1022.4	10 289.63 (171.915) 295.00 40.6 - 542.3	15 299.49 (146.247) 349.30 88.7 - 520.0	16 304.94 (226.782) 217.40 130.9 - 994.9
Week 4	n Mean (SD) Median Min – Max	15 352.29 (293.065) 265.10 128.9 - 1308.7	10 267.47 (146.375) 324.65 30.0 - 494.9	15 222.15 (130.382) 237.30 68.5 - 532.0	16 161.84 (133.164 113.50 30.3 - 553.2
CFB at Week 4	n Mean (SD) Median Min – Max	15 -2.62 (96.176) -7.30 -137.3 - 286.3	10 -22.16 (120.138) -16.15 -222.1 - 238.8	15 -77.34 (96.843) -82.10 -281.6 - 158.8	16 -143.09 (119.617) -143.60 -441.7 - 43.8
Modelled Adjusted CFB at Week 4	n Adjusted Mean (SE) 95% CI	15 4.99 (26.563) (-48.33, 58.32)	10 -26.73 (32.385) (-91.75, 38.28)	15 -80.07 (26.425) (-133.12, -27.02)	16 -144.81 (25.574) (-196.15, -93.47)

Summary of Change from Baseline in Ferritin (UG/L) by Visit

		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Baseline	n Mean (SD) Median Min – Max	15 276.8 (159.29) 218.0 56 - 621	12 281.2 (264.63) 172.0 29 - 731	17 364.4 (267.79) 304.0 64 - 1177	17 311.2 (267.25) 197.0 73 - 1054
Week 4	n Mean (SD) Median Min – Max	15 252.5 (145.94) 233.0 34 - 534	12 245.3 (225.59) 147.5 19 - 663	17 356.2 (501.81) 221.0 39 - 2187	17 209.5 (212.03) 105.0 41 - 774
CFB at Week 4	n Mean (SD) Median Min – Max	15 -24.3 (38.61) -21.0 -93 - 45	12 -35.8 (54.68) -20.5 -174 - 23	17 -8.2 (268.77) -69.0 -162 - 1010	17 -101.8 (91.07) -99.0 -280 - 35
Modelled Adjusted CFB at Week 4	n Adjusted Mean (SE) 95% CI	15 -19.9 (39.29) (-98.6, 58.8)	12 -32.0 (43.88) (-119.9, 55.9)	17 -14.7 (37.06) (-89.0, 59.5)	17 -101.7 (36.81) (-175.4, -28.0)

Summary of Change from Baseline in Transferrin (g/L) y Visit

		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Baseline	n Mean (SD) Median Min – Max	15 1.982 (0.3089) 1.940 1.60 - 2.80	12 2.260 (0.3542) 2.290 1.69 - 3.03	17 2.055 (0.4191) 1.820 1.63 - 2.85	17 2.244 (0.4813) 2.140 1.58 - 3.14
Week 4	n Mean (SD) Median Min – Max	15 1.993 (0.2254) 2.030 1.59 - 2.32	12 2.288 (0.3210) 2.295 1.86 - 2.91	17 2.349 (0.5384) 2.320 1.62 - 3.38	17 2.632 (0.6050) 2.590 1.92 - 4.04
CFB at Week 4	n Mean (SD) Median Min – Max	15 0.011 (0.2646) 0.000 -0.51 - 0.59	12 0.028 (0.2743) 0.020 -0.35 - 0.52	17 0.294 (0.3442) 0.240 -0.37 - 0.84	17 0.388 (0.3550) 0.240 -0.05 - 1.34

