Statistical Analysis Plan

Clinical trial protocol title:	A microdose Study to Evaluate the Biodistribution of [^{11}C]-GSK2256098 in the Lungs and Heart of Healthy Subjects and Pulmonary Arterial Hypertension (PAH) Patients using Positron Emission Tomography (PET)
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Number of pages:	46
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1 List of abbreviations

AE	Adverse Event
APTT	Activated Partial Thromboplastin Time
BMI	Body Mass Index
CRF	Case Report Form
CT	Computerised Tomography
CTR	Clinical Trial Report
ECG	Electrocardiogram
FAK	Focal adhesion kinase
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
HMR	Hammersmith Medicines Research
HPD	Highest Posterior Density
HV	Healthy Volunteers
ICH	International Conference on Harmonization
IMP	Investigational Medicine Product
INR	International Normalised Ratio
IPF	Idiopathic Pulmonary Fibrosis
MCMC	Monte Carlo Markov Chain
MedDRA	Medical Dictionary for Regulatory Activities
N	Number of subjects
n	Number of observed subjects
PAH	Pulmonary Arterial Hypertension
PDF	Portable Document Format
PET	Positron Emission Tomography
PT	Prothrombin Time
Q1	Lower quartile
Q3	Upper quartile
ROI	Region of Interest
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard deviation
SUV	Standardised Uptake Value
TEAE	Treatment-Emergent Adverse Event
TT	Thrombin time
VT	Volume of Distribution

2 Signatures

The following persons have read and agreed the content of this Statistical Analysis Plan:

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3 Introduction

This Statistical Analysis Plan (SAP) is based on the current trial protocol (Amendment 3, 22Apr2016) and CRF (version 1, 28Sep2015). Where statistical methods differ substantially between this SAP and the protocol, that will be identified in this document.

This SAP describes the datasets and the statistical methods to be used for the reporting and analysis of all data collected during the trial except then genetics sample data.

If a future protocol amendment necessitates a substantial change to the statistical analysis of the trial data, this SAP will be amended accordingly. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP, those unplanned analyses will not be described in an amended SAP, but they will be identified in the integrated clinical trial report (CTR). Any deviations from this SAP will be documented in the CTR.

This SAP has been written in consideration of the following guidelines:

- International Conference on Harmonization (ICH) E9, Guidance for Industry: Statistical Principles for Clinical Trials (ICH E9 1998)1; and
- ICH E3, Guidance for Industry: Structure and Content of Clinical Study Reports (ICH E3 1995)2.

Statistical analysis will be done using SAS® 9.3 on a Windows PC.

4 Study Objective(s) and Endpoint(s)

4.1 Study Objective(s)

4.1.1 Primary Objective(s)

To compare the uptake of [^{11}C]-GSK2256098 in the heart and lungs of PAH patients versus the heart and lungs of healthy control subjects

4.1.2 Exploratory Objective(s)

To explore the spatial distribution of [^{11}C]-GSK2256098 uptake in the heart and lungs of PAH patients versus the heart and lungs of healthy control subjects.

4.2 Study Endpoint(s)

4.2.1 Primary Endpoint(s)

Uptake of [^{11}C]-GSK2256098 in the heart and lung (assessed as the volume of distribution (V_T) and/or standardised uptake values (SUV)) as measured by PET

4.2.2 Exploratory Endpoint(s)

Qualitative assessment of the spatial distribution of [^{11}C]-GSK2256098 uptake in the heart and lungs

4.3 Statistical Hypotheses

No formal statistical testing will be done. Instead an estimation approach has been adopted. Simple Bayesian methods will be used to quantify the evidence which the study generates about the endpoints themselves, and about contrasts (probability ratios) of these endpoints.

5 Study Design

This is cross-sectional study exploring the uptake of [^{11}C]-GSK2256098 in PAH patients and in healthy (age and gender-matched) volunteers.

It is a non-randomised, open label study where all volunteers will receive one microdose of the radiolabelled compound.

Up to 12 healthy subjects and 12 PAH patients (including those with a prolonged QTcF interval ≤ 500ms) will be enrolled to provide sufficient PET data to quantify the uptake of [11C]-GSK2256098 in the heart and lungs.

