SUPPLEMENTAL MATERIAL

Statistical Model for Hemoglobin Changes

A random coefficient mixed effects linear regression model was used to derive the primary efficacy endpoint, modeled change in hemoglobin from baseline over 4 weeks of treatment, for each trial. This model included fixed effects for hemoglobin baseline, treatment assignment, and treatment by day interaction, with the intercept and slope treated as random effects.

Estimated individual hemoglobin changes from this model were taken forward into the models described below to explore the dose-response relationship across the GSK1278863 dose range studied. This did not include the rhEPO comparator arm for the HDD study.

For the Non-Dialysis Study

4-parameter Bayesian E_{max} model with the following form:

$$\Delta\text{hemoglobin} = E_0 + \frac{(E_{max} - E_0)}{1 + (ED_{50} / \text{dose})^{Gamma}} + \epsilon$$

Where:

- Δhemoglobin is the modeled change in hemoglobin over time from the mixed-effects regression analysis
- E_0 is the placebo response
- E_{max} is the maximum response
- Gamma is the slope parameter

- ED_{50} is the dose that attains the intermediate response (ie, where $(E_0+E_{max})/2$ is attained)
- ε is a normally distributed random error with mean zero and variance of 1/τ.

Posterior estimates (mean, standard deviation [SD], median, Markov chain Monte Carlo (MCMC) error, and 95% confidence interval [CI]) were calculated for the model parameters E_{max}, E_0, ED_{50}, and gamma. The estimated E_{max} dose-response curve with a 95% CI was graphically displayed by overlaying on the observed data.

Prior distributions for the E_{max} parameters were determined *a priori* taking into account the findings from a previous Phase 2a study (NCT01047397), with stronger confidence in the prior distributions for the placebo response (E_0) and maximum response (E_{max}). However, for the dose that attains the intermediate response (ED_{50}) and the slope parameter (gamma), the greater uncertainty was reflected in the prior distributions:

E_{max} Model Parameter	**Bayesian Prior**
E_0 (response at dose zero)	~normal (-0.5, 0.5)
E_{max} (maximum effect)	~normal (3.0, 0.4)
Gamma (slope parameter)	~uniform (0.5, 5.0)
ED_{50} (dose that attains the intermediate response)	~uniform (0.1, 7.5)
Prior for individual subject variability around mean hemoglobin slope ($\tau = 1/SD^2$)	~gamma (1,1)

Convergence of the chains to the posterior distribution was assessed using the Gelman-Rubin statistic, the MCMC error of the chains, autocorrelation plots, and visual inspection of the trace plots of the 4 chains to ensure proper chain mixing after the application of thinning.

From this estimation model, the following key inferences were determined:

- Estimation of the minimal effective dose (MED), defined as the smallest dose to achieve a placebo-corrected change in hemoglobin of 0.5 g/dL over 4 weeks
- Estimation of the target dose, defined as the dose to achieve a placebo-corrected change in hemoglobin of 1 g/dL over 4 weeks
- Identification of the effective dose range, defined as the range of doses in which the placebo-corrected hemoglobin change was between 0.5 and 1.5 g/dL over 4 weeks
- Estimation of the maximum acceptable dose, defined as the smallest dose beyond which the placebo-corrected hemoglobin change exceeds 2.5 g/dL over 4 weeks

The statistical model poorly estimated hemoglobin effects for doses of GSK1278863 above 10 mg (doses that were not studied in either trial).

To assess the robustness of the primary efficacy conclusions, sensitivity analyses were performed using noninformative priors. A 3-parameter E_{max} model also was investigated. The main model presented was determined to be the best fit.

For the HDD Study

Linear dose-response analysis and explored using the model:

$$\Delta Hgb_{\mathrm{ij}} = \alpha + \beta Dose_i + \epsilon_{ij}$$

where:

- ΔHgb is the modeled change in hemoglobin over time from the mixed-effects regression analysisα is the intercept and β is the slope parameter

From this estimated model, the following key inferences were determined:

- Estimation of the GSK1278863 dose that achieved a stable hemoglobin (predicted mean 0 g/dL change from baseline) over 4 weeks
- Estimation of the GSK1278863 dose that achieved a predicted mean 1 g/dL increase over 4 weeks

All data up until investigational product discontinuation were included in the ITT analysis. Baseline hemoglobin values were calculated as the average of the 3 values during the screening period.

Mean, SD, 95% CI, and other summary statistics of each endpoint were calculated for each treatment group. Skewed data were log-transformed, with the percentage change from baseline presented. Analyses were performed using SAS® software version 9.1.3 or higher (SAS Institute Inc., Cary, NC, USA). WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) was used to determine the Bayesian E_{max} model in the non-dialysis study.

