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Title:	Clinical Pharmacology Reporting and Analysis Plan for a repeat-dose, open-label, parallel-group study to assess the pharmacokinetics of GSK1278863 and metabolites in subjects with End Stage Renal Disease undergoing peritoneal dialysis.

Compound Number: GSK1278863

Effective Date: 14-SEP-2017

Description:

The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in the Clinical Pharmacology Study Report for Protocol 200942. This study is intended to characterize the pharmacokinetics of GSK1278863 and its metabolites in subjects with end stage renal disease (ESRD) undergoing peritoneal dialysis. This document will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

Subject: GSK1278863, Prolyl hydroxylase inhibitor, Anemia, Chronic kidney disease, peritoneal dialysis, erythropoiesis stimulating agents, analysed in, pharmacokinetics

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
ANOVA	Analysis of Variance
APD	Ambulatory Peritoneal Dialysis
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC (0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
%AUCex	Percentage of AUC (0-∞) obtained by extrapolation
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
AUC (0-τ)	Area under the concentration-time curve over the dosing interval
BMI	Body mass index
BP	Blood pressure
BPM	Beat Per Minute
BQL	Below the quantification limit
BUN	Blood urea nitrogen
CAPD	Continuous Ambulatory Peritoneal Dialysis
CBC	Complete blood count
Cmax	Maximum observed concentration
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IU	International Unit
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
MRT	Mean residence time
MSDS	Material Safety Data Sheet
msec	Milliseconds
NQ	Non-quantifiable concentration measured as below LLQ
PD	Pharmacodynamic
PGx	Pharmacogenetics
PK	Pharmacokinetic
PSRI	Periodic Safety Reports for Investigators
QC	Quality control
QD	Once daily
RAP	Reporting and Analysis Plan
t OR tlast	Time of last observed quantifiable concentration
t½	Terminal phase half-life
τ	Dosing interval
tlag	Lag time before observation of drug concentrations in sampled matrix
tmax	Time of occurrence of Cmax

ULN	Upper limit of normal
WBC	White blood cells

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Pharmacology Study Report for Protocol 200942:

Revision Chronology: Protocol		
2013N179529_00	2014-APR-11	Original
2013N179529_01	2014-JUN-06	Amendment No. 1
2013N179529_02	2014-JUN-24	Amendment No. 2
2013N179529_03	2014-JUL-01	Amendment No. 3
2013N179529_04	2014-DEC-12	Amendment No. 4
2013N179529_05	2015-SEP-10	Amendment No. 5
2013N179529_06	2016-JUN-20	Amendment No. 6

All decisions regarding final analysis, as defined in this RAP document, have been made prior to Database Freeze (unblinding) of the study data.

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. Study Objective(s)

2.1.1. Primary Objective(s)

Objectives	Endpoints
Primary	
Characterize the steady-state PK of GSK1278863 and metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13) in ESRD subjects undergoing peritoneal dialysis	• [AUC(0-τ), AUC (0-∞)] (Day 1 only), and Cmax of GSK1278863 and metabolites on Day 1 and Day 14
Secondary	
Evaluate the safety and tolerability of GSK1278863 in ESRD subjects undergoing peritoneal dialysis	• Subject incidence of treatment emergent adverse events, including clinically-significant changes in physical exams, laboratory safety tests, ECG and vital signs
Characterize the peritoneal dialysis clearance of GSK1278863 and metabolites in ESRD subjects undergoing peritoneal dialysis	• Peritoneal dialysis clearance, tmax and t½ of GSK1278863 and metabolites on Day 1 and Day 14 • Accumulation ratio and time invariance ratio (as data permit) of GSK1278863 and metabolites
Characterize the plasma profile of erythropoietin and hepcidin after repeat dose administration of GSK1278863 in ESRD subjects undergoing peritoneal dialysis	• Erythropoietin and hepcidin plasma concentrations
Exploratory	
Characterize the plasma protein binding of steady-state GSK1278863 and select metabolites in ESRD subjects undergoing peritoneal dialysis	• Steady-state GSK1278863 and metabolite unbound concentration and free fraction
Characterize the effect of different peritoneal dialysis solutions on GSK1278863 and metabolites in ESRD subjects undergoing peritoneal dialysis	• Descriptive summary of GSK1278863 and metabolite PK by different peritoneal dialysis solutions utilized

3. STUDY DESIGN

This is a repeat-dose, open label, 2 cohort study to assess the pharmacokinetics of GSK1278863 and metabolites in ESRD subjects undergoing peritoneal dialysis. GSK1278863 (5 mg) will be orally administered once daily for 14 days to approximately 12 ESRD subjects;

- Cohort 1 will enrol subjects on continuous ambulatory peritoneal dialysis (CAPD) to complete all dosing and critical assessments
- Cohort 2 will enrol subjects on automated peritoneal dialysis (APD) to complete all dosing and critical assessments.

Further details about the study design can be found in Section 3 of the protocol.

4. PLANNED ANALYSES

4.1. Interim Analyses

- Informal PK reviews will be conducted throughout the study to assist Phase III development of the compound

4.2. Final Analyses

The final planned analyses will be performed after all subjects have completed the study and after database freeze. See Section *8* to Section 10 for all final planned analyses for this study.

5. ANALYSIS POPULATIONS

All Screened Population

The "All Screened" population will be defined as all subjects screened.

Enrolled Population

All participants who were enrolled for the trial and for whom a record exists on the study database.

All Subjects Population
Any subject enrolled into the study who receives at least one dose of study medication will be included in the 'All Subjects' Population. This will be the population used for the study population and safety analyses.

Pharmacokinetic Population

The 'PK Population' is defined as subjects in the 'All Subjects' population for whom a pharmacokinetic sample was obtained and analysed. This will be the population used for the Pharmacokinetic displays.

6. HYPOTHESES AND TREATMENT COMPARISONS

Precision Estimation

This study is designed to estimate pharmacokinetic endpoints of GSK1278863 and metabolites in ESRD patients undergoing peritoneal dialysis following repeat administration of 5 mg once daily GSK1278863.

There will be two cohorts of subjects in this study: subjects with CAPD and subjects with APD.

No formal statistical hypotheses will be tested. An estimation approach will be used to evaluate the comparisons of interest, with point estimates and associated 90% confidence intervals presented to provide a range of plausible values for the comparisons.