6 Time and Events Table

Procedure	Screening (up to 30 days prior to scan)	Scanning visit	Follow-up (2-4 weeks post-last dose)	Notes
Informed consent	X			
Inclusion and exclusion criteria	X			
Demography	X			
Brief physical	X	X	X	On the scanning day, to be completed pre-scan, prior to the administration of the peptide.
Medical / Medical history	X			
Vital signs	X	X		On the scanning day, to be conducted pre and post scan.
12-lead ECG	X			
Alcohol breath test	X	X		
Urine drug and cotinine screen	X			
Healthy subjects only: spirometry	X			
Coagulation profile	X			This will include PT (Prothrombin time), APTT (Activated Partial Thromboplastin Time) and Thrombin Time (TT)
PAH patients only (who have been on Warfarin): INR		X		Sample to confirm suitability for scanning day can be done up to 3 days prior to the day of the scan
HIV, Hep B and Hep C screen	X			If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
Clinical chemistry and Haematology	X			
Urinalysis	X			
Allen's test	X	X		
i.v dose of [^{11}C]-GSK2256098		X		
PET scan		X		PET scanning will be started at the same time as injection of the radioligand and PET data will be collected for up to 90 minutes post administration.

Procedure	Screening (up to 30 days prior to scan)	Scanning visit	Follow-up (2-4 weeks post-last dose)	Notes
Attenuation CT scan		X		Lasting seconds to minute prior to start of PET scan. If subject gets off the bed for a comfort break midway through the PET scan, another CT scan will be performed prior to re-starting acquisition of PET data
Genetics sample		X		Genetic Informed consent must be obtained before collecting a sample
Samples for plasma radioactivity measurements & whole blood		X		Blood samples will be collected during scanning for plasma and whole blood radioactivity measurements.
AE/SAE review		X	X	
Concomitant medication review	X	X	X	

7 Planned Analyses

7.1 Interim Analyses

No formal interim "testing" of any statistical hypothesis will be performed.

The strength of evidence in the PET data (about differential expression levels between patients and HVs) will be reviewed once five patients and five healthy volunteers have been studied in the PET scanner, and the relevant functional endpoints have been derived by Imanova scientists for heart chamber and whole lung regions. From that point onwards, the data will be monitored continuously (or as near as possible given practicalities of study operationalisation)

7.1.1 Persons responsible for analysis

PPD	(HMR)	Statistician
PPD	PPD	SAS Programmer

7.2 Final Analysis

The database will be locked once all subjects have completed the study, data have been entered and all queries resolved. The final analysis will be carried out following database lock.

7.2.1 Persons responsible for analysis

PPD	(HMR)	Statistician
PPD	(HMR)	SAS Programmer
PPD	(HMR)	Data Manager

8 Sample Size Considerations

There is little known about the likely mean values of the PET-derived functional primary endpoints (Volume of distribution, and/or some form of integrated SUV) in this

population. Therefore our sample size is driven by a mixture of:

(i) what is known about between-subject variability from relevant, recent PET studies,
(ii) feasibility, and
(iii) flexibility.

An ongoing study investigating the validation and dosimetry of a PET ligand in healthy subjects and patients with IPF (study RES116235) has been able to draw firm conclusions about similar endpoints (in terms of the estimation methods we describe below) using around 5 subjects. Therefore we will set five patients and five age-matched HVs as our initial target sample size.

From that point onwards, the data will be monitored continuously (or as near as possible given practicalities of study operationalisation), and at each step the following decisions will be made:

- Stop, and conclude that there is strong evidence of differential FAK expression (as measured by the study endpoints) between patients and HVs.
- Stop, and conclude that there is insufficient evidence of any great difference, and furthermore (conditional on observed data i.e. in a formal Bayesian sense) there is low probability that an increase in sample size will reverse such a conclusion
- Continue to enrol patient-HV pairs, and re-evaluate the decision.

This iterative cycle will be followed up until a maximum of twelve patients and twelve HVs have been recruited into the study.

8.1 Sample Size Re-estimation or Adjustment

The first statistical evaluation of the data will occur once five patients and five healthy volunteers have been studied in the PET scanner, and the relevant functional endpoints (such as V_T) have been derived from their scan data by Imanova scientists. At this point, the statistical analysis (set out below) will be carried out, and, based on those results, the team may decide to recruit more subjects, up to a total of twelve patients and twelve healthy volunteers.

