Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for Study 201964: A Phase 1 study to demonstrate the relative bioavailability and bioequivalence of fixed dose combinations of ambrisentan and tadalafil in healthy subjects
Compound Number	:	GSK3380154
Effective Date	:	31-JUL-2017

Description :

The purpose of this reporting and analysis plan (RAP) is to describe:

- Planned analyses and outputs to be included in the Clinical Pharmacology Study Report for Protocol 201964.
- Describe the safety, tolerability and pharmacokinetics for the study that will be provided to the study team members to convey the content of the reporting efforts, specifically Statistical Analysis Complete (SAC) deliverable.

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1. REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the Reporting and Analysis Plan
Purpose	The purpose of this reporting and analysis plan (RAP) is to describe: • Planned analyses and output to be included in the Clinical Pharmacology Study Report for Protocol 201964. • Describe the safety, tolerability, pharmacokinetics required for the study which will be provided to the study team members to convey the content of the reporting efforts, specifically Statistical Analysis Complete (SAC) deliverable.
Protocol	• Reporting and Analysis Plan is based on protocol (Substantial Protocol Amendment 3 Dated: 25-MAY-2017) for study 201964 [GlaxoSmithKline Document Number: 2015N232335_03].
Primary Objective / Endpoint	• To characterise the relative bioavailability of ambrisentan and tadalafil following administration of candidate tablet formulations of the FDC (ambrisentan 10 mg + tadalafil 40 mg) relative to reference monotherapies tested (ambrisentan 10 mg & tadalafil 40 mg) taken concurrently in healthy human subjects under fasting conditions. o Endpoints: Plasma PK parameters: C_{max}, $AUC_{(0-\infty)}$, and $AUC_{(0-t)}$ of ambrisentan and tadalafil in FDC and reference treatments • To establish bioequivalence of the candidate FDC (ambrisentan 10 mg + tadalafil 40 mg) relative to reference monotherapies tested (ambrisentan 10 mg & tadalafil 40 mg) taken concurrently in healthy human subjects under fed and fasted conditions. o Endpoints: $AUC_{(0-t)}$, $AUC_{(0-inf)}$, C_{max} • To establish bioequivalence of the FDC (ambrisentan 5 mg + tadalafil 40 mg) relative to reference monotherapies tested (ambrisentan 5 mg & tadalafil 40 mg) taken concurrently in healthy human subjects under fasted conditions. o Endpoints: $AUC_{(0-t)}$, $AUC_{(0-inf)}$, C_{max} • To establish bioequivalence of the FDC (ambrisentan 5 mg + tadalafil 20 mg) relative to reference monotherapies tested (ambrisentan 5 mg & tadalafil 20 mg) taken concurrently in healthy human subjects under fasted conditions. o Endpoints: $AUC_{(0-t)}$, $AUC_{(0-inf)}$, C_{max}
Secondary Objective / Endpoint	• To characterise the secondary PK parameters of the FDC and reference treatments in healthy human subjects under fed and fasted conditions. o Endpoints: Plasma PK parameters including; $AUC_{(0-t)}/AUC_{(0-inf)}$, t_{max}, $t_{1/2}$ of ambrisentan and tadalafil in FDC and reference treatments • To monitor the safety and tolerability of the FDC candidate tablets compared to the reference in healthy human subjects under fed and fasting conditions. o Endpoints: Safety and Tolerability of all treatments as assessed by vital signs, ECG, clinical laboratory safety data and review of adverse events
Study Design	• Single-centre, open-label, randomised, crossover design with 4 study parts (Part 1, Part 2, Part 3A, Part 3B). Each study part of the study will be, up to, a 5 way cross over, in healthy subjects. • Approximately 20 subjects are planned to enrol for study part 1 and part 2. Thirty-three subjects are planned to enrol in each study part 3A and part 3B.
Analysis Population	• Safety Population: All subjects enrolled into the study who have received at least one

Overview	Key Elements of the Reporting and Analysis Plan
	dose of investigational product will be included in the Safety Population. • Pharmacokinetic Concentration Population: The PK Concentration Population will include all subjects for whom at least one PK sample was obtained and analyzed. • Pharmacokinetic Parameter Population: For each PK parameter, the PK Parameter Population will include all subjects who provide PK parameter data.
Hypothesis	• There are no formal hypotheses being tested for study part 1 and part 2 • Part 3A of the study is designed to test the bioequivalence of a FDC of ambrisentan 10 mg + tadalafil 40 mg (test) relative to reference monotherapies of ambrisentan 10 mg & tadalafil 40 mg taken concurrently (reference) in healthy subjects in both the fed and fasted states. The null hypothesis is that the true ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference), for each primary PK endpoint, is either less than 0.80 or greater than 1.25. The alternate hypothesis is that the true ratio of the test treatment geometric mean to the reference treatment geometric mean is at least 0.80 and no greater than 1.25. • Part 3B of the study is designed similar to Part 3A and will test (1) the bioequivalence of a FDC of ambrisentan 5 mg + tadalafil 40 mg (test) relative to reference monotherapies of ambrisentan 5 mg & tadalafil 40 mg taken concurrently (reference) and (2) the bioequivalence of a FDC of ambrisentan 5 mg + tadalafil 20 mg (test) relative to reference monotherapies of ambrisentan 5 mg & tadalafil 20 mg taken concurrently (reference), in healthy subjects in the fasted states. Therefore, the analysis approach for bioequivalence for Part 3A is applicable to Part 3B.
Primary Analyses	• For each primary pharmacokinetic endpoints AUC (0-∞), AUC (0-t) and Cmax, point estimates and corresponding 90% confidence intervals will be constructed using ANOVA and Mixed model for the ratio of the geometric mean of the test treatment to that of the reference treatment, μ(test)/μ(reference) • Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively by treatment. Descriptive summary table, graphics, and treatment will also be provided. • Systemic exposure of ambrisentan and tadalafil will be evaluated when administered as the FDC compared to administration as the monotherapies concurrently, using loge- transformed AUC(0-∞), AUC(0-t) and Cmax in ANOVA model. • Bioequivalence test for part 3A and part 3B
Secondary Analyses	Pharmacokinetic: • Secondary PK parameters of the FDC and reference treatments in healthy human subjects under both fed and fasted conditions. • PK parameters of potential candidate FDC formulations in healthy human subjects under fed and fasted conditions. • Safety and tolerability of the FDC candidate tablets compared to the reference in healthy human subjects under both fed and fasted conditions. • All PK concentration data, derived PK parameters, tmax, and t½, data and Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.
Exploratory Analyses	• There are no exploratory Endpoints in the protocol.