Efficacy Endpoints

Hemoglobin

Non-Dialysis Study

Dose-response analyses suggest that, on average, doses of GSK1278863 between 1.5 and 8.6 mg would be effective in achieving placebo-corrected changes in hemoglobin of 0.5 to 1.5 g/dL over 4 weeks, with the dose that is predicted to increase hemoglobin by 1 g/dL over 4 weeks being 3.9 mg (credible interval 2.9-5.0 mg). The smallest dose predicted to achieve a placebo corrected change of 0.5 g/dL over 4 weeks was 1.5 mg (95% credible interval 0.8 to 2.4 mg). Because the dose-response model was a poor predictor of efficacy at higher doses than those included in this trial, the smallest dose beyond which the placebo corrected change exceeds 2.0 g/dL over 4 weeks was estimated with a wide 95% credible interval (21-1420 mg) and the maximum acceptable dose was not able to be estimated. Increases from baseline started to emerge after 1 week of treatment (**Figure 1**) with the 5-mg GSK1278863 dose, and 50% of subjects in this treatment group achieved a hemoglobin increase ≥1 g/dL over 4 weeks.

Four subjects reached the pre-specified hemoglobin stopping criteria during the trial based on point-of-care testing and were withdrawn from the study: one subject receiving placebo and one subject receiving 2 mg GSK1278863 had a hemoglobin decrease of more than 2 g/dL in one week, and one subject receiving 0.5 mg GSK1278863 and one subject receiving 2 mg GSK1278863 had a hemoglobin increase of more than 2 g/dL over 1 week. No subjects had a hemoglobin concentration that exceeded 13 g/dL at any time during the trial as measured by the point-of-care hemoglobin device.

HDD Study

Dose-response analyses suggest, the dose of GSK1278863 estimated to achieve a stable hemoglobin level over 4 weeks is 4.6 mg (95% CI: 3.8-6.0) and the estimated dose that achieved a mean 1 g/dL increase in hemoglobin over 4 weeks was 7.8 mg (95% CI: 6.3-10.7).

Hemoglobin variability: During the treatment period, 37% of subjects receiving 5 mg GSK1278863 had hemoglobin values that remained within ±0.5 g/dL of baseline hemoglobin, as compared with 35% of subjects treated with rhEPO.

A total of 5 subjects reached protocol-defined hemoglobin stopping criteria based on point-of-care hemoglobin testing. Three subjects treated with GSK1278863 reached the protocol-defined hemoglobin stopping criteria during the study treatment period and were withdrawn (one subject at each dose of GSK1278863: the subjects in the 0.5 and 2 mg GSK1278863 groups had hemoglobin concentrations of <8.0 g/dL; the subject in the 5 mg GSK1278863 group had a hemoglobin increase of ≥2 g/dL from previous visit). Two subjects reached the hemoglobin stopping criteria at the end of the study treatment period (week 4 visit); one subject each in the 2 and 5 mg arms had a hemoglobin increase of ≥2 g/dL from previous visit and hemoglobin concentration of ≥13 g/L, respectively.

Hematocrit, Red Blood Cell Count, and Reticulocyte Percentage

Mean baseline and Week 4 change from baseline in hematocrit, red blood cell count, and reticulocyte percentage are depicted in **Supplementary Table 1**.

High-Sensitivity C-Reactive Protein

The effect of GSK1278863 on hsCRP was measured in this study because of data that suggest that PHIs may have anti-inflammatory properties.[1] Mean baseline values of hsCRP, were >3 mg/L, a level indicative of high risk for cardiovascular disease, in all treatment groups; this finding is not surprising due to the inflammation associated with CKD.[2] There was no effect of GSK1278863 on levels of hsCRP; however, there was considerable variability in this measurement and insufficient sample size for a robust assessment (**Supplemental Table 3**).

Lipid Parameters

Lipid parameters were measured in the non-fasting state. Over the 4 weeks of treatment with GSK1278863, dose-dependent decreases in total cholesterol, HDL-c and directly-measured LDL-c were observed, although variability was large (**Supplemental Table 4)**.

Serious Adverse Events

A summary of the SAEs in the trial are depicted in **Supplemental Table 2**.

Pharmacokinetic Endpoints

Plasma samples for population pharmacokinetic (PK) analysis were collected over 2 scheduled visits (week 2: 4-8 h post dose, then 1, 2, and 3 h after this first sample; week 4: pre dose, 1, 2 and 3 h post dose). Thus, in the HDD study, all samples were

collected shortly before, during or after a dialysis session. GSK1278863 and 6 metabolites (M2, M3, M4, M5, M6, and M13)[3] were assayed by validated LC/MS/MS methods. The lower and upper limits of quantification of the assay were 0.1 and 100 ng/mL, and all analytes had acceptable inter- and intra-assay precision (all coefficients of variation were <10%) and accuracy (all within 11.7% of nominal concentration). Plasma PK data from these two studies were combined with PK data from two other GSK1278863 studies: a prior study in subjects with CKD (4 PK samples collected up to 6 h post-dose on 3 occasions; NCT01047397),[4] and a Phase 1 study in healthy subjects (full PK profile up to 24 h post dose; NCT01319006). Forty eight subjects in the non-dialysis study and 53 subjects in the HDD study contributed at least one PK sample to this analysis. The overall population pharmacokinetic dataset included 1555 samples from 181 subjects.