Table 1 Treatment and Other Sub-Group Descriptions for Data Displays

Randomisation		Final Data Display (i.e. HARP / other)
Treatment	**Cohort Description**	**Cohort**
5 mg GSK1278863	Continuous Ambulatory Peritoneal Dialysis	CAPD
	Automated Peritoneal Dialysis	APD

7. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

7.1. Reporting Conventions

- All data displays will be presented according to the Integrated Data Standards Library (IDSL) reporting standards, where applicable. In general, data will be listed by cohort, subject, and time point and summarized by cohort (i.e. by CAPD, APD and combined) and time point

- Analyses will be performed using the 9.1.3 version of the SAS System or higher (SAS is a registered trademark of the SAS Institute Inc., Cary, NC, USA). Programs will be imported into HARP and the final output will be produced by running drivers in HARP.

- Data collected at unplanned (i.e. unscheduled) time points will not be included in the summaries by visit unless otherwise stated. Unscheduled or unplanned readings will be presented in the listings and they will be included when determining worst-case flagging for post-baseline summaries.

- In all data displays, planned and actual relative times will be relative to the study drug dosing time of the relevant dosing session.

- Planned times relative to study drug dosing will be used in all summary tables and summary (mean and median) figures.

- Actual times relative to study drug will be used in all listings and individual PK figures.

- Refer to IDSL standards (when applicable) for decimal place conventions. Raw data will generally be presented to the same number of decimal places as it was collected.

- All data will be reported according to the actual treatment the subject received. Any departures from the planned treatment according to the randomization schedule will be documented in the report.

- All observations that occurred prior to dosing will be considered as part of the pre-dose period. All observations that occur during dosing will be attributed to the subject's treatment. Observations occurring after 28 days after the last dose of study medication will not be recorded in the database.

- Deviations from the analyses in the RAP will be identified in the final clinical pharmacology study report.

7.2. Data Management

Data Type	Source	Format of Data	Planned Date of Final File[1]	Responsibility
Safety	SDTM datasets	CDISC	DBF	CPDS
Biomarker	External CRO	CSV file	DBF+X[4] days	CPDS
SDTM PC	PK concentration data merged with SI PK	CDISC	DBF + X Days	SDTM Conversion Service (SCS)
Winnonlin file created from ADPC (PK Conc)	Analysis Dataset for PK Concentrations	CSV file	SDTM PC + X[4]Days	QSI (Prog)
PK Parameter	Winnonlin-posted to HARP by CPMS[3]	CSV file	PK Conc Winnonlin + X[4] days[2]	CPMS
SDTM PP	PK parameter data	CDISC	PK Parameter Winnonlin + X[4] days[2]	SDTM Conversion Service (SCS)

1. This is for study teams to determine upfront if there is a possibility of not meeting the completion of the CPSR within 6 months of LSLV (i.e. novel data that may not be available until several months after LSLV).
2. Provided source data is clean.
3. PK concentration data is released via SMS2000 by DMPK and the SI PK dataset contains date/times and PK sample ID.
4. Standard timelines are not followed for this study.

7.3. Premature Withdrawal and Missing Data

All subjects who withdraw prematurely from the study/study drug will be documented and the reason for their withdrawal recorded in the final Clinical Pharmacology Study Report (CPSR). All available data from subjects who withdraw will be listed and all available planned data will be included in the summaries according to the populations defined in Section 5.

In the event that the study is prematurely discontinued, all available data will be listed and a review carried out by the study team to assess which statistical analyses are still considered appropriate.

7.4. Baseline Definition

The following table indicates the baseline day to be used in any change from baseline listings / summaries / graphical presentations or as a covariate in a statistical analysis:

Parameter	**Baseline Days Collected**			**Baseline To Be Used in Analysis / Summaries**
	Screening	**Day -1**	**Day 1 Predose**	
Safety:				
ECG	X	X		Day -1
Vital Signs	X	X		Day -1
Lab	X	X		Day -1
EPO, Hepcidin			X	Day 1 Predose

.

7.5. Derived and Transformed Data

7.5.1. Demographic and Population parameters

7.5.1.1. Study Day

Study day will be calculated as number of days from baseline date, as outlined below:

Scenario	**Study Day**
reference date is missing	study day = missing
reference date < IP start date	study day = reference date – IP start date
reference date ≥ IP start date	study day = reference date – (IP start date + 1)

7.5.1.2. Date of Birth

Note that only the year of birth has been captured, so all dates of birth are 30th June XXXX, where XXXX is the year of birth.

7.5.1.3. Age

Age is calculated based on screening date, using date of birth, truncated to integer value. Note that only the year of birth has been collected where the day and month would be 30th June for all patients. Therefore, the derivation of age will be approximate.

The derivation of age will be footnoted on appropriate displays.

7.5.1.4. Body Mass Index (BMI)

Body Mass Index (BMI) is calculated as follows:

BMI = weight in kg / (height in cm)^2

7.5.1.5. Exposure

Exposure is calculated as follows:

Study Drug Exposure (days) = (Treatment Stop Date – Treatment Start Date) + 1

7.5.2. Safety Parameters

7.5.2.1. Adverse Events

Note that the database has been designed such that AE Onset date is missing, unknown or complete; a partial/incomplete AE onset date will be considered as missing.

AE

AE Onset Time since First Dose	= AE Onset Date – Treatment Start Date (if treatment start date > AE onset date) = AE Onset Date – Treatment Start Date + 1 (if treatment start date <= AE onset date) = missing otherwise
AE Duration (in days)	= AE Resolution Date – AE Onset Date + 1
AE is "On Treatment"	if the AE onset date is on or after the treatment start date and on or before the treatment stop date
AE is "Post-Treatment"	if the AE onset date is after the treatment stop date
AE is considered drug-related	if the relationship is marked 'Yes' on the case report form, or the value is missing

7.5.3. Change from Baseline

The change from baseline will be calculated by subtracting the baseline values from the individual post-randomisation values. If either the baseline or post-randomisation value is missing, the change from baseline is set to missing as well.

7.5.4. Pharmacokinetic Parameters

For the purposes of calculating summary statistics and for statistical analysis, all PK parameters with the exception of tmax will be $\log_e$ transformed.

Between subject coefficient of variation CV_b (%) will be calculated according to the following methods:

Untransformed Data : 100 * (SD/Mean) where SD is the standard deviation of the untransformed data

Transformed Data : SQRT(exp(SD^2-1)) * 100where SD is the standard deviation of the $\log_e$-transformed data.