2. SUMMARY OF KEY PROTOCOL INFORMATION

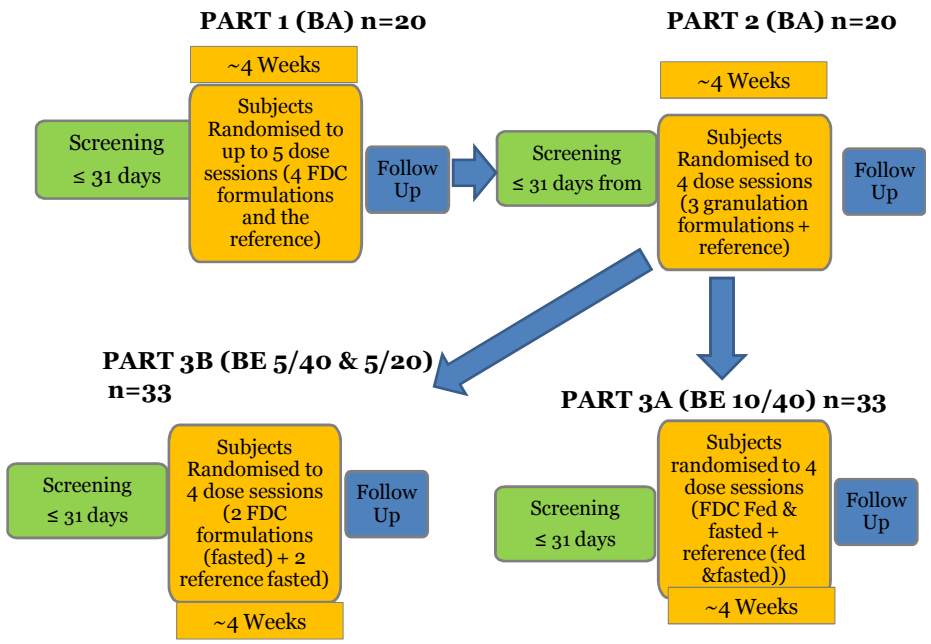
2.1. Changes to the Protocol Defined Statistical Analysis Plan

The bioequivalence testing with PK parameters based on nominal PK sampling time for Part 3A and Part 3B are removed from the current analysis plan due to the withdraw of Brazil submission from global submission plan.

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary	**Primary**
To characterise the relative bioavailability of ambrisentan and tadalafil following administration of candidate tablet formulations of the FDC (ambrisentan 10 mg + tadalafil 40 mg) relative to reference monotherapies tested (ambrisentan 10 mg & tadalafil 40 mg) taken concurrently in healthy human subjects under fasting conditions.	Plasma PK parameters: C_{max}, $AUC_{(0-\infty)}$, and $AUC_{(0-t)}$ of ambrisentan and tadalafil in FDC and reference treatments
To establish bioequivalence of the candidate FDC (ambrisentan 10 mg + tadalafil 40 mg) relative to reference monotherapies tested (ambrisentan 10 mg & tadalafil 40 mg) taken concurrently in healthy human subjects under fed and fasted conditions.	$AUC_{(0-t)}$,$AUC_{(0-inf)}$,C_{max}
To establish bioequivalence of the FDC (ambrisentan 5 mg + tadalafil 40 mg) relative to reference monotherapies tested (ambrisentan 5 mg & tadalafil 40 mg) taken concurrently in healthy human subjects under fasted conditions.	$AUC_{(0-t)}$, $AUC_{(0-inf)}$,C_{max}
To establish bioequivalence of the FDC (ambrisentan 5 mg + tadalafil 20 mg) relative to reference monotherapies tested (ambrisentan 5 mg & tadalafil 20 mg) taken concurrently in healthy human subjects under fasted conditions.	$AUC_{(0-t)}$, $AUC_{(0-inf)}$,C_{max}
Secondary Objectives	**Secondary Endpoints**
To characterise the secondary PK parameters of the FDC and reference treatments in healthy human subjects under fed and fasted conditions.	Plasma PK parameters including; $AUC_{(0-t)}/AUC_{(0-inf)}$,t_{max}, $t_{1/2}$ of ambrisentan and tadalafil in FDC and reference treatments
To monitor the safety and tolerability of the FDC candidate tablets compared to the reference in healthy human subjects under fed and fasting conditions.	Safety and Tolerability of all treatments as assessed by vital signs, ECG, clinical laboratory safety data and review of adverse events

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	Single centre, Phase 1, single dose, randomised, open label, crossover study in healthy volunteers with 3 study parts; Part 1 will include a 5 way cross-over, and Part 2 and 3 (A&B) will each include a 4 way cross-over.
Dosing	• All subjects will attend the unit for Screening within 31 days of their first dose. • There will be a minimum washout of 7 days between each dose in study Part 1 and 2. In study Part 3 there will be a minimum of 10 days between each dose. • A Follow-Up Visit should be completed within 7-14 days of completion of a subject's last dose.
Treatment Assignment	Eligible subjects will be randomised to the order of treatment in the respective study part in which they are included, with the order in which these treatments are administered being in accordance with the randomisation schedule.

This is a single centre, Phase 1, single dose, randomised, open label, crossover study in healthy volunteers with 3 study parts; Part 1 will include a 5 way cross-over, and Part 2 and 3 (A&B) will each include a 4 way cross-over. Subjects will be randomised treatment sequences in accordance with the randomisation schedule generated by the

study accountable statistician prior to the start of each study part, using validated internal GSK software (RandAll NG).

All subjects will attend the unit for Screening within 31 days of their first dose. The Clinical Unit has an approved panel screening protocol which may be utilised to identify eligible study candidates based on the defined study inclusion/ exclusion criteria.

Eligible subjects will be randomised to order of treatment in that study parts in which they are included and the order in which these treatments are administered will be in accordance with the randomisation schedule.

There will be a minimum washout of 7 days between each dose in study Part 1 and 2. In study Part 3 there will be a minimum of 10 days between each dose. A Follow-Up Visit should be completed within 7-14 days of completion of a subject's last dose.

The utility of each of the 3 study parts is as follows:

Part 1

This study part, will have 5 dose sessions and will be used to characterise the relative bioavailability, safety and tolerability of four formulations of the fixed dose combination (ambrisentan 10 mg + tadalafil 40 mg) and the reference of the 2 monotherapy components taken concurrently (ambrisentan 10 mg & tadalafil 40 mg). All doses will be taken in the fasted state.

Part 2

This study part will have 4 dose sessions and will evaluate the bioavailability, safety and tolerability of 3 different granulation sizes for a single FDC (ambrisentan 10 mg + tadalafil 40 mg) compared to the reference of the 2 monotherapy components taken concurrently (ambrisentan 10 mg & tadalafil 40 mg). All doses are taken in the fasted state.

Part 3A

Part 3A of the study is set to establish bioequivalence between the candidate FDC from Part 2. This study part will have 4 dose sessions and will assess the bioequivalence, in both the fed and fasted state, of the FDC against the reference ambrisentan 10 mg + tadalafil 40mg monotherapies in the fed and fasted state. The fed arms of this part will have a standard high fat breakfast (EMEA, 2010).

Part 3B

Part 3B of the study is set to establish bioequivalence between the Fixed Dose Combination of an additional two dose strengths (ambrisentan 5 mg + tadalafil 40mg and ambrisentan 5 mg + tadalafil 20mg) . This study part will have 4 dose sessions and will assess the bioequivalence of the two FDC dose strengths against the reference ambrisentan 5 mg + tadalafil 40mg monotherapies and ambrisentan 5 mg + tadalafil 20mg monotherapies in the fasted state.

Approximately 20 healthy adult subjects will be randomized to study Part 1 and an additional 20 healthy adult subjects in Part 2, such that at least 16 evaluable subjects complete each part of the study. Approximately 33 healthy subjects will be randomized to study Part 3A, such that at least 26 evaluable subjects complete part 3A of the study. An additional 33 healthy subjects will be randomised to Part 3B, such that at least 26 evaluable subjects complete part 3B of the study.

The treatments proposed per study part and treatment Key for study Part1, Part2 and Part3 are given in Table 1. The treatment sequences used in the study are given in Table 2.