9 Analysis Populations

The following populations will be identified:

Screened Population:	all subjects who signed an informed consent form and were evaluated for study participation.
Safety Population:	All patients and subjects who received the microdose of study drug.

The primary endpoint will be analysed using the Safety Population.

9.1 Analysis Datasets

All analysis datasets will be based on observed data, except as outlined in Section 12.2.

10 Treatment Comparisons

The comparison of interest is uptake of [^{11}C]-GSK2256098 in PAH patients versus healthy volunteers.

11 General Considerations for Data Analyses

11.1 Data Display Group Descriptors

The sort order for groups will be PAH patients then healthy control subjects. When a total column is included, it immediately follows the groups which it aggregates.

Listings of data will be sorted and displayed by group, subject number, and also by date and time if applicable.

The group descriptions to be used on all tables and listings are:

Groups

PAH Patients
Healthy Volunteers

11.2 Conventions for Summary Statistics and Data Displays

The minimum set of summary statistics for numeric variables will be: n, mean, standard deviation (or standard error), median, minimum and maximum

Categorical data will be summarised in frequency tables with n and percentage. Summaries of a categorical variable will include all recorded values.

The minimum and maximum values will be presented with the same number of decimal places as the raw data collected on the CRF (or to 3 significant figures for derived parameters). The mean and percentiles (e.g. median, Q1, and Q3) will be presented using one additional decimal place. The standard deviation and standard error will be presented using two additional decimal places.

12 Data Handling Conventions

12.1 Premature Withdrawal and Missing Data

All subjects who withdraw prematurely from the study or study drug will be included in the statistical analyses.

If a subject completes the treatment period but has missing data, then this will be made apparent in the subject listings. Missing data will not be imputed except for as outlined in Section 12.2.

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

Data collected at unscheduled time points during the study will not be used in the summaries or data analyses. They will be included in the listings.

If time information (i.e. hours and/or minutes) for adverse events or concomitant medication is missing, but the day is present, then the time will be calculated in days. If date information is partial or missing, then any derived times (e.g. AE start time from last study medication) will be listed as missing.

12.2 Derived and Transformed Data

V_T and mean SUV will be derived by Imanova for regions including heart chamber and whole lung.

The CT images obtained for attenuation correction (AC) of the PET [CT-AC)] are used to delineate the left and right lung and both the CT-AC and the region of interest (ROI) image are resampled to the PET space. Time activity curves are extracted using the predefined ROI image. Standardized uptake values (SUV) are generated by averaging the time activity curves between two time points (to be defined depending on the kinetics of the tracer in the lungs) and normalising to the injected dose per unit mass.

An image derived input function is generated using a region of interest in the pulmonary artery. This input function is used together with a compartmental model to derive the volume of distribution (V_T) in each region of interest.

12.3 Assessment Windows

No assessment windows are defined for this report.

12.4 Values of Potential Clinical Importance

Any laboratory value outside the reference range for that variable (Appendix B) will be flagged as a value of a potential clinical importance

A vital signs result will be considered to be of potential clinical importance if it falls outside the relevant range below:

Vital Sign	**Range**
Supine/semi-recumbent systolic blood pressure	85–160 mm Hg
Supine/semi-recumbent diastolic blood pressure	40–90 mm Hg
Supine/semi-recumbent heart rate	40–100 beats/min
Respiration rate	8–20 per min
Oral temperature	35.5–37.8°C

13 Study Population

13.1 Disposition of Subjects

All analyses will use the safety population.

The disposition of all subjects (patients and healthy volunteers) in the safety population will be summarised including number of subjects screened, the number of subjects who failed screening, number completing the study by group, and number withdrawn from the study.

All subjects who withdraw or are withdrawn from the study will be listed by treatment, with the reason for withdrawal.

A listing of analysis populations will be provided.

13.2 Protocol Deviations

Before closing the database, data listings will be reviewed to identify any significant deviations and determine whether the data should be excluded from any analysis populations.

Major protocol deviations include subjects who:

- Entered the study even though they did not satisfy the entry criteria.
- Met the criteria for withdrawal from the study but were not withdrawn.
- Received the wrong treatment or incorrect dose.
- Received an excluded concomitant therapy.
- Received investigational product(s) past the expiration date.
- Healthy volunteers who are not matched to a PAH patient on gender or with age not within ± 5 years

A summary table of the important deviations will be provided.