7.5.5. Multiple Measurements at One Timepoint

Where multiple measurements are recorded for a particular time point, the mean of the measurements will be calculated and used in any derivation of summary statistics. However, all available data will be listed.

Where more than the specified number of measurements has been taken, the most recently recorded values will be used in the derivation of the appropriate summary measure (i.e. mean or maximum).

7.6. Values of Potential Clinical Importance

The following tables display the ranges to be used for flagging values of potential clinical importance for various parameters. These values will be flagged on the listings.

Laboratory Values of Potential Clinical Importance (Renal Failure)

7.6.1. Laboratory Values

Laboratory Parameter	Units	Clinical Concern Range	
		Low Flag	High Flag
Albumin	g/L	< 30 g/L	>55 g/L
Aspartate Aminotransferase	IU/L		≥3x ULRR
Alanine Aminotransferase	IU/L		≥3x ULRR
Bilirubin (total and direct/indirect)	μmol/L		≥2x ULRR
Calcium	mmol/L	> 0.5 mmol/L below LLRR	> 0.25 mmol/L above ULRR
Glucose, fasting	mmol/L	<3.9	>22
Sodium	mmol/L	<130	>150

Laboratory Parameter	Units	Clinical Concern Range	
		Low Flag	High Flag
Total CO2	mmol/L	<20	>32
GGT	IU/L		>=2ULRR
Alkaline phosphatase	IU/L		>=3xULRR
Uric Acid	Mg/dL		>6.0 mg/dL
Total Protein	IU/L	<LLRR	>15 g/L bove ULRR
Potassium (serum)	mmol/L	> 0.5 mmol/L below LLRR	> 1.0 mmol/L above ULRR

Laboratory Parameter	Units	Clinical Concern Range	
		Low Flag (< x)	High Flag (>x)
Hemoglobin	g/dL	< 7.5	>=13.0
Platelet Count	GI/L	< 80x GI/L	> 500x GI/L
WBC Count	GI/L	> 1x GI/L below LLRR	>5x GI/L above ULRR
Neutrophils	GI/L	< 0.5x LLRR	
Lymphocytes	GI/L	< 0.5x LLRR	

Laboratory Parameter	Units	Clinical Concern Range	
		Low Flag (< x)	High Flag (>x)
Ferritin	ng/mL		> 1200
TSAT	%	<15	>40

7.6.2. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	≤85	≥180
Diastolic Blood Pressure	mmHg	≤45	≥110
Heart Rate	bpm	≤40	≥110

Notes:

- At visits where BP and HR are assessed in triplicate, the average of the 3 values will be used to assess PCI criteria.
- For subjects who undergo in-clinic dialysis, the post-dialysis BP and HR values will be used to assess PCI criteria, unless otherwise specified.

7.6.3. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute QTc interval	msec		>480 if with bundle branch block
Change from Baseline			
QTcB or QTcF	msec		>60 msec

8. STUDY POPULATION

It was initially expected that 30 subjects (15 in each cohort) would be needed to be recruited in order to ensure that at least 12 subjects (6 in each cohort) completed the trial. However, during the informal review of the available PK data it was determined that there were no clinically-significant differences in PK between the CAPD/APD and CKD populations, therefore the planned number of subjects was reduced to enrol 7 subjects and 5 subjects completed the study in order to minimize unnecessary additional subject exposure.

Study population data will be summarised by, or under the direct auspices of, Clinical Statistics, GlaxoSmithKline.

The precise format and content of Study Population tables and listings are shown in Section 14.1.1 and Section 14.1.5 of the RAP.

The tables will use the “All Subjects” population unless otherwise specified.

8.1. Subject Disposition and Demographics

A listing of subject withdrawals will include all subjects who prematurely discontinued from the study. This listing will include the discontinuation information for each subject, if there are any, including dates of discontinuation and reason for premature discontinuation. The number of subjects who completed, withdrew, and reasons for withdrawal will be tabulated.

A listing indicating whether a subject was included in each of the analysis populations will be prepared. The number of subjects included in each analysis population will be tabulated.

Demographic and racial data will be summarized using the "All Subjects" population.

8.2. Protocol Deviations

As outlined in the protocol deviation plan the protocol deviations will be discussed and reviewed by the study team. The frequency of the review may be amended dependent on the outcome of the initial reviews. Any protocol deviations identified will be entered into InForm eCRF. Prior to each review the DQL will run the protocol deviation check log and protocol deviation log report in InForm, discrepancies will be resolved and the report issued to the reviewing study team.

All protocol deviations that are data based will be listed.

8.3. Concomitant Medications

All medications will be coded using the GSK Drug dictionary. Medications will be classified into preferred term and body system, using the GSK-Drug Anatomical Therapeutic Clinical (ATC) classification. ATC level 1 (the body system) will be shown. Medications will be sorted in descending order of total incidence across treatment groups for the ATC level 1 and in descending order of total incidence for the preferred term within each ATC level.

Medications will be defined as follows, where it should be noted that a medication can be counted in more than one phase:

Prior	- any medication taken up to, but not including, the start date of study medication (pre-treatment phase). Therefore, prior medications have stopped prior to the subject taking study medication.
Concomitant	- if a medication is started or stopped on the same day of taking the first or last dose of randomised investigational product then this will be considered a concomitant medication (on-treatment phase) - any medication started before last day in the study and the drug stop date is either missing or on or after treatment start date - any medication with start date missing yet the stop date is on or after treatment start date - if both start and stop dates are missing the drug is specifically indicated as continuing in the trial.
Post study	- any drug with start date on or after last day in the study will be considered post-study drug. This will not be summarized with concomitant drugs but will be included in data listing.

In situations where the concomitant medication status of the drug cannot be determined, available relevant information will be reviewed on a case-by-case basis to determine the status whether it should be considered 'concomitant' or 'post-study' by Clinical; the decision of the clinical group will be considered final. However, if such determination cannot be made unambiguously, the medication will be considered concomitant.

Concurrent medications will be listed, and summarized by generic term, if more than 20 concomitant medications were used.

9. SAFETY ANALYSES

Safety data will be summarised and listed by, or under the direct auspices of Clinical Statistics, GlaxoSmithKline.

The precise format and content of Safety tables, ICH and Other listings are shown in Section 14.1.2, Section 14.1.5 and Section 14.1.6 of the RAP.

The tables will use the "All Subjects" population unless otherwise specified.