Table 1 Treatment Key for Part 1, Part 2 and Part 3

Treatment	Description
Part 1	
F1	ambrisentan and tadalafil FDC1 (10mg/40mg)
F2	ambrisentan and tadalafil FDC2 (10mg/40mg)
F3	ambrisentan and tadalafil FDC3 (10mg/40mg)
F4	ambrisentan and tadalafil FDC4 (10mg/40mg)
R	ambrisentan and tadalafil monotherapies taken concurrently (10mg/40mg)
Part 2	
FG1	ambrisentan and tadalafil FDC-G1 (10mg/40mg) granulation size 1
FG2	ambrisentan and tadalafil FDC-G2 (10mg/40mg) granulation size 2
FG3	ambrisentan and tadalafil FDC-G3 (10mg/40mg) granulation size 3
R	ambrisentan and tadalafil monotherapies taken concurrently (10mg/40mg)
Part 3A	
X1	ambrisentan and tadalafil FDC-G1 or 2 or 3 (10mg/40mg) fed
X2	ambrisentan and tadalafil FDC-G1 or 2 or 3 (10mg/40mg) fasted
R1	ambrisentan and tadalafil monotherapies taken concurrently (10mg/40mg), fed
R2	ambrisentan and tadalafil monotherapies taken concurrently (10mg/40mg), fasted
Part 3B	
Y1	ambrisentan and tadalafil FDC (5mg/40mg), fasted
Y2	ambrisentan and tadalafil FDC (5mg/20mg), fasted
R3	ambrisentan and tadalafil monotherapies taken concurrently (5mg/40mg), fasted
R4	ambrisentan and tadalafil monotherapies taken concurrently (5mg/20mg), fasted

Table 2 Treatment Sequences for Part 1, Part 2 and Part 3

Study Parts	Number of Treatments	Sequence assignments	Allocation ratio
Part 1	5	F1/ F2/ R/ F3/ F4 F2/ F3/ F1/ F4/ R F3/ F4/ F2/ R/ F1 F4/ R/ F3/ F1/ F2 R/ F1/ F4/ F2/ F3 F4/ F3/ R/ F2/ F1 R/ F4/ F1/ F3/ F2 F1/ R/ F2/ F4/ F3 F2/ F1/ F3/ R/ F4 F3/ F2/ F4/ F1/ R	1:1:1:1:1:1:1:1:1:1
Part 2	4	FG1/ FG2/ R/ FG3 FG2/ FG3/ FG1/ R FG3/ R/ FG2/ FG1 R/ FG1/ FG3/ FG2	1:1:1:1
Part 3A	4	X1/ R1/ R2/ X2 R1/ X2/ X1/ R2 X2/ R2/ R1/ X1 R2/ X1/ X2/ R1	1:1:1:1
Part 3B	4	Y1/ R3/ R4/ Y2 R3/ Y2/ Y1/ R4 Y2/ R4/ R3/ Y1 R4/ Y1/ Y2/ R3	1:1:1:1

Full details of the design of the study can be found in the protocol.

2.4. Statistical Hypotheses

No formal hypothesis will be tested for study Part 1 and Part 2. An estimation approach will be used to (i) estimate the bioavailability of the FDC formulations relative to the monotherapies taken concurrently, (ii) for each primary pharmacokinetic endpoint, point estimates and corresponding 90% confidence intervals will be constructed for the ratio of the geometric mean of the test treatment (FDC formulations) to the geometric mean of the reference treatment (co-administration of ambrisentan and tadalafil), μ(test)/ μ(reference). The objective of Part 2 is to assess whether differences in granulation size impact the pharmacokinetics of ambrisentan and tadalafil; the estimation approach for bioavailability is therefore applicable to Part 2.

Part 3A of the study is designed to test the bioequivalence of a FDC of ambrisentan 10 mg + tadalafil 40 mg (test) relative to reference monotherapies of ambrisentan 10 mg & tadalafil 40 mg taken concurrently (reference) in healthy subjects in both the fed and fasted states. The null hypothesis is that the true ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference), for each primary PK endpoint, is either less than 0.80 or greater than 1.25. The alternate

hypothesis is that the true ratio of the test treatment geometric mean to the reference treatment geometric mean is at least 0.80 and no greater than 1.25. Symbolically, this is expressed as follows:

$$H(0): \mu(\text{test})/\mu(\text{reference}) < 0.80 \text{ or } \mu(\text{test})/\mu(\text{reference}) > 1.25,$$

i.e., treatments are not bioequivalent.

versus

$$H(1): 0.80 \leq \mu(\text{test})/\mu(\text{reference}) \leq 1.25,$$

i.e., treatments are bioequivalent.

For each PK parameter designated as a primary endpoint, a two one-sided t-test (TOST) procedure (Schuirmann, 1987) with α=0.05 for each one-sided test will be used to test this set of hypotheses. This is equivalent to requiring that a 90% interval for the true ratio of test to reference geometric means falls entirely within the range of 0.80 to 1.25.

Part 3B of the study is designed similar to Part 3A and will test (1) the bioequivalence of a FDC of ambrisentan 5 mg + tadalafil 40 mg (test) relative to reference monotherapies of ambrisentan 5 mg & tadalafil 40 mg taken concurrently (reference) and (2) the bioequivalence of a FDC of ambrisentan 5 mg + tadalafil 20 mg (test) relative to reference monotherapies of ambrisentan 5 mg & tadalafil 20 mg taken concurrently (reference), in healthy subjects in the fasted states. Therefore, the analysis approach for bioequivalence for Part 3A is applicable to Part 3B.

No formal hypothesis will be tested for the secondary pharmacokinetic endpoints. Point estimates and corresponding 90% confidence intervals will be constructed for the comparison between test treatment and reference treatment as described in Section 8.

3. PLANNED ANALYSES

3.1. Interim Analyses

No formal interim is planned. However, ongoing analyses of pharmacokinetic data will be performed in Part 1, Part 2, Part 3A and 3B of the study in order to direct development of the FDC for later parts of the study. Headline results based on statistical analysis using preliminary pharmacokinetic data with nominal time may be produced when 80% and 100% subjects complete Part 1, Part 2, Part 3A and 3B of the study to assist development of FDCs. Treatment and period information from the crossover design may be used in the analysis; sequence information may also be included depending on availability.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

[1] All subjects have completed the study as defined in the protocol.

[2] All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.

[3] All criteria for unblinding the randomisation codes have been met.

[4] Randomisation codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Endpoint(s) Evaluated
Screened Population	• All subjects who were Screened in the study	• Screen failures
Per Protocol Population	• All randomized subjects who receive at least one dose of study treatment and who comply with the protocol.	• Deviation leading to exclusion
Safety Population	• All subjects enrolled into the study who have received at least one dose of investigational product will be included in the Safety Population.	• Study Population • Safety
Pharmacokinetic Concentration Population	• The PK Concentration Population will include all subjects for whom at least one PK sample was obtained and analyzed.	• PK Concentration
Pharmacokinetic Parameter Population	• For each PK parameter, the PK Parameter Population will include all subjects who provide PK parameter data.	• PK Parameter
Complete Treatment/Reference PK Parameter Population	• All subjects in PK Parameter Population who have completed • 1. In part 3A : both FDC and reference within fed or fasted state • 2. In part 3B : both FDC and reference within ambrisentan and tadalafil FDC 5mg/40mg or ambrisentan and tadalafil FDC 5mg/20mg	• Statistical analysis

NOTES :

- Please refer to Section 10.11 which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
  - Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
  - This dataset will be the basis for the summaries and listings of protocol deviations.
- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.
- Important deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

- There are no planned examination of covariates and subgroups.
- There are no planned adjustments for multiple comparisons or multiplicity.

Table 3 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 3 Overview of Appendices

Section	Component
10.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
10.2	Appendix 2: Data Management
10.3	Appendix 3: Time & Events Table
10.4	Appendix 4: Treatment States and Phases
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.6	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
10.8	Appendix 8: Values of Potential Clinical Importance
10.9	Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the "Safety" population, unless otherwise specified.