A listing of inclusions/ exclusion deviations will be provided.

A listing of all important deviations will be provided.

13.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics (e.g. physical examination, vital signs, Allen's test and INR) will be listed and summarised. A summary of age ranges of subjects will be presented.

A summary of the difference in ages between the matched pairs will also be presented.

Subjects who take concomitant medication will be listed. All non-trial medication will be coded by GSK.

13.4 Treatment Compliance

Dates and times of dosing will be listed (Listing 16.2.1.1).

14 Safety Analyses

The dates and times of treatment dosing will be listed to indicate exposure to the study medication (Listing 16.2.1.1).

14.1 Adverse Events

Adverse events will be coded by GSK.

All adverse events will be listed. Subject numbers for specified adverse events will be listed. A listing of the relationship between system organ class and verbatim text will also be presented.

The number of subjects with at least one treatment-emergent adverse event (TEAE) will be tabulated by actual treatment and MedDRA system organ class. A treatment-emergent adverse event is defined as an event emerging during treatment having been absent pre-treatment or having worsened relative to pre-treatment[1].

For each of the following, the number of subjects with adverse events will be summarised:

- TEAEs by system organ class and preferred term
- IMP-related (as recorded by the Investigator) TEAEs by system organ class and preferred term

Subjects with more than one TEAE will be counted only once, at causality, for each system organ class/preferred term. Multiple TEAEs in a subject will be counted once per system organ class and preferred term. Adverse events with missing severity and/or causality will be treated as severe and related to IMP, respectively.

Summaries will be sorted by system organ class and decreasing total incidence of preferred term.

14.2 Serious Adverse Events

Serious Adverse Events will be summarised by by system organ class and preferred term.

A listing of the reasons for considering a serious adverse event will be provided.

14.3 Other Safety Measures

14.3.1 Clinical Laboratory Evaluations

All laboratory values of potential clinical importance will be listed.

14.3.2 Vital signs

Vital signs evaluation pre- and post-scan at the scanning visit will be summarised by group. Vital signs of potential clinical importance will be listed.

14.3.3 Physical examination

Abnormal physical examination findings will be listed by group.

14.4 Positron Emission Tomography

Positron Emission Tomography (PET) parameters will be summarised using the safety population.

Each PET parameter (V_T and mean SUV) will be listed and summarised by region and group.

A Bayesian approach to the analysis of the PET parameters will be used.

For any important endpoint, we describe our uncertainty concerning its true value with a probability density function, $p(\theta)$, say. (Suppose 'θ' represents Volume of Distribution, derived from the PET and blood sample data. The following argument will apply to any such endpoint which takes numerical values on the real line.) Pre-study start, we will characterise $p(\theta)$ in such a way that our "prior belief" about the true endpoint's value is entirely diffuse over the real line (this approach implies that all conclusions about the endpoint are driven only by the data gathered in the study).

We will gather evidence about the endpoint in the data from the study, which we will characterise via its likelihood function (derived from the relevant sampling distribution, $l(x|\theta)$, say, where 'x' stands for 'data'). From the likelihood function the usual summary statistics for the endpoint are derived.

It is highly likely, based on similar PET studies, that a Normal likelihood function will be suitable. This will have an unknown mean and known variance taken from the raw data (i.e.

$x_j \sim N(\theta_j, \sigma_j^2)$ where j is the PAH patient group or the HV group). An uninformative conjugate Normal prior density function with mean zero and a vast variance will be adopted for the group mean ($P(\theta_j) = N(0, \sigma_{0,j}^2)$) leading to the standard Normal posterior density functions for the endpoints of interest (Should the data not support a Normal likelihood function, alternative parametric forms, such as a log-Normal density, will be investigated). In order for the prior to be sufficiently non-informative, the variance of the prior will be approximately 100 times the variance of the data.