9.1. Extent of Exposure

A listing of exposure data will be a by-subject listing including the cohort, treatment administered with the dates and times of treatment administration.

9.2. Adverse Events

All adverse events (AEs) will be coded and classified according to system organ class, high level term, and preferred term using GSK MedDRA. All AEs will be listed. A listing of subject numbers for individual AEs will also be prepared. A summary, overall and by treatment, of the number and percent of subjects reporting each event at least once will be generated for all AEs and also for drug-related AEs. A listing of the relationship of AE body systems, group terms and verbatim text will also be produced.

9.3. Deaths and Serious Adverse Events

In addition to the listing described above, deaths and serious AEs (SAEs), if they occur, will also be listed and summarized separately.

9.4. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

If any subject withdraws due to an AE, then a listing and a summary by treatment will be provided for these subject(s).

9.5. Clinical Laboratory Evaluations

A listing for hematology and clinical chemistry values of potential clinical importance as described in Section 7.6, will be produced where applicable.

For hematology and clinical chemistry data, descriptive summaries for actual values by time point will be produced. A summary of urinalysis dipstick data and a listing of urinalysis data will be produced.

9.6. Vital Signs and Body Weight

Listing of vital signs values of potential clinical importance as described in Section 7.6, will be produced where applicable. Descriptive summaries for absolute and change from baseline values for vital signs by time point will be produced.

9.7. Electrocardiograms

Descriptive summaries for absolute and change from baseline values of ECG values by time point will be produced.

ECG findings will be summarized with the highest (worst) severity across replicated assessments at the specified time point used.

ECG abnormalities of clinical significance, if they occur, will be listed for each subject.

10. PHARMACOKINETIC ANALYSES

The reconciliation of the PK Case Report Form (CRF) and SMS2000 data will be performed by, or under the direct auspices of, Clinical Pharmacology Data Sciences (CPDS), GlaxoSmithKline.

The merge of PK concentration data, randomisation and CRF data will be performed by, or under the direct auspices of, QSI (Programmer), GlaxoSmithKline.

Derivation of pharmacokinetic parameters will be performed by, or under the direct auspices of, Clinical Pharmacology Modelling and Simulation (CPMS), GlaxoSmithKline.

Statistical analysis of pharmacokinetic parameters will be performed by, or under the direct auspices of, Clinical Statistics, GlaxoSmithKline.

The precise format and content of PK tables, figures, and listings are shown in Section 14.1.3 and Section 14.1.6 of the RAP.

10.1. Drug Concentration Measures

Concentrations of GSK1278863 and its metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13)) in plasma will be listed and summarized by cohort (i.e., CAPD, APD and both combined) and nominal time. Standard summary statistics will be calculated (i.e. mean, standard deviation, median, minimum and maximum). Refer to the PK Guidance document, GUI_51487 (3.0), for more information regarding the treatment of plasma concentrations below the assay's lower limit of quantification (NQ).
Individual plasma concentration-time profiles and median/mean profiles by treatment cohort will be plotted. Each of the figures will contain one plot on the untransformed scale (i.e. a linear plot) and one plot on the log transformed scale (i.e. log-linear plot). See Section 14.1.3 and Section 14.1.5 Pharmacokinetic Source Figures and Tables for details.

GSK1278863 and metabolite protein binding (as a percentage) will be presented in tabular form and will be summarized descriptively. Metabolite-to-parent exposure ratios (corrected for molecular weight) will also be calculated and summarized descriptively.

Volume of drained dialysate plus concentrations and amounts of GSK1278863 and its metabolites (GSK2391220(M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6), GSK2531401 (M13)) in the dialysate will be listed and summarized by cohort (i.e., CAPD, APD and both combined).

10.2. Deriving and Summarizing Pharmacokinetic Parameters

From the plasma concentration-time data of parent GSK1278863 and metabolites (GSK2391220 (M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6) and GSK2531401 (M13)), the following pharmacokinetic parameters will be determined, as data permit:

Day 1: Maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve AUC(0-τ) and AUC(0-∞), and apparent terminal phase half-life (t½).

Day 14: Cmax, tmax, AUC(0-τ), and apparent terminal phase half-life (t½). AUC(0-∞), AUC(0-τ), and Cmax following single (Day 1) and repeat doses (Day 14) will be used for determination of accumulation and time-invariance ratios.

Day 12 to 15: Trough concentration (Ctau, or Cτ) samples collected on Days 12 to 15 will be used to assess attainment of steady state.

- Note, to comply with CDISC reporting requirements, the following parameters also will be determined:
    - Tlast
    - Where t½ and/or AUC(0-∞) have been derived the following parameters should also be included in the PKPAR file: No_points_lambda_z, Lambda_z_lower, Lambda_z_upper, Tlast
    - If partial areas have been calculated, the following parameters should also be reported (if not included as above): No_points_lambda_z, Lambda_z_lower, Lambda_z_upper

Other Plasma PK Analyses: GSK1278863 and select metabolite (GSK2487818 (M4), GSK2506102 (M5)) unbound concentration and free fraction (as a percentage) will be presented in tabular form and will be summarized descriptively. Metabolite-to-parent exposure ratios (corrected for molecular weight) will also be calculated and summarized descriptively.

- **Percent protein bound will be calculated using the formula:**

  % Bound = (Concentration in plasma – Concentration in ultrafitrate) * 100 / Concentration in plasma

- **% Metabolite to parent ratios:** (GSK2391220(M2), GSK2506104 (M3), GSK2487818 (M4), GSK2506102 (M5), GSK2531398 (M6) and GSK2531401 (M13)) (metabolites, M) to GSK1278863 (parent) AUC and Cmax ratios will be determined (as a percentage, including a correction for molecular weight, Mr), for example:

  M : GSK1278863 % = 100* ($AUC_M/AUC_{GSK1278863}$) * ($Mr_{GSK1278863}/Mr_M$)

  Parameters to be used in this calculation are:

  Day 1: Cmax, AUC(0-τ), AUC(0-∞)

Day 14: Cmax, AUC(0-τ)

- Molecular weights for compounds are:

Compound	Molecular Weight (g/mol)
GSK1278863	393.442
GSK2391220 (M2)	425.442
GSK2506104 (M3)	425.442
GSK2487818 (M4)	425.442
GSK2506102 (M5)	425.442
GSK2531398 (M6)	425.442
GSK2531401 (M13)	441.442

- **Percent drug related marterial (%DRM):** will be determined for parent as well as each metabolite, where the denominator is the sum of the exposures of all analytes. Where all these AUCs are corrected for molecular weight (Mr).