Table 4 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 4 Overview of Planned Study Population Analyses

Display Type	Data Display's Generated		
	Figure	Table	Listing
Randomisation			
Randomisation			Y
Subject Disposition			
Subject Disposition		Y	
Exposure to study treatment		Y	
Reasons for Screening Failures		Y	Y
Reasons for Withdrawals		Y	Y
Protocol Deviations		Y	Y
Randomised and Actual Treatments			Y
Inclusion and Exclusion Criteria Deviations			Y
Demography			
Demographics Characteristics		Y	Y
Race & Racial Combinations		Y	Y
Study Populations		Y	
Medical Condition & Concomitant Medications			
Medical Conditions (Current/Past)		Y	
Concomitant Medication		Y	

NOTES:
- Y = Yes display generated.

7. SAFETY ANALYSES

Safety data will be summarised and listed by, or under the direct auspices of, clinical statistics at India (Programmer), GlaxoSmithKline.

Statistical analyses, when applicable, of safety data will be performed by, or under the direct auspices of, clinical statistics (Statistician), GlaxoSmithKline.

The primary safety analyses will be based on the "Safety" population, unless otherwise specified.

7.1. During the Study

As required, ongoing data reviews will be conducted by the study team of the safety data, throughout the trial progression.

7.1.1. Overview of Planned Analyses

Table 5 provides an overview of the planned analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 5 Overview of Planned Safety Analyses

Endpoint	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Adverse Events								
All AE's	Y			Y				
All Drug-Related AE's	Y							
Serious AE's	Y			Y				
Withdrawal AE's[1]	Y			Y				
Laboratory Values								
Clinical Chemistry				Y	Y			
Hematology [1]				Y	Y			
Urinalysis (Dipstick)				Y				
ECG's								
ECG Findings	Y							
ECG Values					Y			
Emergent QTc Values	Y							
Vital Signs								
Vitals Values					Y			

NOTES :

- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Listings will include subject's numbers for individual AE's & AE system organ classes, preferred terms and verbatim text.

8. 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 Science and Study Operations (CPSSO), GlaxoSmithKline.

The merge of PK concentration data, randomisation and CRF data will be performed by, or under the direct auspices of, Clinical Statistics, GlaxoSmithKline.

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

8.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses will be based on the "Pharmacokinetic" population, unless otherwise specified.

Table 6 Overview of Planned Pharmacokinetic Analyses

Endpoints	Untransformed				Log-Transformed			
	Summary		Individual		Summary		Individual	
	F	T	F	L	F	T	F	L
Plasma Drug Concentrations	Y [1] [2]	Y	Y [1]	Y				
Derived PK Parameters		Y	Y	Y		Y		
Statistical Analysis PK Parameters					Y	Y		

NOTES :

- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

1. Linear and Semi-Log plots will be created on the same display.
2. Separate Mean (± SD) and Median plots will be generated.

8.2. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 10.5.3 Reporting Process & Standards).

Concentrations of ambrisentan and tadalafil in plasma will be listed and summarised by treatment and actual time. Standard summary statistics will be calculated (i.e. arithmetic mean, standard deviation, median, minimum and maximum). Refer to the PK Guidance document, titled Non-Compartmental Analysis of Pharmacokinetic Data (GUI_51487) for more information regarding the treatment of concentrations below the assay's lower limit of quantification (NQ).

Individual plasma concentration-time profiles and median/mean profiles by treatment 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 $\log_e$-transformed scale (i.e., log-linear plot). In addition, a plot showing all individual subjects for each treatment will be produced (both linear and log-linear).

8.3. Pharmacokinetic Parameters

For the purposes of inferential statistical analysis, PK parameters AUC and Cmax will be $\log_e$-transformed prior to analysis.

Summary statistics will be based on untransformed data and in addition for transformed parameters the geometric mean (and 95% confidence intervals), sd of $\log_e$-transformed data and between subjects coefficient of variation (%CVb) will be presented (see Section 10).

For $\log_e$-transformed PK parameters, the between subjects coefficient of variation (%CVb) will be calculated according to the following method:

$$\%CVb=100 * (SQRT (EXP (SD \text{ of } \log_e\text{-transformed})^2-1))$$

For PK parameters analysed after $\log_e$-transformation, within subject coefficient of variation (%CVw) will be calculated according to the following method:

$$\%CVw=100*(SQRT (EXP(\sigma_w^2)-1))$$

where σ_w^2 is the mean squares error (MSE) from the statistical model.

8.3.1. Deriving Pharmacokinetic Parameters

The following pharmacokinetic parameters will be determined from the plasma concentration-time data for each treatment. The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using WinNonlin (version 6.3)

All calculations of non-compartmental parameters will be based on actual sampling times.

- AUC(0-t): area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.

- AUC (0-∞): area under the concentration-time curve extrapolated to infinity will be calculated as follows: AUC = AUC(0-t) + C(t)/λz.

- Cmax: maximum observed concentration, determined directly from the concentration-time data.

- tmax: time to reach Cmax, determined directly from the concentration-time data.

- $t_{½}$: apparent terminal half-life will be calculated as follows: $t_{½} = \ln 2/\lambda z$.

The individual subject ratios of test to reference treatment will be calculated for AUC(0-t), AUC(0-∞) and Cmax.

Derived pharmacokinetic parameters will be listed by subject and treatment. Listings will also include the individual subject ratios for AUC(0-∞) and Cmax, and also the first point, last point and number of points used in the determination of λz.

For each of the parameters AUC (0-t), AUC (0-∞) and Cmax, the following summary statistics will be calculated and tabulated by treatment (dose):

- **Untransformed Data :** N, n, arithmetic mean, 95% confidence interval (CI) for the arithmetic mean, SD, median, minimum, maximum
- **Log_e-transformed Data:** Geometric mean, 95% CI for the geometric mean, SD of log_e-transformed data and %CVb

For tmax, $t_{½}$ and %AUCex the summary statistics specified for untransformed data above will be generated.

8.4. Statistical Analysis

AUC (0-t), AUC (0-∞) and Cmax will be analysed after log_e-transformation.

According to EMA guidilines on **GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE (**2010, Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**),** following log_e-transformation of pharmacokinetic parameters of ambrisentan and tadalafil, AUC(0-∞) and AUC(0-t) and Cmax will be separately analysed using fixed effect ANOVA model with fixed effect terms for sequence, subject within sequence, period and treatment (formulation). The Kenward & Roger (KR) degrees of freedom approach will be used. As a sensitivity analysis, mixed effect model with fixed effect terms for period, sequence and treatment (formulation), and subject as random effect term (i.e. ANOVA method using period, sequence and treatment as fixed effect, and subject as random effect) will be performed.

Point estimates for the adjusted means on the loge scale, the mean difference between treatments and associated 90% confidence interval for the contrast (test-reference) will be constructed using the residual variance. The point estimate and confidence interval will then be exponentially back-transformed to obtain adjusted (least square) geometric means for each treatment, and point estimates and associated 90% confidence interval for the ratio test/reference. Point estimates and 90% confidence intervals for AUC and Cmax will be reported to 4 decimal places with no rounding.

Estimates of within-subject variability (%CVw) for AUC(0-∞) and AUC(0-t) and Cmax of ambrisentan and tadalafil will also be provided. %CVw represents a pooled measure of within-subject variability across all treatments.

Residual plots will be visually inspected for identification of potential outliers in the analysis.

For tmax the summary statistics specified for untransformed data will be generated.

Time profile for PK concentration for individual subjects will be plotted by formulation and treatment.

Comparative plots will be provided showing individual values by treatment for each of the PK parameters AUC(0-∞) and AUC(0-t) and Cmax.

Treatment Comparative Plots of adjusted geometric mean (90% CI) with Individual Subject Plasma PK Parameters (AUC (0-∞), AUC (0-t) and Cmax) will be generated.

Plots will also be provided showing the adjusted geometric mean ratio of test to reference treatment for AUC(0-∞) and AUC(0-t) and Cmax together with 90% confidence intervals.