We will apply Bayes' theorem to derive the posterior density function $p(\theta_j \mid x_j)$. We will use PROC MCMC in SAS. The number of burn-in iterations will be at least 10,000 and the number of MCMC iterations, excluding the burn-in iterations will be at least 5000. These samples may be thinned if autocorrelation is high. An example of the SAS code for a normal likelihood function is given below:

```
ods output PostSummaries = PostSummaries PostIntervals = PostIntervals
PosteriorSample = PosteriorSample;

PROC MCMC data = BayesianTest nmc = 5000 nbi = 10000 monitor=(_parms_ muratio);
 parms mu1 mu2;
 muratio = mu1/mu2;
MODEL PAH ~ norm(mu1, sd = 1;
MODEL HVs ~ norm(mu2, sd = 1);
prior mu1 mu2 ~ normal(0, sd = 100);
preddist outpred = BayesianPred nsim = 5000 covariates = PredCovariates;
by  endpoint region;
run;
```

The posterior distribution for each endpoint will be summarised by region and group, including the mean, median, SD, interquartile range and 95% credible interval based on the highest posterior density (HPD) interval.

Samples from the posterior distribution for the group mean $p(\theta_j|x_j)$ for the PAH patients and for the HV subjects will be used to determine the posterior distribution for the ratio of group means (PAH patients to HV subjects). The posterior distribution for the ratio of group means

will be summarised by region and endpoint. Plots of the median and 95% credible interval for the posterior distribution of the group mean and the ratio of group means will be presented for each endpoint and region. Individual subject data will also be included on the plot using a different symbol for each match pairs of subjects. Each plot will also include the posterior distribution of the ratio of the group means.

Samples from the posterior distribution of the ratio of group means will be used to determine the probability that the ratio of the endpoint in PAH patients to HV subjects exceeds 1 for each endpoint and region. This will be repeated for other values to allow us to plot to provide a graph of the "probability that this ratio exceeds a certain value, plotted against ratio, for ratios in the range 0.5 to 2 will be presented for each endpoint and region.

15 References

1. International Conference on Harmonization, 1998. Statistical Principles for Clinical Trials - ICH Harmonised Tripartite Guideline. Guidance for Industry, E9, FDA federal register, Vol 63, 1998, p49583. Available at: http://www.fda.gov/cder/guidance.
2. International Conference on Harmonization, 1995. Structure and Content of Clinical Study Reports - ICH Harmonised Tripartite Guideline. Guidance for Industry, E3, FDA federal register, Vol 61, 1996, p37320. Available at: http://www.fda.gov/cder/guidance.

16 ATTACHMENTS

16.1 Data Display Requirements

Data displays will be stored in individual PDF files with formatting of:

- pagesize will be 8.5" x 11" (US Letter sized paper)
- margins will be 1.25" top and bottom and 0.87" right and left on a landscape page
- font will be Arial 10.

There will be a bookmark to the first page of each display. Bookmark text will include display type (Table, Figure, Listing), display number and the verbatim text of the data display. Bookmarks will link directly to the first page of the data display rather than executing a Java script.

16.2 Table of Contents for Data Display Specifications

For overall page layout refer to Appendix A.

The numbering in the tables below will take precedence over the numbering in the shells.

The following tables and figures will be produced (templates provided in Section 16.2 and 16.3):

The following tables and figures will be produced (templates provided in Section 16.2.1 and 16.2.2):

Table	Description	Population	Source Listing	Template (Shells below)
10.1	Summary of Subject Disposition	Screened	16.2.1.2, 16.2.3.1	T_SD1
10.2	Summary of Important Protocol Deviations	Safety	16.2.2.2	T_DV_GK
14.1	DEMOGRAPHIC DATA			
14.1	Summary of Demographic Characteristics	Safety	16.2.4.1	T_DM1_PG
14.2	Summary of Age Ranges	Safety	16.2.4.1	T_AGE_GSK
14.3	Summary of Age Matching	Safety	16.2.4.1	T_DM2
14.3	SAFETY DATA			
14.3.1.1	Summary of Treatment-Emergent Adverse Events	Safety	16.2.7.1	T_AE1
14.3.1.2	Summary of Drug-Related Treatment-Emergent Adverse Events	Safety	16.2.7.1	T_AE1
14.3.2	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	Safety	16.2.7.1	T_AE2
14.3.3	Narratives of deaths and other serious adverse events	Safety	16.2.7.1	-
14.3.4	Summary of Vital Signs at Scanning Visit	Safety	-	T_VS1
14.4	PET DATA			
14.4.1	Summary of Volume of Distribution (V_T) and Mean Standardised Uptake Values (SUV), by Group and Region	Safety	16.2.9.1	T_PT1_GK
14.4.2	Summary of the Posterior Distribution for Volume of Distribution (V_T)and Mean Standardised Uptake Values (SUV), by Group and Region	Safety	16.2.9.1	T_PT2_GK
14.4.3	Summary of the Posterior Distribution of the Ratio of Group Means for Volume of Distribution (V_T) and Mean Standardised Uptake Values (SUV), by Region	Safety	16.2.9.1	T_PT3_GK
14.4.4	Posterior Probability that the Ratio of Group Means for Volume of Distribution (V_T) and Mean Standardised Uptake Values (SUV) Exceeds a Certain Value, by Region	Safety	16.2.9.1	T_PT4_GK