Population PK analyses were conducted using NONMEM 7.2 (ICON Development Solutions, Ellicott City, MD). The PK of GSK1278863 following oral administration was adequately described by a linear two-compartment model with first-order absorption, absorption lag-time, and first-order elimination. Apparent central volume of distribution was estimated to be 8.94, 23.6, and 39.6 L in healthy subjects, subjects with CKD not on dialysis (Stage 3/4/5) and subjects with CKD on dialysis (Stage 5D), respectively. The absorption rate constant of GSK1278873 was also slightly slower in subjects receiving doses up to 5 mg versus those receiving doses >5 mg (0.562 h^{-1} versus 0.915 h^{-1}). These observed differences may be biased because of the different pharmacokinetic sampling schemes employed in the studies included in this analysis; however, at this stage this is not considered clinically meaningful. The different

sampling schemes employed at the week 2 and week 4 visit in the two presented studies can also bias the exposure parameter estimates; therefore, exposure parameters were calculated without regard to visit-to-visit variability. The apparent oral clearance of GSK1278863 was consistent with prior observations and was not changed in subjects with CKD or those receiving dialysis.

The parent GSK1278863 PK model was then used as an input into the metabolite model. Each metabolite was modeled as 1 compartment with first-order input (equivalent to the clearance of parent GSK1278863) and output. As the fraction of the GSK1278863 dose converted to each metabolite is unknown, the apparent clearance and volume of each parameter were estimated. Clearance of metabolites was reduced by 70%-90% in subjects with CKD. Body weight was also a weak predictor of the clearance of metabolite M13, but is not considered to be clinically relevant. As the start and stop of times of dialysis were not collected in the HDD study, the impact of that procedure on metabolite exposure could not be adequately assessed in this analysis.

A summary of derived GSK1278863 and metabolite exposure parameters from both studies is shown in **Supplemental Table 5**.

Plasma GSK1278863 and metabolite exposure increased in proportion to dose and overall exhibited moderate variability between subjects (coefficients of variation for GSK1278863 PK parameters ranging from 27.3% to 98.2%).

Population pharmacokinetic analysis did not identify any clinically relevant covariates of GSK1278863 exposure, and pharmacokinetic parameters were generally consistent with observations from healthy subjects. Compared to healthy subjects, the exposure of GSK1278863 metabolites was increased in subjects with CKD, although

their contribution to the overall pharmacodynamic effect of GSK1278863 is unknown. Between-subject pharmacokinetic parameter variability was higher in these studies than in previous studies in healthy subjects,[3] which is likely a result of subject heterogeneity in the current study as well as the limited pharmacokinetic sampling scheme employed.

Clinical Investigative Sites

The following investigators participated in the studies and screened at least one subject:

Non-Dialysis Study

PI Last Name	PI First Name	Institution Name	Town/City	State/County	Country
Aggarwal	Naresh	Aggarwal and Associates Ltd	Brampton	Ontario	Canada
Scott-Douglas	Nairne	Sheldon M. Chumir Health Center	Calgary	Alberta	Canada
Muirhead	Norman	London Health Sciences Centre	London	Ontario	Canada
Goluch	Richard	Health Sciences North	Sudbury	Ontario	Canada
Brunkhorst	Reinhard	KRH Klinikum Lehrte	Lehrte	Niedersachsen	Germany
Kraatz	Uwe	Praxis Dr. med. Uwe Kraatz	Demmin	Mecklenburg-Vorpommern	Germany
Bernardo	Marializa	Southwest Houston Research	Houston	Texas	United States
Diamond	Susan	San Antonio Kidney Disease Center Physicians Group, P.L.L.C.	San Antonio	Texas	United States
El-Shahawy	Mohamed	Academic Medical Research Institute	Los Angeles	California	United States
Hole	Susan	Riverside Clinical Research	Edgewater	Florida	United States
Mai	Christopher	Century Clinical Research, Inc	Daytona Beach	Florida	United States
Pish	Richard	Pish Medical Associates	Uniontown	Pennsylvania	United States
Zeig	Steven	Pines Clinical Research Inc.	Pembroke Pines	Florida	United States
Betts	Judith	Research Management, Inc.	Austin	Texas	United States