The SAS output from the statistical models and the assessment of assumptions underlying the models will be included in a listing of supportive SAS output.

9. REFERENCES

EMEA. Guidance on the Investigation of Bioequivalence. 2010.

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

10. APPENDICES

Section	Appendix
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Section 10.11	Appendix 11: List of Data Displays
Section 10.12	Appendix 12: Example Mock Shells for Data Displays

10.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

A subject meeting any of the following criteria will be excluded from the Per Protocol population:

Exclusion Description
Any protocol deviation that may affect a subject's PK samples (collection, storage, processing, transport and analyses) will be reviewed by the study team to determine whether or not the sample will be excluded

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)

1. A blood pressure <100/55 mm Hg.
2. Haemoglobin below normal range:
   - Hb < 133 g/L for males
   - Hb< 114 g/L for females
3. ALT and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
4. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
5. QTc> 450 msec

   NOTES:

   - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.
   - For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

CONCOMITANT MEDICATIONS
6. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.

RELEVANT HABITS
7. History of regular alcohol consumption within 6 months of the study defined as: • An average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits. 8. Smoking more than 5 cigarettes per week and subjects must be able to abstain from smoking for a 24 hour period prior to dose and any time whilst in the clinical unit.

CONTRAINDICATIONS
9. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates their participation.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
10. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at Screening or within 3 months prior to first dose of study treatment. . 11. A positive test for HIV antibody. 12. A positive pre-study drug/alcohol screen. 13. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within previous 3 months 14. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 3 months, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). 15. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

10.2. Appendix 2: Data Management

Data Type	Source	Format of Data	Planned Date of Final File[1]	Responsibility
Safety	Database	SDTM	SDL	CPSSO
PC SDTM	Reconciliation and merge PK Conc.	dat file	SDL + 5 Working Days[1]	BIB and CRO
ADPC	SDTM PC	CSV file	PC SDTM + 5 Working Days[1]	QSI
PK Parameters	CSV file	PK Harp	ADPC + 7 Working Days	CPMS
PP SDTM	PK parameter file	SDTM	PK parameters + 5 Working Days	CPMS and CRO

1. Provided source data is clean
2. PK concentration data is released via SMS2000 by DMPK and the SDTM PK dataset contains date/times and PK sample ID

10.3. Appendix 3: Time & Events

Procedure	Screen	Part 1, 2 and 3A and 3B. Each dose in each Part repeats this schedule.																FU	Notes
Day	**≤-31**	**-1**	**1**											**2**		**3**	**4**	**≥7-14**	
Time (hrs)			**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**4**	**8**	**12**	**18**	**24**	**36**	**48**	**72**		
Outpatient visit	x																x	x	
Admission to unit		x																	
Informed consent	x																		
Inclusion and exclusion criteria	x	x																	
Demography	x																		
Full physical exam including height and weight	x																		
Brief Physical																		x	
Medical history (includes substance usage)	x																		
HIV, Hep B and Hep C screen]	x																		
Laboratory assessments (include liver chemistries)	x	x														x		x	Only Screening labs need to be taken in fasted state.
Serum hCG Pregnancy test	x																	x	Female subjects only
Urine hCG Pregnancy test		x																	Female subjects only
Breathalyser and Smokerlyzer	x	x																	
DOA testing	x	x																	
12-lead ECG	x		x			x		x		x		x		x			x	x	Triplicate at screen and baseline, single measure at other times, unless out of range then triplicates should be performed
Vital signs	x		x		x	x		x		x	x	x		x		x	x	x	
24hr Holter	x																		
Randomisation			x																Randomised prior to first dose only
Study Treatment				x															
AE/SAE review	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	SAEs from Screen. AEs from first dose
Concomitant medication review	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
PK Sample			x		x	x	x	x	x	x	x	x	x	x	x	x	x		

Procedure	Screen	Part 1, 2 and 3A and 3B. Each dose in each Part repeats this schedule.																FU	Notes
Day	**≤-31**	**-1**	**1**										**2**		**3**	**4**		**≥7-14**	
Time (hrs)			**Pre-dose**	**0**	**0.5**	**1**	**1.5**	**2**	**2.5**	**4**	**8**	**12**	**18**	**24**	**36**	**48**	**72**		
Discharge from Unit																x			For logistical reasons subjects may remain in-unit for the 72 hr assessments if they prefer.

10.4. Appendix 4: Treatment States and Phases

10.4.1. Treatment Phases

Assessments and events will be classified according to the time of occurrence relative to dosing.

Treatment Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start date < Date ≤ Study Treatment Stop Date
Post-Treatment	Date > Study Treatment Stop Date

10.4.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start and/or stop date of the study treatment.

10.4.2.1. Treatment States for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-Treatment	If AE onset date is on or after treatment start date & on or before the treatment stop date Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date [+ 1]
Post-Treatment	If AE onset date is after the treatment stop date AE Start Date > Study Treatment Stop Date
Onset Time Since First Dose (Days)	If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 Missing otherwise
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on eCRF OR value is missing

NOTES:

- If the study treatment stop date is missing then the AE will be considered to be On-Treatment.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Study Treatment Display Descriptors

Randomisation		Final Data Display (i.e. HARP / other)
Code	**Treatment Description**	**Treatment Description**
F1	ambrisentan and tadalafil FDC1 (10mg/40mg)	F1
F2	ambrisentan and tadalafil FDC2 (10mg/40mg)	F2
F3	ambrisentan and tadalafil FDC3 (10mg/40mg)	F3
F4	ambrisentan and tadalafil FDC4 (10mg/40mg)	F4
R	ambrisentan and tadalafil monotherapies taken concurrently (10mg/40mg)	R
FG1	ambrisentan and tadalafil FDC-G1 (10mg/40mg) granulation size 1	FG1
FG2	ambrisentan and tadalafil FDC-G2 (10mg/40mg) granulation size 2	FG2
FG3	ambrisentan and tadalafil FDC-G3 (10mg/40mg) granulation size 3	FG3
X1	ambrisentan and tadalafil FDC-G1 or 2 or 3 (10mg/40mg) fed	X1
X2	ambrisentan and tadalafil FDC-G1 or 2 or 3 (10mg/40mg) fasted	X2
R1	ambrisentan and tadalafil monotherapies taken concurrently (10mg/40mg), fed	R1
R2	ambrisentan and tadalafil monotherapies taken concurrently (10mg/40mg), fasted	R2
Y1	ambrisentan and tadalafil FDC (5mg/40mg), fasted	Y1
Y2	ambrisentan and tadalafil FDC (5mg/20mg), fasted	Y2
R3	ambrisentan and tadalafil monotherapies taken concurrently (5mg/40mg), fasted	R3
R4	ambrisentan and tadalafil monotherapies taken concurrently (5mg/20mg), fasted	R4

NOTES: Add footnotes for data display treatment description based on randomisaiton treatment description

10.5.2. Baseline Definition & Derivations

10.5.2.1. Baseline Definitions

For all endpoints (expect as noted in the table) the baseline value will be the latest pre-dose assessment.

Table 7 Baseline Definitions

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Safety				
12 Lead ECG & Vital Signs	X		X	Day 1 (Pre Dose)
Haematology	X	X		Day -1
Clinical Chemistry	X	X		Day -1

10.5.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.5.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

10.5.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS and R software will be used.	
Reporting Area	
HARP Server	: US1SALX00259-HARP PROD-US
HARP Area	: \ARPROD\GSK1325760\mid201964\Final
QC Spreadsheet	: \ARWORK\ GSK1325760\ mid201964\Final\Documents
Analysis Datasets	
• Analysis datasets will be created according to CDISC dataset standards	
Generation of RTF Files	
• RTF files will be generated.	