Figure	Description	Population	Source Listing	Template (Shells below)
14.1	PET DATA	Safety		
14.1.1.1	Plot of the Posterior Distribution of the Volume of Distribution (V_T) for the Group Means and the Ratio of the Group Means, by Region	Safety	16.2.9.1	F_PT1_GK
14.1.1.2	Plot of the Posterior Distribution of the Mean Standardised Uptake Values (SUV) for the Group Means and the Ratio of the Group Means, by Region	Safety	16.2.9.1	F_PT1_GK
14.1.2.1	Plot of the Posterior Probability that the Ratio of the Group Means Exceeds a Certain Value for the Volume of Distribution (V_T), by Region	Safety	16.2.9.1	F_PT2_GK
14.1.2.2	Plot of the Posterior Probability that the Ratio of Group Means Exceeds a Certain Value for Mean Standardised Uptake Values (SUV), by Region	Safety	16.2.9.1	F_PT2_GK

The following abbreviated listings will be produced (templates provided in Section 16.2.3):

Listing	Description	Template (Shells below)
16.2.1	Study dates & disposition of subjects	
16.2.1.1	Listing of Study Dates	L_SD1_PG
16.2.1.2	Listing of Reasons for Withdrawal	L_SD2_PG
16.2.2	Protocol deviations	
16.2.2.1	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	L_DV1_PG
16.2.2.2	Listing of Important Protocol Deviations	L_DV2_PG
16.2.3	Analysis sets, including subjects excluded from analysis	
16.2.3.1	Listing of Analysis Populations	L_AN1_PG
16.2.4	Demographic data & concomitant medication	
16.2.4.1	Listing of Demographic Characteristics	L_DM1_PG
16.2.4.2	Listing of Concomitant Medications	L_CM1_PG
16.2.5	Study drug administration	
16.2.5.1	Listing of Exposure Data	L_EX1_PG

16.2.7	Adverse events	
16.2.7.1	Listing of All Adverse Events	L_AE1_PG
16.2.7.2	Listing of Serious Adverse Events	L_AE1_PG
16.2.7.3	Listing of Adverse Events Leading to Withdrawal from Study	L_AE1_PG
16.2.7.4	Listing of Subject Numbers for Specified Adverse Events	L_AE1_GSK
16.2.7.5	Listing of Reasons for Considering a Serious Adverse Event	L_AE3_GSK
16.2.7.6	Listing of Relationship between System Organ Class and Verbatim Text	L_AE2_GSK
16.2.8	Laboratory values	
16.2.8.1	Listing of Clinical Chemistry Abnormalities of Potential Clinical Importance	L_LB1_PG
16.2.8.2	Listing of Haematology Abnormalities of Potential Clinical Significance	L_LB1_PG
16.2.8	Vital signs, ECGs and physical findings	
16.2.8.1	Listing of Vital Signs of Potential Clinical Importance	L_VS1_PG
16.2.8.2	Listing of ECG data	L_EG1_PG
16.2.6.3	Listing of Abnormal ECG Findings	L_EG2_PG
16.2.9	PET Data	
16.2.9.1	Listing of Volume of Distribution (V_T) and Mean Standardised Uptake Values (SUV)	L_PET_GK

16.3 Data Display Specifications

16.3.1 Table Outlines

Template T_SD1

Table 10.1 Summary of Subject Disposition

Population	Status	Reason for Withdrawal	PAH Patients	Healthy Volunteers	All Subjects
Screened population	Included				
	Failed screening				
Safety population	Included				
	Completed				
	Withdrawn				
		Adverse Event			
		Lack of efficacy			
		Subject reached protocol-defined stopping criteria			
		Study closed/terminated			
		Lost to follow-up			
		Investigator discretion			
		Withdrew consent			