  Example:
  $\%DRM_{GSK1278863} = 100* AUC_{GSK1278863} / (AUC_{GSK1278863}+AUC_{M2}+AUC_{M3}+AUC_{M4}+AUC_{M5}+AUC_{M6}+AUC_{M13})$.

  Parameters to be used in this calculation are:

  Day 1: AUC(0-τ), AUC(0-∞)

  Day 14: AUC(0-τ)

- Peritoneal dialysis clearance of GSK1278863 and metabolites will be calculated from Day 14 dialysate excretion data as total amount of analyte excreted over 24 h divided by plasma AUC(0-τ).

CLd = Ae (0-τ) / AUC(0-τ)

where Ae is the amount of analyte excreted in dialysate over the 24 h dialysate collection period

Ae = total dialysate volume * dialysate concentration

All the derived parameters described above will be listed. For each of these parameters, except t_{max}, the following summary statistics will be calculated for each cohort (CAPD,APD and combined) as well as different peritoneal dialysis solution (number of categories to be determined) : median, maximum, minimum, arithmetic mean, standard deviation, coefficient of variation, geometric mean, 95% confidence interval for the

geometric mean and standard deviation of logarithmically transformed data. For t_{max}, median, maximum, minimum, arithmetic mean and standard deviation will be calculated. The first point, last point and number of points used in the determination of λ_z will be included on the listing of the derived parameters.

10.3. Statistical Analyses

Descriptive statistics (n, arithmetic mean and associated 95% confidence interval, standard deviation, minimum, median, maximum) will be calculated for all pharmacokinetic endpoints of GSK1278863 and metabolites by Cohort. In addition geometric means, associated 90% CIs, and estimates of between-subject CVs (CVb (%)), will be calculated for each Cohort where

Geometric mean=exp (mean on $\log_e$ scale)

CVb (%)=SQRT(exp(SD**2)-1)x100, where SD is the standard deviation of the $\log_e$-transformed data.

Steady State Assessment

Trough concentration (Cτ) samples collected on the specified days (Days 12, 13, 14, and the 24 h post-dose sample on Day 14) will be used to assess attainment of steady state. Individual trough concentration data Cτ will be plotted and listed. Cτ will be summarized by day and cohort, and the mean and median plots will be provided.

Steady state will be assessed separately for GSK1278863 and metabolites in each cohort.

A linear mixed effects ANOVA model will be used to evaluate steady state for GSK1278863 and each metabolite. The dependent variable will be log-transformed Predose (trough) concentrations (Cτ) on Days 12 to 15. Independent variables in the model include day (as a continuous variable) as a fixed effect and subject as a random effect.

Assessment of plasma GSK1278863 and metabolites steady state will be assessed by evaluating the estimated slope for the day parameter and associated 90% CI for both the cohorts combined.. A steady state attainment is defined as the 90% confidence interval of the slope including 0.

Secondary Comparisons:

Assessment of Accumulation

To estimate the extent of accumulation for GSK1278863 and metabolites after repeat dosing, the observed accumulation ratio R0 will be determined.

$$R_0 = \frac{AUC(0-\tau)_{ss}}{AUC(0-\tau)}$$

Where AUC(0-τ)ss is AUC from time zero to t h under steady state and AUC (0 -τ) is AUC from time zero to dosing interval at Day 1.
To evaluate the accumulation ratio, statistical analysis of GSK1278863 and metabolite PK data for each cohort will be performed separately after a log transformation of the data.

A mixed effect model will be fitted with day (single and repeat dose), as fixed effects and subject as a random effect. Day 14 will be compared to Day 1 in order to estimate the accumulation ratios, Ro= (AUC (0- τ, Day14): AUC (0- τ, Day1). The ratios will be calculated by back-transforming the difference between the LS means.
Using the pooled estimate of variance, 90% confidence intervals will be calculated for the primary comparisons, and back-transformed to the original scale.

Assessment of Time Invariance
To evaluate the time invariance ratio, statistical analysis of (AUC (0-∞) Day 1) and AUC (0- τ) (Day14), of GSK1278863 and metabolites for each cohort will be performed separately after a log transformation of the data.

A mixed effect model will be fitted with day as a fixed effect and subject as a random effect. Day 14 AUC (0- τ) will be compared to Day 1 AUC (0-∞) in order to estimate the time invariance ratios, RS= AUC (0- τ, Day 14): AUC (0-∞, Day 1). The ratios will be calculated by back-transforming the difference between the LS means.

Using the pooled estimate of variance, 90% confidence intervals will be calculated for the primary comparisons, and back-transformed to the original scale.

11. PHARMACODYNAMIC/BIOMARKER ANALYSES

Plasma erythropoietin and hepcidin concentrations will be presented in graphical and/or tabular form and will be summarized descriptively. The concentration values will be listed by cohort, subject, and time point and will be summarized by cohort and time point.

12. PHARMACOGENETIC ANALYSIS

Samples will be collected and stored. No prospective analyses will be performed.

13. REFERENCES

GlaxoSmithKline Document Number 2013N179529_03 Study ID 200942. A repeat-dose, open-label, parallel-group study to assess the pharmacokinetics of GSK1278863 and metabolites in subjects with End Stage Renal Disease undergoing peritoneal dialysis. (Effective date: 01-JUL-2014)

Schuirmann DJ. 1987. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability, J Pharmacokinetic and Biopharm, 15, 657-680.

Steinijans VW, Diletti, E. Statistical Analysis of Bioavailability Studies: Parametric and Nonparametric Confidence Intervals. Eur J Clin Pharmacol, 1983;24:127-136.

14. ATTACHMENTS

14.1. Table of Contents for Data Display Specifications

For the Clinical Pharmacology Study Report the following section numbering will apply:

Section 8: Study Population

Section 9: Safety

Section 10: Pharmacokinetic

Section 11: Pharmacodynamic / Biomarker

Section 12: Pharmacogenetics Analysis

Listed below are the planned figures, tables and listings to be produced for inclusion in the 200942 clinical study report:

IDSL standard displays beginning with “CP_” are specific to Clinical Pharmacology and can be found in the IDSL database under “Supporting Documentation -> TST use of IDSL Core Choices -> ClinPharm -> All -> Clin Pharm Options for Statistical Displays”.