Reporting Standards
General

Reporting Standards	
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics	
Formats	
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.	
Planned and Actual Time	
• Reporting for tables, figures and formal statistical analyses : o Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. o The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: o Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). o Unscheduled or unplanned readings will be presented within the subject's listings. o Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables. • Unscheduled visits will not be included in figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics.	N, n, arithmetic mean, 90% confidence interval (CI) for the arithmetic mean, SD, median, minimum, maximum

Reporting Standards	
(Un-Transformed)	
Descriptive Summary Statistics. (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and between geometric coefficient of variation (CVb (%)) will be reported. CVb (%) = √ (exp(SD2) - 1) * 100 [NOTE: SD = SD of log transformed data]
Parameters Not Being Log Transformed	tmax, first point, last point and number of points used in the determination of Lambda_z.
Parameters Not Being Summarised	Additionally include tmax, first point, last point and number of points used in the determination of Lambda_z.
Listings	Include the first point, last point and number of points used in the determination of Lambda_z.
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13.	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Multiple Measurements at One Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target then the mean will be taken. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from randomisation date :
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Data ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

10.6.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date is imputed as:
  • Any subject with a missing day will have this imputed as day '15'.
  • Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)^2**

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Subjects who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

10.6.3. Safety

ECG Parameters

RR Interval

- IF RR interval (msec) is not provided directly, then RR can be derived as :

  [1] If QTcB is machine read & QTcF is not provided, then :

$$RR = \left[\left(\frac{QT}{QTcB}\right)^{2}\right] * 1000$$

  [2] If QTcF is machine read and QTcB is not provided, then:

$$RR = \left[\left(\frac{QT}{QTcB}\right)^{3}\right] * 1000$$

- If ECGs are manually read, the RR value preceding the measurement QT interval should be collected values THEN do not derive.

Corrected QT Intervals

- When not entered directly in the eCRF, corrected QT intervals using Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements.
- IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as :

$$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

Adverse Events

Definition of Adverse Events refer to study protocol Appendix 3

Laboratory Parameters

- If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.
  - Example 1: 2 Significant Digits = '< x ' becomes x – 0.01
  - Example 2: 1 Significant Digit = '> x' becomes x + 0.1
  - Example 3: 0 Significant Digits = '< x' becomes x – 1

10.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Withdrawn subjects maybe replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in listings unless otherwise specified. • 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.

10.7.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument :
	  • These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
	  • Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.7.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.

Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event:
	  • Missing Start Day: First of the month will be used unless this is before the start date of investigational product; in this case the study treatment start date will be used (and hence the event is considered On-treatment as per Appendix 4: Treatment States and Phases).
	  • Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will

Element	Reporting Detail
	be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

10.7.2.2. Handling of Partial Dates

Element	Reporting Detail

Concomitant Medications	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  • If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	• The recorded partial date will be displayed in listings.

Adverse Events	• Any partial dates for adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made:
	  • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month.
	  • However, if these results in a date prior to Week 1 Day 1 and the event could possibly have occurred during treatment from the partial information, then the Week 1 Day 1 date will be assumed to be the start date.
	  • The AE will then be considered to start on-treatment (worst case).
	  • If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	• The recorded partial date will be displayed in listings.

10.7.2.3. Handling of PK Concentration Data

Element	Reporting Detail
General	• The PK Population will include all subjects who undergo PK sampling and have evaluable PK assay results. PK assay results from samples collected from a subject with vomiting occurring within 2 times the median Tmax will not be considered as evaluable for that period. This population will be used for the concentration listing, summaries and plotting of the individual concentration-time profiles. • If the pre-dose concentration is ≤ 5% of Cmax value in a subject, the concentration data for that subject without any adjustments will be included in pharmacokinetic and statistical analysis. If the pre-dose concentration is > 5% of Cmax value in a subject, then the

Element	Reporting Detail
	concentration data for that subject will not be included in pharmacokinetic and statistical analysis and only the concentration data of that subject(s) will be presented • If during clinical phase, 3 consecutive samples in any phase i.e. (Absorption, Distribution and Metabolism / Excretion) are found to be missing then data for that subject will not be included in pharmacokinetic and statistical analysis and only the concentration data of that subject(s) will be presented

10.8. Appendix 8: Values of Potential Clinical Importance

10.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	↓0.075	
Hemoglobin	g/L	Male		180
		Female		180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	mmol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Magnesium	mmol/L		0.5	1.23
Phosphorus	mmol/L		0.8	1.6
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO_2	mmol/L		18	32

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 1.5xULN
T. Bilirubin + ALT	µmol/L U/L	High	1.5xULN T. Bilirubin + ≥ 2x ULN ALT

10.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec	> 450	
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec	> 60	
	msec	> 30	≤ 59
	msec	≥ 60	

ECG Parameter	Units	Post Dose QTcF			
Category					
QTc Values by Category	msec	≤ 450	> 450	> 480	> 500

10.8.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

10.9. Appendix 9: Model Checking and Diagnostics for Statistical Analyses.

10.9.1. Statistical Analysis Assumptions

Endpoint(s)	• AUC(0-∞), AUC(0-t), and Cmax
Analysis	• Statistical analysis of derived PK parameters • ANOVA Model • Linear Mixed Model

Assumptions:

- For the Linear Mixed Model, model assumptions will be applied, where treatment regimen, period, sequence as fixed effects and subject within sequence as random effects but appropriate adjustments may be applied based on the data.
- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- An unstructured covariance structure for the G matrix will be used by specifying 'type=UN' on the RANDOM line.
    - In the event that this model fails to converge, alternative covariance structures may be considered such as VC or CS.

  Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model.
- Alternative analyses of the data will be performed if any of the model assumptions appear to be violated. Alternative analyses to be considered include analyses on the original scale without log-transformation, transformations other than natural-log, or nonparametric analyses.

10.10. Appendix 10 - Abbreviations & Trade Marks

10.10.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
AUC	Area under concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
%AUCex	The percentage of AUC(0-∞) obtained by extrapolation
CI	Confidence Interval
Cavg	Average concentration during a dosing interval
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CP	Clinical Programming
CPMS	Clinical Pharmacology Modelling & Simulation
CPSSO	Clinical Pharmacology Sciences and Study Operations
CRF	Case record form
CS	Clinical Statistics
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
CV	Coefficient of variance
Fabs	Absolute bioavailability of drug determined following extravascular and intravascular dosing
FI	Fluctuation Index
Frel	Relative bioavailability of drug determined between two formulations of the same drug following similar or different extravascular route of administration
GLS	Geometric Least-Squares
GSK	GlaxoSmithKline
HARP	Harmonisation for Reporting and Analysis Program
IDSL	Integrated Data Standards Library
λz	Terminal phase rate constant
LLQ	Lower limit of quantification
NC	Not Calculable
NQ	Non-quantifiable concentration measured as below LLQ
PK	Pharmacokinetic
RAP	Reporting and Analysis Plan
SAS	Statistical Analysis System
SD	Standard deviation
SRP	Statistics Resourcing and Programming
t OR tlast	Time of last observed quantifiable concentration
t½	Terminal phase half-life
tmax	Time of occurrence of Cmax

10.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
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SAS
WinNonlin

10.11. Appendix 11: List of Data Displays

10.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.01 to 1.09	N/A
Safety	2.01 to 2.18	N/A
Pharmacokinetic	3.01 to 3.15	3.01 to 3.08
Section	**Listings**	
ICH Listings	1 to 19	
Other Listings	20 to 23	

10.11.2. Mock Example Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 12: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln

NOTES:
- Indicate display is Non-Standard in the 'IDSL/TST ID / Example Shell' or 'Programming Notes' column.

10.11.3. Deliverable [Priority]

Delivery [Priority] [1]	Description
SAC [1]	Final Statistical Analysis Complete

NOTES:
1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort.