PI Last Name	PI First Name	Institution Name	Town/City	State/County	Country
Chuang	Peale	Metrolina Nephrology Associates, P.A.	Charlotte	North Carolina	United States
Khwaja	Samia	North America Research Institute	Azusa	California	United States
Nguyen	Peter	Tarrant Nephrology Associates	Arlington	Texas	United States
Provenzano	Robert	Renaissance Renal Research Institute, LLC	Detroit	Michigan	United States
Shafik	Shawkat	Corsicana Medical Research, PLLC	Corsicana	Texas	United States
Martinez	Gilbert	Catalina Research Institute LLC	Chino	California	United States
Kaupke	Charles	Nephrology Specialist Medical Group	Orange	California	United States
Aiello	Joseph	Mountain Kidney and Hypertension Associates	Asheville	North Carolina	United States
Jamal	Aamir	San Dimas Dialysis Center	San Dimas	California	United States
Mordujovich	Jorge	Kidney and Hypertension Specialists	Miami	Florida	United States
Trespalacios	Fernando	Nephrology Associates of South Miami (SMO)	Miami	Florida	United States
Ralph	Ronald	Research Across America	Houston	Texas	United States
Deodhar	Hem	Northwest Renal Clinic	Portland	Oregon	United States
Munjal	Sandeep	East Coast Institute for Research	Jacksonville	Florida	United States
Sprague	Stuart	Northshore University Health System	Evanston	Illinois	United States
Hamerski	Douglas	Trial Management Associates LLC	Wilmington	North Carolina	United States
Mahmood	Khalid	Independent Clinical Research	Greenville	Texas	United States
Lee	Joseph	Apex Research of Riverside	Riverside	California	United States
Kaveh	Kianoosh	Coastal Nephrology Associates	Port Charlotte	Florida	United States
Murillo	Abel	AMPM Research Clinic	Miami	Florida	United States
Kopyt	Nelson	Northeast Clinical Research Centers, Inc.	Bethlehem	Pennsylvania	United States
Greenwood	Gregory	Brookview Hills Research Associates, LLC	Winston Salem	North Carolina	United States
Narayanan	Mohanram	Scott and White Healthcare	Temple	Texas	United States

PI Last Name	PI First Name	Institution Name	Town/City	State/County	Country
Sligh	Teresa	Providence Clinical Research	North Hollywood	California	United States
Vasin	Dmitri	Renal Remission and Hypertension Clinic	Silverdale	Washington	United States
Lakshminarayanan	Suresh	Discovery Medical Research Group	Ocala	Florida	United States
Patak	Ramachandra	Infosphere Clinical Research	West Hills	California	United States
Remler	Robert	Fellows Research Alliance, Inc	Savannah	Georgia	United States

HDD Study

PI Last Name	PI First Name	Institution Name	Town/City	State/County	Country
Scott-Douglas	Nairne	Sheldon M. Chumir Health Center	Calgary	Alberta	Canada
McMahon	Alan	University of Alberta Hospital	Edmonton	Alberta	Canada
Soroka	Steven	QEII Health Sciences Centre	Halifax	Nova Scotia	Canada
Muirhead	Norman	London Health Sciences Centre	London	Ontario	Canada
Goluch	Richard	Health Sciences North	Sudbury	Ontario	Canada
Aarup	Michael	Odense Universitesafdeling	Odense		Denmark
Oestergaard	Ove Vyff	Roskilde Sygehus	Roskilde		Denmark
Christensen	Jeppe Hagstrup	Aalborg Sygehus Syd	Aalborg		Denmark
Dragoun	Gert-Peter	KfH Kuratorium f. Dialyse u. Nierentransplantation	Aschaffenburg	Bayern	Germany
Sommerer	Claudia	Nierenzentrum Heidelberg	Heidelberg	Baden-Wuerttemberg	Germany
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Kraatz	Uwe	KfH Kuratorium f. Dialyse u. Nierentransplantation	Demmin	Mecklenburg-Vorpommern	Germany
Bækken	Morten	Oslo Universitetssykehus, Ullevål	Oslo		Norway
Holdaas	Hallvard	Oslo Universitetssykehus, Rikshospitalet	Oslo		Norway
Fellström	Bengt	Akademiska Sjukhuset	UPPSALA		Sweden

PI Last Name	PI First Name	Institution Name	Town/City	State/County	Country
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El-Shahawy	Mohamed	Academic Medical Research Institute	Los Angeles	California	United States
Zeig	Steven	Pines Clinical Research Inc.	Pembroke Pines	Florida	United States
Chuang	Peale	Metrolina Nephrology Associates, P.A.	Charlotte	North Carolina	United States
Khwaja	Samia	North America Research Institute	Lynwood	California	United States
Nguyen	Peter	Tarrant Nephrology Associates	Arlington	Texas	United States
Provenzano	Robert	Renaissance Renal Research Institute, LLC	Detroit	Michigan	United States
Ghantous	Walid	North Suburban Nephrology, LLC	Gurnee	Illinois	United States
Jamal	Aamir	North America Research Institute	Azusa	California	United States
Mordujovich	Jorge	Kidney and Hypertension Specialists	Miami	Florida	United States
Darwish	Riad	American Institute of Research	Whittier	California	United States
Hiremath	Anand	Nephrology Hypertension Clinic	Southgate	Michigan	United States
Lee	Joseph	Apex Research of Riverside	Riverside	California	United States
Martinez	Carlos	Martinez Renal Physicians of Georgia	Macon	Georgia	United States
Patak	Ramachandra	Infosphere Clinical Research	West Hills	California	United States
Roer	David	Davita Greater Waterbury	Waterbury	Connecticut	United States
Wright	Steven	US Renal Care	Pine Bluff	Arkansas	United States
Rastogi	Anjay	UCLA Century City Dialysis	Loa Angeles	California	United States
Olivero	Juan	DaVita Med Dialysis	Houstan	Texas	United States
Mahmood	Khalid	Independent Clinical Research	Greenville	Texas	United States
Singh	Bhupinder	Southwest Kidney Institute	Tempe	Arizona	United States
Bloomfield	Rachael	South Florida Nephrology Group	Coral Springs	Florida	United States