Modelled Adjusted CFB at Week 4	n Adjusted Mean (SE) 95% CI	15 -0.010 (0.0826) (-0.176, 0.155)	12 0.047 (0.0917) (-0.137, 0.231)	17 0.283 (0.0766) (0.129, 0.436)	17 0.404 (0.0771) (0.250, 0.559)
Summary of Change from Baseline in Total Iron Binding Capacity (umol/L) by Visit					
		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Baseline	n Mean (SD) Median Min – Max	15 48.9 (4.42) 49.0 42 - 57	12 54.3 (8.49) 54.5 43 - 69	17 51.9 (9.76) 50.0 39 - 74	17 55.1 (9.93) 56.0 41 - 70
Week 4	n Mean (SD) Median Min – Max	15 48.4 (6.27) 47.0 37 - 60	12 54.6 (7.24) 56.0 41 - 67	17 56.9 (12.37) 54.0 41 - 85	17 63.4 (10.90) 62.0 46 - 85
CFB at Week 4	n Mean (SD) Median Min – Max	15 -0.5 (3.72) -1.0 -6 - 8	12 0.3 (6.34) -0.5 -10 - 10	17 5.1 (4.12) 5.0 -2 - 11	17 8.3 (5.54) 6.0 0 - 18
Modelled Adjusted CFB at Week 4	n Adjusted Mean (SE) 95% CI	15 -0.5 (1.32) (-3.2, 2.1)	12 0.4 (1.45) (-2.5, 3.3)	17 5.1 (1.21) (2.6, 7.5)	17 8.3 (1.23) (5.9, 10.8)
Summary of Change from Baseline in Transferrin Saturation (%) by Visit					
		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Baseline	n Mean (SD) Median Min – Max	15 23.5 (6.94 24.0 12 - 35	12 21.8 (7.47 21.5 12 - 36	17 25.5 (6.62 26.0 14 - 42	17 26.1 (7.37) 26.0 14 - 42
Week 4	n Mean (SD) Median Min – Max	15 25.0 (6.24) 23.0 18 - 38	12 18.7 (6.54 17.5 10 - 32	17 22.9 (9.04) 21.0 12 - 41	17 22.8 (9.28) 23.0 5 - 46
CFB at Week 4	n Mean (SD) Median Min – Max	15 1.5 (6.08) 1.0 -9 - 11	12 -3.1 (4.85) -4.5 -8 - 8	17 -2.6 (6.18) -3.0 -13 - 10	17 -3.4 (11.27} -3.0 -17 - 26
Modelled Adjusted CFB at Week 4	n Adjusted Mean (SE) 95% CI	15 1.1 (1.84) (-2.6, 4.8)	12 -4.3 (2.09) (-8.5, -0.1)	17 -2.1 (1.73) (-5.6, 1.4)	17 -2.6 (1.74) (-6.1, 0.9)
Summary of Change from Baseline in Total Iron (umol/L) by Visit					
		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Baseline	n Mean (SD) Median Min – Max	15 11.5 (3.54 10.0 6 - 17	12 11.4 (3.15) 12.0 6 - 16	17 12.9 (3.14) 12.0 9 - 20	17 14.2 (4.10) 15.0 8 - 22

Week 4	n Mean (SD) Median Min – Max	15 12.1 (3.06) 11.0 8 - 19	12 9.8 (3.05) 9.0 6 - 16	17 12.5 (4.23) 13.0 6 - 22	17 13.8 (4.80) 14.0 3 - 23
CFB at Week 4	n Mean (SD) Median Min – Max	15 0.6 (2.82) 1.0 -5 - 5	12 -1.7 (3.31) -2.5 -6 - 6	17 -0.4 (3.33) -1.0 -7 - 6	17 -0.4 (6.10) -1.0 -10 - 13
Modelled Adjusted CFB at Week 4	n Adjusted Mean (SE) 95% CI	15 -0.1 (0.97) (-2.0, 1.9)	12 -2.4 (1.08) (-4.5, -0.2)	17 -0.2 (0.90) (-2.0, 1.6)	17 0.6 (0.92) (-1.3, 2.4)

Summary of Change from Baseline in Unsaturated Iron Binding Capacity (umol/L) by Visit

		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Baseline	n Mean (SD) Median Min – Max	15 37.4 (4.91) 37.0 31 - 48	12 42.8 (9.26) 43.0 28 - 59	17 39.0 (9.62) 37.0 27 - 59	17 40.9 (9.34) 42.0 26 - 61
Week 4	n Mean (SD) Median Min – Max	15 36.3 (6.29) 36.0 24 - 49	12 44.8 (8.16) 46.0 28 - 54	17 44.4 (12.83) 43.0 28 - 71	17 49.6 (12.02) 47.0 25 - 67
CFB at Week 4	n Mean (SD) Median Min – Max	15 -1.1 (4.70) -2.0 -7 - 10	12 2.0 (6.22) 2.0 -8 - 11	17 5.4 (5.43) 5.0 -3 - 16	17 8.6 (7.83) 8.0 -8 - 21
Modelled Adjusted CFB at Week 4	n Adjusted Mean (SE) 95% CI	15 -1.1 (1.63) (-4.4, 2.2)	12 2.0 (1.83) (-1.6, 5.7)	17 5.4 (1.52) (2.4, 8.4)	17 8.7 (1.52) (5.6, 11.7)