10.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.01	Safety	ES1	Summary of Subject Disposition	By study parts and overall	SAC [1]
1.02	Screened	ES6	Summary of Reasons for Screening Failure	By study parts and overall	SAC [1]
1.03	Safety	DV1a	Summary of Important Protocol Deviations	By study parts and overall	SAC [1]
1.04	Per Protocol	SA2	Summary of Deviations Leading to Exclusion from Per Protocol Population	By study parts and overall	SAC [1]
Demographics					
1.05	Safety	DM1	Summary of Demographic Characteristics	By study parts and overall	SAC [1]
1.06	Safety	DM5	Summary of Race and Racial Combinations	By study parts and overall	SAC [1]
1.07	Safety	SA1	Summary of Study Populations	By study parts and overall	SAC [1]
Medical Condition & Con Meds					
1.08	Safety	MH1	Summary of [Current/Past] Medical Conditions	By study parts and overall	SAC [1]
1.09	Safety	CM1	Summary of Concomitant Medications	By study parts and overall	SAC [1]

10.11.5. Safety Tables

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
2.01	Safety	EX1	Summary of Extent of Exposure to Study Treatment	By study parts and overall	SAC [1]
Adverse Events					
2.02	Safety	AE1	Summary of All Adverse Events by System Organ Class	Include total column. By study parts and overall	SAC [1]
2.03	Safety	AE5	Summary of All Adverse Events by System Organ Class and Maximum Grade	By study parts and overall	SAC [1]
2.04	Safety	AE3	Summary of Common Adverse Events by Overall Frequency	By study parts and overall	SAC [1]
2.05	Safety	AE5	Summary of Drug-Related Adverse Events by System Organ Class	Include total column. By study parts and overall	SAC [1]
2.06	Safety	AE1	Summary of Serious Adverse Events by System Organ Class	By study parts and overall	SAC [1]
2.07	Safety	AE3	Summary of Adverse Events Leading to Withdrawals from Study / Permanent Discontinuation of Study Treatment	By study parts and overall	SAC [1]
Labs					
2.08	Safety	LB1	Summary of Chemistry Changes from Baseline by Visit	By study parts and overall	SAC [1]

Safety Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.09	Safety	LB3	Summary of Emergent Chemistry Results by Potential Clinical Importance Criteria	By study parts and overall	SAC [1]
2.10	Safety	LB1	Summary of Haematology Changes from Baseline by Visit	By study parts and overall	SAC [1]
2.11	Safety	LB3	Summary of Emergent Chemistry Results by Potential Clinical Importance Criteria	By study parts and overall	SAC [1]
2.12	Safety	UR3	Summary of Urinalysis Dipstick Results	By study parts and overall	SAC [1]
ECGs					
2.13	Safety	EG1	Summary of ECG Findings by Visit	By study parts and overall	SAC [1]
2.14	Safety	EG2	Summary of Maximum Emergent QTc Values by Category.	By study parts and overall	SAC [1]
2.15	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit.	By study parts and overall	SAC [1]
Vital Signs					
2.16	Safety	VS1	Summary of Change from Baseline in Vital Signs by Visit	By study parts and overall	SAC [1]
2.17	Safety	VS2	Summary of Emergent Vital Signs Results by Potential Clinical Importance Criteria	By study parts and overall	SAC [1]
Other					
2.18	Safety	DT1	Summary of Dosing Times and Meal Times	By study parts and overall	SAC [1]

10.11.6. Pharmacokinetic Tables

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
3.01	PK concentration	pkct1	Summary of ambrisentan and tadalafil plasma Concentration-time Data by Treatment	By study parts; do not include drop-out and withdrawal subjects for part 3A and part 3B	SAC [1]
PK Derived Parameters					
3.02	Complete Treatment/ Reference PK parameter	pkpt1	Summary of Untransformed ambrisentan and tadalafil plasma Pharmacokinetic Parameters	Produce for AUC(0-inf), AUC(0-t), Cmax; by Treatment. By study parts, by fed and fast; do not include drop-out and withdrawal subjects	SAC [1]
3.03	PK parameter	pkpt1	Summary of Untransformed ambrisentan and tadalafil plasma Pharmacokinetic Parameters	Produce for AUC(0-inf), AUC(0-t), Cmax; by Treatment. By study parts, by fed and fast; do not include drop-out and withdrawal subjects	SAC [1]
3.04	Complete Treatment/ Reference PK parameter	pkpt3	Summary of Loge-transformed ambrisentan and tadalafil plasma Pharmacokinetic Parameters	Produce for AUC(0-inf), AUC(0-t), Cmax; by Treatment. By study parts, by fed and fast; do not include drop-out and withdrawal subjects	SAC [1]
3.05	PK parameter	pkpt3	Summary of Loge-transformed ambrisentan and tadalafil plasma Pharmacokinetic Parameters	Produce for AUC(0-inf), AUC(0-t), Cmax; by Treatment. By study parts, by fed and fast; do not include drop-out and withdrawal subjects	SAC [1]

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.06	Complete Treatment/ Reference PK parameter	PK_T2	Summary of ambrisentan and tadalafil plasma tmax	By study parts; do not include drop-out and withdrawal subjects	SAC [1]
3.07	PK parameter	PK_T2	Summary of ambrisentan and tadalafil plasma tmax	By study parts; do not include drop-out and withdrawal subjects	SAC [1]
3.08	Complete Treatment/ Reference PK parameter	PK_T1	Summary of Statistical Analysis of Loge-transformed ambrisentan and tadalafil plasma PK Parameters using actual PK sampling time in ANOVA model	Part 3A, by fed or fasted	SAC [1]
3.09	PK parameter	PK_T1	Summary of Statistical Analysis of Loge-transformed ambrisentan and tadalafil plasma PK Parameters using actual PK sampling time in ANOVA model	Part 3A, by fed or fasted	SAC [1]
3.10	Complete Treatment/Reference PK parameter	PK_T1	Summary of Statistical Analysis of Loge-transformed ambrisentan and tadalafil plasma PK Parameters using actual PK sampling time in Linear Mixed model	Part 3A, by fed or fasted	SAC [1]
3.11	PK parameter	PK_T1	Summary of Statistical Analysis of Loge-transformed ambrisentan and tadalafil plasma PK Parameters using actual PK sampling time in Linear Mixed model	Part 3A, by fed or fasted	SAC [1]

Pharmacokinetic Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.12	Complete Treatment/Reference PK parameter	PK_T1	Summary of Statistical Analysis of Loge-transformed ambrisentan and tadalafil plasma PK Parameters using actual PK sampling time in ANOVA model	Part 3B by ambrisentan and tadalafil FDC 5mg/40mg or 5mg/20mg	SAC [1]
3.13	PK parameter	PK_T1	Summary of Statistical Analysis of Loge-transformed ambrisentan and tadalafil plasma PK Parameters using actual PK sampling time in ANOVA model	Part 3B by ambrisentan and tadalafil FDC 5mg/40mg or 5mg/20mg	SAC [1]
3.14	Complete Treatment/Reference PK parameter	PK_T1	Summary of Statistical Analysis of Loge-transformed ambrisentan and tadalafil plasma PK Parameters using actual PK sampling time in Linear Mixed model	Part 3B by ambrisentan and tadalafil FDC 5mg/40mg or 5mg/20mg	SAC [1]
3.15	PK parameter	PK_T1	Summary of Statistical Analysis of Loge-transformed ambrisentan and tadalafil plasma PK Parameters using actual PK sampling time in Linear Mixed model	Part 3B by ambrisentan and tadalafil FDC 5mg/40mg or 5mg/20mg	SAC [1]