PI Last Name	PI First Name	Institution Name	Town/City	State/County	Country
Singh	Harmeet	Western Nephrology and Metabolic Bone Disease, PC	Arvada	Colorado	United States
Shapiro	Warren		Brooklyn	New York	United States
Chang	Ingrid		Westminster	Colorado	United States
Murillo	Abel	AMPM Research Clinic	Miami	Florida	United States
Kathresal	Amarnath	Durham Nephrology Associates	Durham	North Carolina	United States
Narayanan	Mohanram	Killeen Dialysis Center	killeen	Texas	United States
Symonian	Margarita	Margarita Symonian MD, Inc.	Los Angeles	California	United States
Lehrner	Lawrence	Kidney Specialists of Southern Nevada	Las Vegas	Nevada	United States
Acharya	Muralidhar	Outcomes Research International,Inc	Spring Hill	Florida	United States
Sholer	Chris	Chris Sholer,MD,PC	Oklahoma City	Oklahoma	United States

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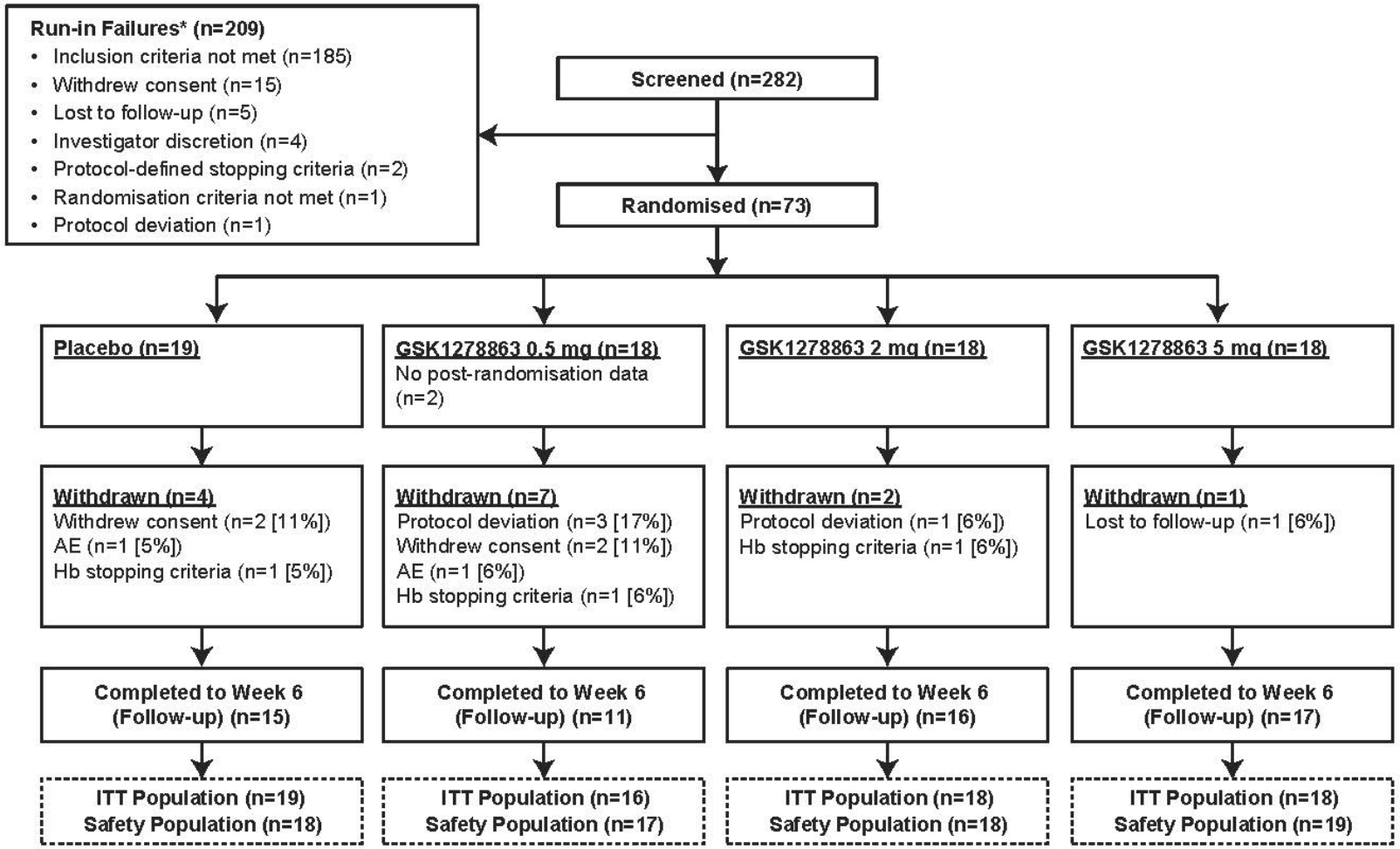