14.1.1. Study Population

Table No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
9.1	All Subjects	ES1a	Summary of Subject Disposition	By Cohorts and both combined	QSI (Prog)	SAC
9.2	All Subjects	DM1	Summary of Demographic Characteristics	1. By Cohorts and both combined 2.Add BMI, Weight ,Height,	QSI (Prog)	SAC
9.3	All Subjects	DM5	Summary of Race and Racial Combinations	By Cohorts and both combined	QSI (Prog)	SAC
9.4	All Subjects	DM6	Summary of Race and Racial Combinations Details	By Cohorts and both combined	QSI (Prog)	SAC
9.5	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID	By Cohorts and both combined	QSI (Prog)	SAC
9.6	Enrolled	DM11	Summary of Age Ranges	By Cohorts and both combined	QSI (Prog)	SAC

14.1.2. Safety Tables

Tables

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
10.1	All Subjects	CP_AE1p	Summary of All Adverse Events	By Cohorts and both combined	QSI (Prog)	SAC
10.2	All Subjects	CP_AE1p	Summary of Drug-Related Adverse Events	By Cohorts and both combined	QSI (Prog)	SAC
10.3	All Subjects	CP_AE1p	Summary of Serious Adverse Events	By Cohorts and both combined	QSI (Prog)	SAC
10.4	All Subjects	CP_AE1p	Summary of AEs Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study	By Cohorts and both combined	QSI (Prog)	SAC
10.5	All Subjects	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	By Cohorts and both combined	QSI (Prog)	SAC
10.6	All Subjects	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	By Cohorts and both combined	QSI (Prog)	SAC
10.7	All Subjects	LB1	Summary of Haematology Laboratory Values	By Cohorts and both combined	QSI (Prog)	SAC
10.8	All Subjects	LB1	Summary of Change from Baseline in Haematology Laboratory Values	By Cohorts and both combined	QSI (Prog)	SAC
10.9	All Subjects	LB1	Summary of Chemistry Laboratory Values	By Cohorts and both combined	QSI (Prog)	SAC

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
10.10	All Subjects	LB1	Summary of Change from Baseline in Chemistry Laboratory Values	By Cohorts and both combined	QSI (Prog)	SAC
10.11	All Subjects	EG1	Summary of ECG Findings	By Cohorts and both combined description	QSI (Prog)	SAC
10.11	All Subjects	EG2	Summary of ECG Values	By Cohorts and both combined	QSI (Prog)	SAC
10.12	All Subjects	EG2	Summary of Change from Baseline in ECG Values	By Cohorts and both combined	QSI (Prog)	SAC
10.13	All Subjects	VS1	Summary of Vital Signs	By Cohorts and both combined	QSI (Prog)	SAC
10.14	All Subjects	VS1	Summary of Change from Baseline for Vital Signs	By Cohorts and both combined	QSI (Prog)	SAC

14.1.3. Pharmacokinetic Figures and Tables

Figures

Figure No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
11.1	*PK*	PKCF1p	Individual Plasma GSK1278863 Concentration-Time Plots – by Subjects	*1.* x-axis should display Actual relative time 2. Include line for LLQ along with footnote defining LLQ value. 3. Include values below LLQ.	*QSI (Prog)*	*SAC*
11.2	*PK*	PKCF1p	Individual Plasma GSK2391220 (M2) Concentration-Time Plots – by Subjects		*QSI(Prog)*	*SAC*
11.3	*PK*	*PKCF1p*	Individual Plasma GSK2506104 (M3) Concentration-Time Plots – by Subjects		*QSI(Prog)*	*SAC*
11.4	*PK*	*PKCF1p*	Individual Plasma GSK2487818 (M4) Concentration-Time Plots – by Subjects		*QSI(Prog)*	*SAC*
11.5	*PK*	*PKCF1p*	Individual Plasma GSK2506102 (M5) Concentration-Time Plots – by Subjects		*QSI(Prog)*	*SAC*
11.6	*PK*	*PKCF1p*	Individual Plasma GSK2531398 (M6) Concentration-Time Plots – by Subjects		*QSI(Prog)*	*SAC*
11.7	*PK*	*PKCF1p*	Individual Plasma GSK2531401 (M13) Concentration-Time Plots – by Subjects		*QSI(Prog)*	*SAC*

Figure No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
11.8	*PK*	PKCF4	Mean (± SD) Plasma GSK1278863 Concentration-Time Plots (Linear and Semi-log) by Cohort	1. X-axis displays planned relative time 2. Include line for LLQ along with footnote defining LLQ value. 3. Can do both the cohorts in one page by adding legends	*QSI (Prog)*	*SAC*
11.9	*PK*	PKCF4	Mean (± SD) Plasma GSK2391220 (M2) Concentration-Time Plots (Linear and Semi-log) by Cohort	Can do both the cohorts in one page by adding legends	*QSI(Prog)*	*SAC*
11.10	*PK*	PKCF4	Mean (±SD) Plasma GSK2506104 (M3) Concentration-Time Plots (Linear and Semi-log) by Cohort		*QSI(Prog)*	*SAC*
11.11	*PK*	PKCF4	Mean (±SD) Plasma GSK2487818 (M4) Concentration-Time Plots (Linear and Semi-log) by Cohort		*QSI(Prog)*	*SAC*
11.12	*PK*	PKCF4	Mean (±SD) Plasma GSK2506102 (M5) Concentration-Time Plots (Linear and Semi-log) by Cohort		*QSI(Prog)*	*SAC*
11.13	*PK*	PKCF4	Mean (±SD) Plasma GSK2531398 (M6) Concentration-Time Plots (Linear and Semi-log) by Cohort		*QSI(Prog)*	*SAC*
11.14	*PK*	PKCF4	Mean (±SD) Plasma GSK2531401 (M13) Concentration-Time Plots (Linear and Semi-log) by Cohort		*QSI(Prog)*	*SAC*