Source: Listing 16.2.xx

Programming notes: *Continued with all treatment groups.*

Template T_DV_GK

Table 10.2 Summary of Important Protocol Deviations

Category/Subcategory	PAH Patients (N=xx) n (%)	Healthy Volunteers (N=xx) n (%)
Any protocol deviations	20 (20%)	22 (22%)
Assessments and/or procedures	10 (10%)	8 (8%)
Failure to report SAE, pregnancy, or liver function abnormalities per protocol	4 (4%)	6 (6%)
Randomization procedures	4 (4%)	6 (6%)
Study treatment supply procedures	4 (4%)	6 (6%)
Other	4 (4%)	6 (6%)
Eligibility criteria not met	6 (6%)	8 (8%)
Not withdrawn after developing withdrawal criteria	10 (10%)	8 (8%)
Not discontinued from study treatment	4 (4%)	6 (6%)
Not withdrawn from study	6 (6%)	8 (8%)
Received wrong treatment or incorrect dose	10 (10%)	8 (8%)
Prohibited medication or device	4 (4%)	6 (6%)
Visit Window	10 (10%)	8 (8%)
Other protocol deviation category	6 (6%)	8 (8%)

Source: Listing 16.2.xx

Template T_DM1

Table 14.1 Summary of Demographic Characteristics

Variable	Statistics	PAH Patients (N=xx)	Healthy Volunteers (N=xx)	All Subjects (N=xx)
Age (y)	n			
	Mean			
	SD			
	Min			
	Median			
	Max			
Gender				
	Female (%)			
	Male (%)			
Race	American Indian or Alaskan			
	Native (%)			
	Asian (%)			
	Black (%)			
	Native Hawaiian or other			
	Pacific Islander (%)			
	White (%)			
	Other (%)			
Ethnicity	Hispanic or Latino (%)			
	Not Hispanic or Latino (%)			
Height (cm)	n			
	Mean			
	SD			
	Min			
	Median			
	Max			
Weight (kg)	n			
	Mean			
	SD			
	Min			

Variable	Statistics	PAH Patients (N=xx)	Healthy Volunteers (N=xx)	All Subjects (N=xx)
	Median			
	Max			
BMI (kg/m2)	n			
	Mean			
	SD			
	Min			
	Median			
	Max			
Smoker	Yes (%)			
	No (%)			
Cigarettes*	n			
(Pack Years)	Mean			
	SD			
	Min			
	Median			
	Max			
Optional (units)				

*includes only those subjects who smoke
Source: Listing 16.2.xx

Programming notes: *Continued with all treatment groups and additional demographic characteristics*

Template T_AGE_GSK

Table 14.3.6.xx Summary of Age Ranges

	No Treatment (N=1)	Treatment A (N=100)	Treatment B (N=100)	Total (N=201)
Age Ranges				
In utero	0	2 (2%)	2 (2%)	4 (2%)
Preterm newborn infants (gestational age <37 weeks)	0	1 (1%)	1 (1%)	2 (1%)
Newborns (0-27 days)	0	3 (3%)	3 (3%)	6 (3%)
Infants and toddlers (28 days-23 months)	0	4 (4%)	4 (4%)	8 (4%)
Children (2-11 years)	0	3 (3%)	3 (3%)	6 (3%)
Adolescents (12-17 years)	0	1 (1%)	1 (1%)	2 (1%)
Adult (18-64 years)	0	59 (59%)	59 (59%)	118 (59%)
>=65-84 years	0	26 (26%)	26 (26%)	52 (26%)
>=85 years	1 (100%)	1 (1%)	1 (1%)	3 (1%)

Template T_DM2

Table 14.3.6.xx Summary of Age Matching

	Difference in matched pairs (PAH-HV)				
n*	Mean	SD	Median	Min	Max

Source: Listing 16.2.xx

Programming notes: *Add the footnote n* number of matched pairs*

Template T_AE1

Table 14.3.3.xx Summary of Treatment-Emergent Adverse Events

		PAH Patients (N=xx)		Healthy Volunteers (N=xx)	
System Organ Class	Preferred Term	n	%	n	%
Number of subjects with AEs					
Gastrointestinal disorders	Total number of subjects				
	Abdominal discomfort				
	Abdominal pain				
	↓				
Nervous system disorders	Total number of subjects				
	Dizziness				
	Headache				
	↓				
↓	↓				

*Subjects with ≥1 adverse event are counted only once per system organ class and preferred term.