10.11.7. Pharmacokinetic Figures

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Individual Concentration Plots					
3.01	PK Concentration	pkcf1x	Individual Subject ambrisentan and tadalafil plasma Concentration-time Plot (Linear and Semi-log) by treatment then by Subject	Paginate by Subject. By study parts, Part 3A, by fed or fasted state Part 3B by ambrisentan and tadalafil FDC 5mg/40mg or 5mg/20mg	SAC [1]
3.02	PK Concentration	pkcf6	Individual Subject ambrisentan and tadalafil plasma Concentration-time Plot (Linear and Semi-log) by Treatment	*Spaghetti plots, all subjects by treatment.* By study parts, Part 3A, by fed or fasted state Part 3B by ambrisentan and tadalafil FDC 5mg/40mg or 5mg/20mg	SAC [1]
Mean / Median Concentration Plots					
3.03	PK Concentration	pkcf4	Arithmetic mean (+SD) ambrisentan and tadalafil plasma Concentration-time Plot (Linear and Semi-log)	Paginate by Treatment. By study parts,	SAC [1]
3.04	PK Concentration	pkcf5	Median (range) ambrisentan and tadalafil plasma Concentration-time Plot (Linear and Semi-log)	Paginate by Treatment. By study parts,	SAC [1]

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.05	Complete Treatment/ Reference PK parameter	pkpf3	Comparative Plot of Individual Subject ambrisentan and tadalafil plasma PK Parameters vs Treatment	Produce for AUC(0-inf), AUC(0-t), Cmax; By study parts, Part 3A, by fed or fasted state, by actual or protocol PK sampling time, by ANOVA or linear mixed model Part 3B by ambrisentan and tadalafil FDC 5mg/40mg or 5mg/20mg, by actual or protocol PK sampling time, by ANOVA or linear mixed model	SAC [1]
3.06	PK parameter	pkpf3	Comparative Plot of Individual Subject ambrisentan and tadalafil plasma PK Parameters vs Treatment	Produce for AUC(0-inf), AUC(0-t), Cmax; By study parts, Part 3A, by fed or fasted state, by actual or protocol PK sampling time, by ANOVA or linear mixed model Part 3B by ambrisentan and tadalafil FDC 5mg/40mg or 5mg/20mg, by actual or protocol PK sampling time, by ANOVA or linear mixed model	SAC [1]
3.07	Complete Treatment/ Reference PK parameter	PK_F1	Geometric Mean Treatment Ratio and 90% CI of ambrisentan and tadalafil plasma PK Parameters	Produce for AUC(0-inf), AUC(0-t), Cmax Part 3A, by fed or fasted state, by actual or protocol PK sampling time, by ANOVA or linear mixed model Part 3B by ambrisentan and tadalafil FDC 5mg/40mg or 5mg/20mg, by actual or protocol PK sampling time, by ANOVA or linear mixed model	SAC [1]

Pharmacokinetic Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.08	PK parameter	PK_F1	Geometric Mean Treatment Ratio and 90% CI of ambrisentan and tadalafil plasma PK Parameters	Produce for AUC(0-inf), AUC(0-t), Cmax Part 3A, by fed or fasted state, by actual or protocol PK sampling time, by ANOVA or linear mixed model Part 3B by ambrisentan and tadalafil FDC 5mg/40mg or 5mg/20mg, by actual or protocol PK sampling time, by ANOVA or linear mixed model	SAC [1]

10.11.8. ICH Listings

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Randomisation					
1	Safety	CP_TA1	Listing of Randomised and Actual Treatments Sequence	By study parts and overall	SAC [1]
Subject Disposition					
2	Safety	ES2	Listing of Reasons for Study Withdrawal	By study parts and overall	SAC [1]
3	Screened	ES7	Listing of Reasons for Screening Failure	By study parts and overall	SAC [1]
4	Safety	SA3a	Listing of Subjects Excluded from Any Populations	By study parts and overall	SAC [1]
5	Safety	DV2	Listing of Important Protocol Deviations	By study parts and overall	SAC [1]
6	Per Protocol	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	By study parts and overall	SAC [1]
Demographics					
7	Safety	DM2	Listing of Demographic Characteristics	By study parts and overall	SAC [1]
8	Safety	DM9	Listing of Race	By study parts and overall	SAC [1]
Exposure					
9	Safety	EX3	Listing of Exposure	By study parts and overall	SAC [1]
Adverse Events					

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
10	Safety	AE7	Listings of Subject Numbers for Individual Adverse Events	By study parts and overall	SAC [1]
11	Safety	AE7	Listing of All Adverse Events	By study parts and overall	SAC [1]
12	Safety	AE8	Listing of Serious Adverse Events	By study parts and overall	SAC [1]
13	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	By study parts and overall	SAC [1]
LABS					
14	Safety	LB5	Listing of Haematology Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance	By study parts and overall	SAC [1]
15	Safety	LB5	Listing of Clinical Chemistry Laboratory Data for Subjects Abnormalities of Potential Clinical Importance	By study parts and overall	SAC [1]
16	Safety	UR2b	Listing of Urinalysis Data Data for Subjects Abnormalities of Potential Clinical Importance.	By study parts and overall	SAC [1]
ECGs					
17	Safety	EG3	Listing of ECG Values for Subjects with Abnormalities of Potential Clinical Importance	By study parts and overall	SAC [1]
Vital Signs					
18	Safety	CP_VS4	Listing of Vital Signs for Subjects with Abnormalities of Potential Clinical Importance	By study parts and overall	SAC [1]

ICH Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Other					
19	Safety	CP_ML1p	Listing of Dosing Times, Meal Start and End Times on Fed Treatment Days	By study parts and overall	SAC [1]

10.11.9. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
20	*PK concentration*	*pkcl1x*	*Listing of ambrisentan and tadalafil* plasma *Concentration-time Data*	By study parts	SAC [1]
21	*PK parameter*	*pkpl1x*	*Listing of ambrisentan and tadalafil* plasma *Pharmacokinetic Parameters*	By study parts *To include AUC(0-t),AUC(0-inf), Cmax andTmax* ,	SAC [1]
22	*PK parameter*	*pkpl2*	*Listing of ambrisentan and tadalafil* plasma *Pharmacokinetic Parameter Ratios*	*To include AUC(0-t),AUC(0-inf), Cmax*, by study parts	SAC [1]
23	*PK parameter*	*N/A*	*Supportive SAS Output from Statistical Analysis of Log_e-transformed ambrisentan and tadalafil* plasma *Pharmacokinetic Parameters*	By study parts	SAC [1]

10.12. Appendix 12: Example Mock Shells for Data Displays

Example : PK_*T1*
Protocol : *insert protocol number*
Population : PK

Table *2.4*
Summary of Statistical Analysis of Log_e-transformed $AnalyteMatrix$ PK Parameters

Parameter	*Comparison Test vs Reference*	*Adjusted Geometric Mean (Dose normalised)*		*Ratio (Test/Ref)*	*90% Confidence Interval for Ratio*	*%CVw*
		n Test	*n Ref*			
AUC(0-inf)(units)	*Test treatment description vs Reference treatment description*	*x xx.xx*	*x xx.xx*	*x.xxxx*	*(x.xxxx, x.xxxx)*	*xx.x*
AUC(0-t)(units)	*Test treatment description vs Reference treatment description*	*x xx.xx*	*x xx.xx*	*x.xxxx*	*(x.xxxx, x.xxxx)*	*xx.x*
Cmax(units)	*Test treatment description vs Reference treatment description*	*x xx.xx*	*x xx.xx*	*x.xxxx*	*(x.xxxx, x.xxxx)*	*xx.x*

Figure *2.5*
Geometric Mean Treatment Ratio and 90% CI of AnalyteMatrix PK Parameters