Figure No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
11.15	*PK*	PKCF5	Median (range) Plasma GSK1278863 Concentration-Time Plots (Linear and Semi-log) by Cohort	1. Include bars for range. 2. X-axis displays planned relative time. 3. Include line for LLQ along with footnote defining LLQ value. 3. Can do both the cohorts in one page by adding legends	*QSI (Prog)*	*SAC*
11.16	*PK*	PKCF5	Median (range) Plasma GSK2391220 (M2) Concentration-Time Plots (Linear and Semi-log) by Cohort	Can do both the cohorts in one page by adding legends	*QSI(Prog)*	*SAC*
11.17	*PK*	PKCF5	Median (range) Plasma GSK2506104 (M3) Concentration-Time Plots (Linear and Semi-log) by Cohort		*QSI(Prog)*	*SAC*
11.18	*PK*	PKCF5	Median (range) Plasma GSK2487818 (M4) Concentration-Time Plots (Linear and Semi-log) by Cohort		*QSI(Prog)*	*SAC*
11.19	*PK*	PKCF5	Median (range) Plasma GSK2506102 (M5) Concentration-Time Plots (Linear and Semi-log) by Cohort		*QSI(Prog)*	*SAC*
11.20	*PK*	PKCF5	Median (range) Plasma GSK2531398 (M6) Concentration-Time Plots (Linear and Semi-log) by Cohort		*QSI(Prog)*	*SAC*
11.21	*PK*	PKCF5	Median (range) Plasma GSK2531401 (M13) Concentration-Time Plots (Linear and Semi-log) by Cohort		*QSI(Prog)*	*SAC*

Figure No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
11.22	*PK*	PKCF1p	Individual Plasma GSK1278863 Concentration-Time Plots – by Cohort	Can do both the cohorts in one page by adding legends	QSI(Prog)	SAC
11.23	*PK*	PKCF6	Individual Plasma GSK2391220 (M2) Concentration-Time Plots by Cohort (Linear and Semi-Log)	Can do both the cohorts in one page by adding legends	*QSI(Prog)*	*SAC*
11.24	*PK*	*PKCF6*	Individual Plasma GSK2506104 (M3) Concentration-Time Plots by Cohort (Linear and Semi-Log)		*QSI(Prog)*	*SAC*
11.25	*PK*	*PKCF6*	Individual Plasma GSK2487818 (M4) Concentration-Time Plots by Cohort (Linear and Semi-Log)		*QSI(Prog)*	*SAC*
11.26	*PK*	*PKCF6*	Individual Plasma GSK2506102 (M5) Concentration-Time Plots by Cohort (Linear and Semi-Log)		*QSI(Prog)*	*SAC*
11.27	*PK*	*PKCF6*	Individual Plasma GSK2531398 (M6) Concentration-Time Plots by Cohort (Linear and Semi-Log)		*QSI(Prog)*	*SAC*
11.28	*PK*	*PKCF6*	Individual Plasma GSK2531401 (M13) Concentration-Time Plots by Cohort (Linear and Semi-Log)		*QSI(Prog)*	*SAC*
11.29	*PK*	*PKCF6*	Individual Plasma Concentration-Time Plots by Analyte at Predose (Linear and Semi Log)		*QSI (Prog)*	*SAC*
11.30	*PK*	*PKCF6*	Mean Plasma Concentration-Time Plots by Analyte at Predose (Linear and Semi Log)		*QSI (Prog)*	*SAC*
11.31	*PK*	*PKCF6*	Median Plasma Concentration-Time Plots by Analyte at Predose (Linear and Semi Log)		*QSI (Prog)*	*SAC*

Tables

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
11.1	*PK*	PKCT1	Summary of Plasma GSK1278863 and its metabolites Concentration-Time Data	By Cohort and combined Refer Table 1 for Cohort description	*QSI(Prog)*	*SAC*
11.2	PK	PKPT4	Summary of Derived Plasma Pharmacokinetic Parameters of GSK1278863 and its Metabolites	1.By Cohort and combined Refer Table 1 for Cohort description	QSI(Prog)	SAC
11.3	PK	Exhibit 1	Summary of Analysis Results for Steady-State Pharmacokinetic Profile of Trough concentration ($C\tau$) for each Metabolite		*QSI(Stat)*	*SAC*
11.4	PK	Exhibit 2	Summary of Results of Statistical Analysis of Derived Plasma GSK1278863 Parameters to Assess Accumulation for each Metabolite		*QSI(Stat)*	*SAC*
11.5	PK	Exhibit 3	Summary of Results of Statistical Analysis of Derived Plasma GSK1278863 Parameters to Assess Time Invariance for each Metabolite		*QSI(Stat)*	*SAC*
11.6	PK	PKCT1	Summary of Percent Protein Bound of Plasma GSK1278863 and select metabolites		*QSI (Stat)*	*SAC*

14.1.4. Pharmacodynamic Figures and Tables

Figures

Figure No.	Population	IDSL No. / Example Shell	Title	Programming Notes	*Responsibility*	*Deliverable Priority*
12.1	All Subjects	PKCF1p	Individual Plasma Erythropoietin Concentration-Time Plots – by Subjects	1. x-axis should display Actual relative time 2. Include line for LLQ along with footnote defining LLQ value. 3. Include values below LLQ.	*QSI (Prog)*	*SAC*
12.2	All Subjects	PKCF1p	Individual Hepcidin Concentration-Time Plots – by Subjects		*QSI(Prog)*	*SAC*
12.3	All Subjects	PKCF4	Mean (±SD) Plasma Erythropoietin Concentration-Time Plots (Linear and Semi-log) by Cohort	1. X-axis displays planned relative time 2. Include line for LLQ along with footnote defining LLQ value.	*QSI (Prog)*	*SAC*
12.4	All Subjects	PKCF4	Mean (±SD) Hepcidin Concentration-Time Plots (Linear and Semi-log) by Cohort		*QSI(Prog)*	*SAC*
12.5	All Subjects	PKCF5	Median (range) Plasma Erythropoietin Concentration-Time Plots (Linear and Semi-log) by Cohort	1. Include bars for range. 2. X-axis displays planned relative time. 3. Include line for LLQ along with footnote defining LLQ value.	*QSI (Prog)*	*SAC*
12.6	All Subjects	PKCF5	Median (range) Hepcidin Concentration-Time Plots (Linear and Semi-log) by Cohort		*QSI(Prog)*	*SAC*

Figure No.	Population	IDSL No. / Example Shell	Title	Programming Notes	*Responsibility*	*Deliverable Priority*
12.7	All Subjects	PKCF6	Individual Plasma Erythropoietin Concentration-Time Plots by Cohort (Linear and Semi-Log)		*QSI(Prog)*	*SAC*
12.8	All Subjects	PKCF6	Individual Hepcidin Concentration-Time Plots by Cohort (Linear and Semi-Log)		*QSI(Prog)*	*SAC*