Summary of Change from Baseline High Sensitivity C-Reactive Protein (mg/L) by Visit

		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Baseline	n Mean (SD) Median Min – Max	15 3.64 (3.239) 2.80 0.3 - 9.9	11 8.13 (9.956) 2.80 0.2 - 31.5	16 6.20 (12.333) 2.05 0.2 - 51.0	17 4.03 (5.081) 1.50 0..3 - 19.7
Week 4	n Mean (SD) Median Min – Max	15 3.85 (3.233) 3.50 0.5 - 11.0	12 10.83 (10.649) 7.90 0.3 - 33.3	17 4.26 (4.189) 2.40 0.2 - 13.9	17 5.79 (9.195) 2.70 0.2 - 38.6
CFB at Week 4	n Mean (SD) Median Min – Max	15 0.21 (2.212) 0.30 -2.7 - 6.6	11 0.65 (3.383) 0.10 -5.7 - 6.5	16 -2.09 (11.708) 0.10 -43.3 - 8.5	17 1.76 (9.378) 0.00 -8.2 - 37.1
Modelled Adjusted CFB at Week 4	n Adjusted Mean (SE) 95% CI	15 -0.87 (1.583) (-4.04, 2.31)	11 2.51 (1.861) (-1.22, 6.24)	16 -1.49 (1.528) (-4.56, 1.57)	17 0.94 (1.485) (-2.04, 3.92)

Other Pharmacodynamic Markers

Summary of Change from Baseline in Hematocrit (%) by Visit					
		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Baseline	n	19	16	18	18
	Mean (SD)	29.82 (2.377)	29.88 (1.931)	29.40 (2.24)	30.73 (2.563)
	Median	30.10	29.70	29.35	30.80
	Min : Max	25.6 : 34.7	26.0 : 33.4	25.7 : 32.9	23.5 : 34.2
Week 1	n	19	16	18	18
CFB	Mean (SD)	-0.15 (1.385)	-0.29 (1.976)	-0.35 (0.941)	0.39 (1.616)
	Median	0.20	-0.05	-0.25	0.50
	Min : Max	-4.2 : 1.5	-3.5 : 3.2	-1.8 : 1.7	-2.6 : 2.8
Week 2	n	17	13	16	18
CFB	Mean (SD)	0.35 (1.854)	0.11 (1.570)	0.24 (1.683)	1.64 (2.103)
	Median	0.50	0.60	0.45	1.90
	Min : Max	-2.2 :4.0	-3.0 : 3.2	-2.2 : 3.6	-2.0 : 5.1
Week 3	n	18	12	17	17
CFB	Mean (SD)	-0.24 (1.752)	-0.56 (1.148)	0.08 (1.406)	2.11 (2.257)
	Median	-0.15	-0.551	0.10	2.3
	Min : Max	-3.8 : 2.9	-2.5 : 1.4	-3.4 : 2.2	-1.8 : 6.0
Week 4	n	15	11	16	16
CFB	Mean (SD)	-0.50 (1.958)	-0.14 (1.204)	1.16 (2.566)	3.38 (2.052)
	Median	-0.05	-0.20	0.40	3.95
	Min : Max	-5.6 : 2.3	-2.2 : 2.4	-0.8 : 9.3	-0.1 : 7.9
Week 6 FU	n	16	12	16	17
CFB	Mean (SD)	-0.45 (1.874)	0.07 (1.631)	0.83 (1.224)	2.75 (2.905)
	Median	-0.80	0.20	0.90	2.40
	Min : Max	-2.7 : 3.3	-3.8 : 2.8	-1.6 :2.5	-1.3 : 11.8