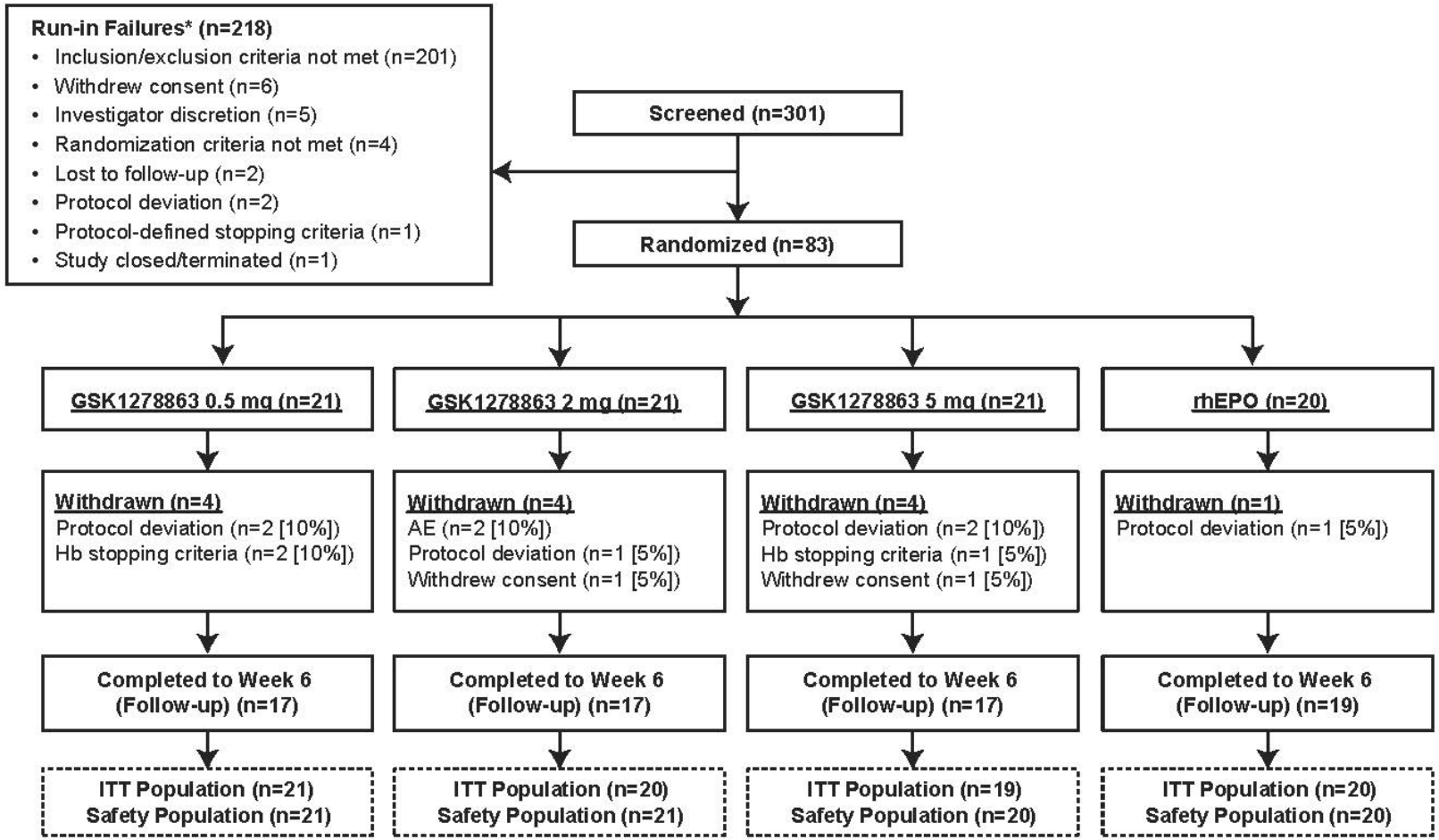
2. Niihata K, Tomosugi N, Uehata T, et al: Serum hepcidin-25 levels predict the progression of renal anemia in patients with non-dialysis chronic kidney disease. Nephrol Dial Transplant 27: 4378. 2012
3. Johnson BM, Stier BA, Caltabiano S: Effect of food and gemfibrozil on the pharmacokinetics of the novel prolyl hydroxylase inhibitor GSK1278863. *Clin Pharmacol Drug Devel* 3**:** 109-117, 2013
4. Brigandi RA, Johnson B, Oei C, Westerman ME, Olbina G, Kumar S, Russ SF: Induction of erythropoiesis in anemic patients by prolylhydroxylase inhibitor in a repeat dose, randomized placebo controlled trial [abstract]. *J Am Soc Nephrol* 23(suppl): 662A, 2012

Supplemental Figure 1. CONSORT flow diagram of patient enrolment and progress through the (**A**) non-dialysis study and (**B**) HDD study.