Tables

Table No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
12.1	All Subjects	PKPT 4	Summary Statistics of Hepcidin and Erythropoietin	By Cohort and both combined	QSI (Prog)	SAC

14.1.5. ICH Listings

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
1	All Subjects	DM2	Listing of Demographic Characteristics	1. By Cohorts 2. Add BMI, Weight ,Height,	*QSI(Prog)*	*SAC*
2	All Subjects	DM9	Listing of Race	By Cohorts	*QSI(Prog)*	*SAC*
3	All Subjects	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	By Cohorts	*QSI(Prog)*	*SAC*
4	All Subjects	DV2	Listing of Protocol Deviations	By Cohorts	*QSI (Prog)*	*SAC*
5	All Subjects	ES2	Listing of Reasons for Withdrawal	By Cohorts	*QSI(Prog)*	*SAC*
6	All Subjects	CP_CM3	Listing of Concomitant Medication by Generic Term	By Cohorts	*QSI(Prog)*	*SAC*
7	All Subjects	EX3	Listing of Exposure data	By Cohorts	*QSI(Prog)*	*SAC*
8	All Subjects	AE7	Listing of Subject Numbers for Individual Adverse Events	By Cohorts	*QSI(Prog)*	*SAC*
9	All Subjects	CP_AE8	Listing of All Adverse Events	By Cohorts	*QSI(Prog)*	*SAC*
10	All Subjects	CP_AE8a	Listing of SAE	By Cohorts	*QSI(Prog)*	*SAC*
11	All Subjects	CP_AE8	Listing of AE leading to Withdrawal	By Cohorts	*QSI(Prog)*	*SAC*
12	All Subjects	CP_LB5	Listing of Haematology Abnormalities of Potential Clinical Importance	By Cohorts	*QSI(Prog)*	*SAC*
13	All Subjects	CP_LB6	Listing of all Hemeatology Laboratory Data for Subjects with PCI Abnormalities	By Cohorts	*QSI(Prog)*	*SAC*

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
14	All Subjects	CP_LB5	Listing of Chemistry Abnormalities of Potential Clinical Importance	By Cohorts	*QSI(Prog)*	*SAC*
15	All Subjects	CP_LB6	Listing of all Clinical Chemistry laboratory Data for subjects with PCI abnormalities	By Cohorts	*QSI(Prog)*	*SAC*
16	All Subjects	CP_EG5	Listing of Abnormal ECG findings	By Cohorts	*QSI(Prog)*	*SAC*
17	All Subjects	CP_EG3	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance	By Cohorts	*QSI(Prog)*	*SAC*
18	All Subjects	CP_VS4	Listing of Vital Signs of Potential Clinical Importance	By Cohorts	*QSI(Prog)*	*SAC*
19	All Subjects	CP_VS4	Listing of all Vital Signs for subjects with any value of Potential Clinical Importance	By Cohorts	*QSI(Prog)*	*SAC*
Conditional Displays: The following displays will only be produced when a liver event has occurred, as defined in the study protocol, and the Liver Event Assessment forms have been completed.						
20	All Subjects	LIVER5	Listing of Liver Events in Relation to Time of Treatment	By Cohorts	QSI(Prog)	SAC
21	All Subjects	LIVER6	Listing of Liver Event Information for RUCAM Score	By Cohorts	QSI (Prog)	SAC
22	All Subjects	LIVER7	Listing of Liver Biopsy Details	By Cohorts	QSI (Prog)	SAC
23	All Subjects	LIVER8	Listing of Liver Imaging Details	By Cohorts	QSI (Prog)	SAC

14.1.6. Other Listings

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Responsibility	Deliverable Priority
1	All Subjects	AE2	Relationship between System Organ Class and Verbatim Text	By Cohorts	*QSI(Prog)*	*SAC*
2	PK	PKCI1P	Listing of Plasma GSK1278863 and Metabolite Pharmacokinetic Concentration-Time Data	By Cohorts	*QSI(Prog)*	*SAC*
3	PK	PKPL1P	Listing of Derived Plasma Pharmacokinetic Parameters of GSK1278863 and its Metabolites	By Cohorts	*QSI(Prog)*	*SAC*
4	PK	PHI113635/Listing 31	Listing of effluent Peritoneal Dialysis Fluid Data	By Cohorts	*QSI(Prog)*	*SAC*
5	All Subjects	PHI113635/Listing 31	Listing of Hepcidin and Erythropoietin	By Cohorts	*QSI(Prog)*	*SAC*
6	PK		Raw SAS Output for Summary of Analysis Results for Steady-State Pharmacokinetic Profile of Trough concentration ($C\tau$)		*QSI(Stat)*	SAC
7	PK		Raw SAS Output for Summary of Results of Statistical Analysis of Derived Plasma GSK1278863 Parameters to Assess Accumulation		*QSI(Stat)*	*SAC*
8	PK		Raw SAS Output for Summary of Results of Statistical Analysis of Derived Plasma GSK1278863 Parameters to Assess Time Invariance		*QSI(Stat)*	*SAC*
9	PK		Raw SAS Output for Summary Analysis Results for Comparison of Pharmacokinetic Parameters of GSK1278863 and its Metabolites using ANOVA		*QSI(Stat)*	*SAC*

14.2. Data Display Specifications (Example Shells)

Example : *Exhibit 1* Page 1 of n
Protocol : *200942*
Population : *PK Population*

Table *xx.x*
Summary of Results of Statistical Analysis to Assess Steady state

Day	Back-Transformed Slope	90% Confidence Interval
1-14	1.05	(1.03, 1.08)

Example : *Exhibit 2*
Protocol : *200942*
Population : *PK Population*

Table x.x
Summary of Results of Statistical Analysis to Estimate Accumulation Ratio

Parameter	Comparison	Geom.LsMean				Ratio	90% Confidence Interval
		n	Test	n	Ref		
AUC(0-t)(pg*hr/mL)	Day 14 vs Day 1	12	0.910	12	0.780	1.166	(0.843, 0.978)

Example : *Exhibit3*
Protocol : *200942*
Population : *PK Population*

Table x.x
Summary of Results of Statistical Analysis to Estimate Time Invariance

Comparison	Geom.LsMean				Ratio	90% Confidence Interval
	n	Test	n	Ref		
AUC(0-τ)Day 14 vs AUC(0-∞)Day 1	12	0.910	12	0.780	1.166	(0.843, 0.978)