Summary of Change from Baseline in Red Blood Cell Counts (10^2/L) by Visit					
		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Baseline	n	19	16	18	18
	Mean (SD)	3.21 (0.350)	3.25 (0.333)	3.13 (0.230)	3.27 (0.329)
	Median	3.20	3.20	3.10	3.30
	Min : Max	2.7 : 3.8	2.8 : 4.1	2.8 : 3.6	2.5 : 3.9
Week 1	n	19	16	18	17
CFB	Mean (SD)	-0.01 (0.137)	-0.03 (0.181)	-0.03 (0.113)	0.04 (0.162)
	Median	0.00	-0.05	0.00	0.00
	Min : Max n	-0.3 : 0.2	-0.3 : 0.3	-0.2 : 0.2	-0.3 : 0.3
Week 2	n	17	13	16	18
CFB	Mean (SD)	0.02 (0.181)	0.03 (0.160)	0.01 (0.165)	0.14 (0.225)
	Median	0.00	0.00	0.00	0.20
	Min : Max	-0.3 : 0.3	-0.3 : 0.3	-0.2 : 0.3	-0.3 : 0.5
Week 3	n	18	12	17	17
CFB	Mean (SD)	-0.03 (0.193)	-0.02 (0.136)	-0.02 (0.147)	0.16 (0.223)
	Median	0.00	-0.05	0.00	0.20
	Min : Max	-0.4 : 0.3	-0.2 : 0.2	-0.3 : 0.2	-0.2 : 0.5
Week 4	n	15	11	16	16
CFB	Mean (SD)	-0.05 (0.181)	0.01 (0.145)	0.09 (0.254)	0.33 (0.209)
	Median	0.00	0.00	0.10	0.35
	Min : Max	-0.5 : 0.2	-0.2 : 0.3	-0.2 : 0.9	0.0 : 0.9
Week 6 FU	n	16	12	16	17
CFB	Mean (SD)	-0.06 (0.182)	0.02 (0.190)	0.08 (0.106)	0.28 (0.347)
	Median	-0.10	0.00	0.10	0.20
	Min : Max	-0.3 : 0.3	-0.4 : 0.3	-0.1 : 0.3	-0.2 : 1.4

Summary of Change from Baseline in Reticulocytes (%) by Visit

		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Baseline	n	19	16	18	18
	Mean (SD)	1.85 (0.574)	1.81 (0.574)	2.11 (0.745)	1.83 (0.697)
	Median	1.80	1.65	2.25	1.85
	Min : Max	0.7 : 2.9	1.2 : 3.1	0.6 : 3.3	0.3 : 3.2
Week 1	n	19	16	18	17
CFB	Mean (SD)	0.05 (0.494)	0.24 (0.443)	0.46 (0.725)	0.95 (0.626)
	Median	0.20	0.30	0.20	0.80
	Min : Max n	-0.9 : 0.7	-0.5 : 1.0	-0.5 : 2.0	0.0 : 1.9
Week 2	n	17	13	16	18
CFB	Mean (SD)	0.01 (0.474)	0.32 (0.458)	0.12 (0.685)	0.85 (0.633)
	Median	-0.10	0.30	0.00	0.85
	Min : Max	-0.7 : 0.9	-0.4 : 1.2	-1.1 : 1.8	-0.5 : 2.2
Week 3	n	18	12	17	17
CFB	Mean (SD)	0.13 (0.479)	0.23 (0.308)	0.15 (0.634)	0.45 (0.525)
	Median	0.00	0.15	0.10	0.40
	Min : Max	-0.7 : 1.0	-0.3 : 0.8	-1.2 : 1.4	-0.8 : 1.3
Week 4	n	15	11	16	16
CFB	Mean (SD)	-0.07 (0.390)	0.11 (0.375)	-0.07 (0.660)	0.49 (532)
	Median	0.00	0.20	-0.10	0.65
	Min : Max	-0.7 : 0.6	-0.6 : 0.7	-0.9 : 1.3	-0.5 :1.2
Week 6 FU	n	16	12	16	17
CFB	Mean (SD)	-0.25 (0.418)	0.05 (0.444)	-0.49 (0.598)	-0.45 (0.516)
	Median	-0.30	0.00	-0.50	-0.30
	Min : Max	-1.1 : 0.6	-0.8 : 0.9	-1.6 : 0.7	-1.7 : 0.5