A.



B.



*Subjects may have more than one reason for failure

Supplemental Table 1. Baseline and mean changes in hematocrit, red blood cell count and reticulocytes after 4 weeks of treatment with GSK1278863

Analyte	Parameter	Non-Dialysis Study				HDD Study			
			GSK1278863				GSK1278863		
		Placebo (N=19)	0.5 mg (N=16)	2 mg (N=18)	5 mg (N=18)	rhEPO (N=20)	0.5 mg (N=21)	2 mg (N=20)	5 mg (N=19)
Hematocrit (%)	n	19	16	18	18	20	21	20	19
	Baseline	29.8±2.4	29.9±1.9	29.4±2.2	30.7±2.6	32.5±1.6	32.2±2.5	32.3±2.5	33.1±2.4
	n	15	11	16	16	19	18	18	15
	CFB at 4 weeks	-0.5±2.0	-0.1±1.2	1.2±2.6	3.4±2.1	-0.2±2.9	-3.2±2.7	-2.6±3.0	-0.3±2.0
Red blood cell count (10^{12}/L)	n	19	16	18	18	20	21	20	19
	Baseline	3.2±0.4	3.3±0.3	3.1±0.2	3.3±0.3	3.4±0.3	3.3±0.3	3.4±0.5	3.4±0.3
	n	15	11	16	16	19	18	18	15
	CFB at 4 weeks	-0.05±0.2	0.01±0.1	0.09±0.3	0.33±0.2	-0.03±0.3	-0.3±0.3	-0.3±0.3	-0.03±0.2
Reticulocytes (%)	n	19	16	18	18	20	21	20	19
	Baseline	1.9±0.6	1.8±0.6	2.1±0.7	1.8±0.7	2.0±0.7	1.6±0.8	1.7±0.6	1.8±0.6
	n	15	11	16	16	19	18	18	15
	CFB at 4 weeks	-0.07±0.4	0.11±0.4	-0.07±0.7	0.49±0.5	-0.3±0.7	-0.4±1.0	-0.3±0.5	-3.0±0.7
Reticulocytes (TI/L)	n	19	16	18	18	20	21	20	19
	Baseline	0.06±0.02	0.06±0.02	0.06±0.02	0.06±0.03	0.07±0.02	0.05±0.02	0.06±0.02	0.06±0.02
	n	15	11	16	16	19	18	18	15
	CFB at 4 weeks	0.0±0.01	0.0±0.01	0.0±0.02	0.02±0.02	-0.01±0.02	-0.01±0.03	-0.01±0.02	-0.002±0.02

Analysis based on the ITT population. Unless otherwise indicated, all values are mean±SD.

rhEPO, recombinant human erythropoietin.

Supplemental Table 2. Summary of Serious Adverse Events

Non-Dialysis study	**HDD study**
Placebo	**rhEPO group**
Appendicitis	Pulmonary edema
	Hyperkalemia
0.5 mg GSK1278863 group	**0.5 mg GSK1278863 group**
	Liver function test abnormal*
	Acute respiratory failure*
2 mg GSK1278863 group	**2 mg GSK1278863 group**
Hypoglycemia	Gastrointestinal hemorrhage
Pancreatitis acute Renal failure acute	Constipation
5 mg GSK1278863 group	
Azotemia	

*SAEs occurred post-therapy

Supplemental Table 3. Baseline and changes in hsCRP after 4 weeks of treatment with GSK1278863

		Non-Dialysis Study				HDD Study			
			GSK1278863				GSK1278863		
Analyte	Parameter	Placebo (N=19)	0.5 mg (N=16)	2 mg (N=18)	5 mg (N=18)	rhEPO (N=20)	0.5 mg (N=21)	2 mg (N=20)	5 mg (N=19)
hsCRP (mg/L)	n	19	15	17	18	20	21	20	19
	Baseline	4.6±5.5	7.9±9.2	6.0±12.0	3.8±5.0	7.8±16.5	9.5±11.7	11.2±21.4	7.5±8.5
	n	15	11	16	17	19	19	18	17
	CFB at 4 weeks	0.2±2.2	0.7±3.4	-2.1±11.7	1.8±9.4	-2.3±18.7	-0.7±7.0	-5.6±19.8	-1.0±5.4

Analysis based on the ITT population. Unless otherwise indicated, all values are mean ± SD.

CFB, change from baseline; hsCRP, high-sensitivity C-reactive protein; rhEPO, recombinant human erythropoietin.