Summary of Change from Baseline in Mean Corpuscular Hemoglobin by Visit

		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Baseline,	n	19	16	18	18
	Mean (SD)	30.81 (2.393)	30.56 (2.132)	31.29 (2.086)	31.06 (1.622)
	Median	30.50	30.50	31.40	31.55
	Min – Max	24.5 - 34.5	25.5 - 33.8 16	26.8 - 34.9 18	27.3 - 33.3 18
Week 1	n	19	16	18	17
CFB	Mean (SD)	0.02 (0.558)	0.02 (0.632)	-0.02 (0.660)	0.04 (0.458)
	Median	0.00	-0.30	0.05	0.10
	Min – Max	-1.2 - 1.2 19	-0.9 – 1.2	-1.2 - 1.3	-0.9 -0.8
Week 2	n	17	13	16	18
CFB	Mean (SD)	-0.01 (0.568)	-0.06 (0.465)	0.15 (0.603)	0.04 (0.469)
	Median	0.00	-0.10	0.30	0.20
	Min – Max	-1.2 - 0.9	-1.0 - 0.8	-0.8 - 1.2	-1.0 - 0.8
Week 3	n	18	12	17	17
CFB	Mean (SD)	0.04 (0.636)	-0.09 (0.675)	0.09 (0.682)	0.15 (0.642)
	Median	0.15	-0.15	0.10	0.20
	Min – Max	-1.4 - 0.9	-1.0 - 1.0	-1.1 - 1.3	-1.0 -0.9
Week 4	N	15	11	16	16
CFB	Mean (SD)	0.21 (0.474)	-0.13 (0.608)	-0.01 (0.613)	0.06 (0.600)
	Median	0.20	-0.10	0.00	0.05
	Min – Max	-1.1 - 0.7	-1.3 - 0.7	-1.0 - 1.4	-1.5 - 0.9
Week 6 FU, n (%	n	16	12	16	17
CFB	Mean (SD)	-0.07 (0.717)	-0.27 (0.810)	0.01 (0.679)	0.05 (0.755)
	Median	0.00	-0.35	0.05	0.10
	Min – Max	-1.5 - 1.0	-1.4 - 1.4	-1.1 - 1.3	-2.2 - 1.0

Summary of Change from Baseline in Vascular endothelial growth factor (VEGF) by Visit					
		Placebo (N=19)	GSK1278863 0.5 mg (N=16)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=18)
Baseline	n Mean (SD) Median Min – Max	18 92.75 (126.451) 49.55 20.8 - 559.2	13 79.02 (60.751) 68.50 19.6 - 242.6	16 83.24 (92.070) 60.10 6.4 - 389.5	18 63.63 (32.415) 54.85 29.2 - 155.2
Peak VEGF	n Mean (SD) Median Min – Max	18 100.91 (94.534) 72.40 34.0 - 453.3	13 145.35 (189.958) 89.20 32.4 - 744.9	16 85.11 (40.924) 85.60 6.4 - 187.3	18 103.26 (67.970) 82.50 33.0 - 326.2
Peak VEGF CFB (Pre-Dose)	n Mean (SD) Median Min – Max	18 8.16 (58.489) 16.60 -157.3 - 77.8	13 66.33 (135.531) 16.80 -2.9 - 502.3	16 1.87 (89.876) 9.55 -311.7 - 98.9	18 39.63 (58.124) 16.90 -31.8 - 236.0
Model Adjusted Peak VEGF CFB (Pre-Dose)	n Adjusted Mean (SE) 95% CI	18 11.44 (19.988) (-28.54, 51.42)	13 66.19 (23.440) (19.30, 113.07)	16 2.77 (21.134) (-39.50, 45.05)	18 35.65 (20.019) (-4.39, 75.70)

Pharmacokinetics						
Summary of Individual Steady-state Plasma GSK1278863 and Metabolite PK Parameter Estimates [Geometric mean (CV%)]						
Analyte	C_{max} (ng/mL)			AUC_T (ng.hr/mL)		
	GSK1278863 0.5 mg (N=13)	GSK1278863 2 mg (N=17)	GSK1278863 5 mg (N=18)	GSK1278863 0.5 mg (N=13)	GSK1278863 2 mg (N=17)	GSK1278863 5 mg (N=18)
GSK1278863	2.68 (92.6)	12.8 (121)	35.7 (143)	10.3 (119)	51.1 (159)	148 (167)
M2	1.03 (27.9)	3.83 (61.4)	10.3 (61.1)	13.0 (38.8)	51.9 (81.3)	140 (65.4)
M3	1.23 (25.1)	4.45 (54.4)	11.8 (64.8)	17.8 (33.4)	67.1 (74.2)	175 (71.6)
M4	0.721 (29.7)	2.74 (84.7)	7.29 (116)	5.54 (60.0)	22.0 (99.0)	63.4 (105)
M5	0.296 (23.7)	1.08 (49.0)	2.81 (79.8)	4.64 (27.7)	17.3 (66.7)	43.5 (86.0)
M6	0.455 (21.9)	1.74 (56.1)	4.43 (83.1)	5.34 (36.3)	21.5 (71.4)	56.3 (85.8)

Safety Results				
Summary of On-Therapy Adverse Events by Preferred Term (Safety Population)				
	Placebo (N=18)	GSK1278863 0.5 mg (N=17)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=19)
Any Event, n (%)	9 (50)	10 (59)	5 (28)	6 (32)
Nausea	2 (11)	2 (12)	0	1 (5)
Asthenia	1 (6)	1 (6)	0	0
Dizziness	1 (6)	1 (6)	0	0
Headache	1 (6)	0	1 (6)	0
Hypertension	1 (6)	0	0	1 (5)
Muscle spasms	0	1 (6)	0	1 (5)
Urinary tract infection	1 (6)	1 (6)	0	0
Vomiting	0	1 (6)	0	1 (5)

Safety Results				
Summary of On-Therapy Adverse Events by Preferred Term (Safety Population)				
Abdominal pain	0	1 (6)	0	0
Abdominal pain upper	1 (6)	0	0	0
Anaemia	0	0	1 (6)	0
Appendicitis	1 (6)	0	0	0
Azotaemia	0	0	0	1 (5)
Blood creatine phosphokinase increased	0	1 (6)	0	0
Conduction disorder	0	1 (6)	0	0
Constipation	0	1 (6)	0	0
Dehydration	1 (6)	0	0	0
Dermatitis	0	1 (6)	0	0
Diarrhoea	0	0	1 (6)	0
Disturbance in attention	0	0	1 (6)	0
Dysgeusia	0	0	1 (6)	0
Dyspnoea	1 (6)	0	0	0
Ecchymosis	1 (6)	0	0	0
Fatigue	0	0	1 (6)	0
Fluid overload	0	0	1 (6)	0
Gastrooesophageal reflux disease	0	1 (6)	0	0
Haematoma	0	0	1 (6)	0
Humerus fracture	0	0	1 (6)	0
Hypoglycaemia	0	0	1 (6)	0
Musculoskeletal pain	1 (6)	0	0	0
Pain in extremity	1 (6)	0	0	0
Myalgia	0	0	1 (6)	0
Nasopharyngitis	0	0	0	1 (5)
Oedema peripheral	1 (6)	0	0	0
Pancreatitis acute	0	0	1 (6)	0
Periodontitis	0	1 (6)	0	0
Periorbital oedema	0	1 (6)	0	0
Rectal haemorrhage	0	1 (6)	0	0
Renal failure acute	0	0	1 (6)	0
Road traffic accident	0	1 (6)	0	0
Sinusitis	0	0	0	1 (5)
Stomatitis	1 (6)	0	0	0
Tooth abscess	0	1 (6)	0	0
Upper respiratory tract infection	0	1 (6)	0	0

Serious Adverse Events - On-Therapy n (%) [n considered by the investigator to be related to study medication]				
	Placebo (N=18)	GSK1278863 0.5 mg (N=17)	GSK1278863 2 mg (N=18)	GSK1278863 5 mg (N=19)
Subjects with non-fatal SAEs n (%)	1 (6)0	0	2 (11)	1 (5)
Appendicitis	1 (6)	0	0	0
Azotaemia/Uremia	0	0	0	1 (5)
Hypoglycemia	0	0	1 (6)	0
Pancreatitis acute	0	0	1 (6)	0
Renal failure acute	0		1 (6)	0
Subjects with fatal SAEs n (%)	0	0	0	0

Conclusion:

GSK1278863 produced dose dependent increases in Hgb concentrations in subjects not currently using rhEPO. Changes in Hgb were accompanied by dose-dependent increases in reticulocytes, RBCs, and hematocrit. GSK1278863 was generally well tolerated at the doses administered in the study.