Supplemental Table 4. Baseline and percent changes in lipid parameters after 4 weeks of treatment with GSK1278863

		Non-Dialysis Study				HDD Study			
			GSK1278863				GSK1278863		
Analyte	Parameter	Placebo (N=19)	0.5 mg (N=16)	2 mg (N=18)	5 mg (N=18)	rhEPO (N=20)	0.5 mg (N=21)	2 mg (N=20)	5 mg (N=19)
Total cholesterol (mmol/L)	n	19	16	17	18	20	20	20	19
	Baseline	4.1	4.5	3.9	4.2	3.6	3.5	3.9	3.7
	95% CI	3.7, 4.6	3.8, 5.2	3.4, 4.6	3.6, 5.0	3.2, 4.1	3.1, 4.0	3.4, 4.5	3.3, 4.2
	n	15	12	16	17	19	18	18	17
	CFB at 4 weeks	-3.8%	-3.8%	-6.2%	-7.4%	2.3%	-2.8%	-4.8%	-2.9%
	95% CI	-7.7, 0.4	-9.5, 2.3	-13.4, 1.6	-16.0, 2.1	-3.3, 8.3	-8.3, 3.0	-9.7, 0.4	-8.1, 2.7
LDL-c (mmol/L)	n	19	16	17	18	20	21	20	19
	Baseline	2.1	2.3	2.0	2.2	1.8	1.8	1.9	1.9
	95% CI	1.8, 2.5	1.9, 2.8	1.6, 2.4	1.8, 2.7	1.5, 2.2	1.5, 2.1	1.6, 2.3	1.6, 2.3
	n	15	12	16	17	19	19	18	17
	CFB at 4 weeks	-3.3%	-2.9%	-7.5%	-13.9%	-0.9%	-7.6%	-12.0%	-8.1%
	95% CI	-10.7, 4.8	-10.3, 5.2	-16.4, 2.3	-22.8, -3.9	-11.3, 10.8	-15.9, 1.6	-19.1, -4.2	-16.7, 1.3
HDL-c (mmol/L)	n	19	16	17	18	20	20	20	19
	Baseline	1.2	1.2	1.2	1.3	1.0	1.1	1.1	1.0
	95% CI	1.1, 1.4	1.0, 1.4	1.0, 1.5	1.1, 1.7	0.9, 1.2	0.9, 1.3	0.9, 1.3	0.9, 1.2
	n	15	12	16	17	19	18	18	17
	CFB at 4 weeks	0.0%	0.08%	-1.3%	-15.6%	-0.1%	-1.2%	1.1%	-8.4%
	95% CI	-6.1, 6.5	-7.2, 7.9	-7.7, 5.6	-24.7, -5.3	-6.3, 6.5	-5.1, 2.8	-5.9, 8.7	-15.7, -0.4

Analysis based on the ITT population. The analyzed data have been log-transformed. Unless otherwise indicated, all values are geometric mean (95% CI).

CFB, percent change from baseline; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; rhEPO, recombinant human erythropoietin.

Supplemental Table 5. Geometric mean (CV%) plasma GSK1278863 and metabolite exposure parameters in subjects with CKD

Analyte	Non-Dialysis Study						HDD Study					
	C_{max} (ng/mL)			AUC_{0-24h} (ng•h/mL)			C_{max} (ng/mL)			AUC_{0-24h} (ng•h/mL)		
	0.5 mg (N=13)	2 mg (N=17)	5 mg (N=18)	0.5 mg (N=13)	2 mg (N=17)	5 mg (N=18)	0.5 mg (N=19)	2 mg (N=17)	5 mg (N=17)	0.5 mg (N=19)	2 mg (N=17)	5 mg (N=17)
GSK1278863	3.50 (56.6)	15.5 (65.7)	41.3 (98.2)	16.1 (27.3)	69.3 (28.7)	179 (42.2)	3.61 (75.4)	10.9 (105)	29.6 (94)	16.5 (32)	61.7 (41.3)	164 (36.2)
M2	1.03 (27.9)	3.83 (61.4)	10.3 (61.1)	13.0 (38.8)	51.9 (81.3)	140 (65.4)	1.10 (37.8)	3.66 (71.6)	10.7 (41.4)	15.5 (43.7)	46.7 (45.8)	142 (47.8)
M3	1.23 (25.1)	4.45 (54.4)	11.8 (64.8)	17.8 (33.4)	67.1 (74.2)	175 (71.6)	1.38 (38.0)	4.20 (50.9)	12.6 (32.8)	23.7 (49.4)	70.2 (65.8)	202 (42.9)
M4	0.721 (29.7)	2.74 (84.7)	7.29 (116)	5.54 (60.0)	22.0 (99.0)	63.4 (105)	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	0.296 (23.7)	1.08 (49.0)	2.81 (79.8)	4.64 (27.7)	17.3 (66.7)	43.5 (86.0)	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	0.455 (21.9)	1.74 (56.1)	4.43 (83.1)	5.34 (36.3)	21.5 (71.4)	56.3 (85.8)	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	0.731 (92.6)	2.95 (58.5)	7.71 (155)	12.3 (87.6)	49.7 (65.6)	135 (154)	0.960 (58.5)	2.59 (69.4)	9.13 (65.6)	16.2 (68.3)	45.8 (93.8)	139 (59.7)

AUC_{0-24h}, area under the plasma concentration-time curve from zero to 24 hours; C_{max}, maximum plasma concentration; CV%, coefficient of variation.