Source: Listing 16.2.xx

Programming notes: *Continued with all treatment groups*
SOCs and PTs are sorted in decreasing order of frequency
Presented for all applicable MedDRA system organ classes and terms.

Template T_AE2

Table 14.3.2x Summary of Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term		PAH Patients (N=100)	Healthy Volunteers (N=200)
ANY EVENT	Number of Subject with SAEs	40 (40%)	40 (20%)
	Number of SAEs	50	50
	Number of Drug-related SAEs	20	20
	Number of Fatal SAEs	10	10
	Number of Drug-related Fatal SAEs	5	5
Infections and infestations			
Diabetic Gangrene	Number of Subject with SAEs	10 (10%)	1 (<1%)
	Number of SAEs	15	1
	Number of Drug-related SAEs	5	0
	Number of Fatal SAEs	2	0
	Number of Drug-related Fatal SAEs	1	0
Erysipelas	Number of Subject with SAEs	1 (<1%)	10 (5%)
	Number of SAEs	1	15
	Number of Drug-related SAEs	0	5
	Number of Fatal SAEs	0	2
	Number of Drug-related Fatal SAEs	0	1

Template T_VS1

Table 14.3.6.xx Summary of Vital Signs at Scanning Visit

	Group	Timepoint	n	Mean	SD	Median	Min	Max
Systolic BP (mmHg)	PAH Patients (N=xx)							
	Healthy Volunteers (N=xx)							

Source: Listing 16.2.xx

Programming notes: *Continued with all variables, treatments and time points*

Template T_PT1_GK

Table 14.3.6.xx Summary of Volume of Distribution (V_T)and Mean Standardised Uptake Values (SUV), by Group and Region

Parameter (units)	Region	Group	n	Mean	SD	Median	Min	Max
Mean SUV		PAH Patients (N=xx)						

Mean SUV is calculated over a xx minute period

Source: Listing 16.2.xx

Programming notes: *Continued with all variables, groups and time points. Replace xx with the time period in the footnote .*

Template T_PT2_GK

Table 14.3.6.xx Summary of the Posterior Distribution for Volume of Distribution (V_T)and Mean Standardised Uptake Values (SUV), by Group and Region

					Posterior distribution P(Θ|/x)					
Parameter	Region	Group	Prior Distribution for Θ	Value of σ used in then model	Mean	SD	Median	25th quartile	75th quartile	95% Credible Interval
Mean SUV	Heart Chamber	PAH Patients (N=xx)	normal(0, sd = 100)	1						
		Healthy Volunteers (N=xx)	normal(0, sd = 100)	1						
	Whole Lung									

Number of MCMC iterations, excluding the burn-in iterations = 5,000. Number of burn-in iterations = 10,000
The PET parameters are assumed to follow a normal distribution with unknown mean Θ and known variance σ^2 (i.e. $N(\Theta, \sigma^2)$)
P(Θ|X) is the posterior distribution for Θ given the PET data x. 95% credible intervals based on the highest posterior density interval.
Mean SUV is calculated over a xx minute period

Source: Listing 16.2.xx

Programming notes: *Continued with all end points, regions and groups. Replace xx with the time period in the footnote .*

Template T_PT3_GK

Table 14.4.3 Summary of the Posterior Distribution of the Ratio of Group Means for Volume of Distribution (V_T)and Mean Standardised Uptake Values (SUV), by Region

		Posterior Distribution $P(\Theta_{PAH}\|x_{PAH})/P(\Theta_{HV}\|x_{HV})$					
variable	Region	Mean	SD	Median	Min	Max	95% Credible Interval
Mean SUV	Heart Chamber						
	Whole Lung						

Number of MCMC iterations, excluding the burn-in iterations = 5,000. Number of burn-in iterations = 10,000
95% credible intervals based on the highest posterior density interval.
Note: PAH = PAH Patients, HV = Healthy Volunteers

Source: Listing 16.2.xx

Template T_PT4_GK

Table 14.3.6.xx Posterior Probability that the Ratio of Group Means for Volume of Distribution (V_T)and Mean Standardised Uptake Values (SUV) Exceeds a Certain Value, by Region

Parameter (units)	Region	P(ratio) > 0.5	P(ratio) > 1	P(ratio) > 2
Mean SUV				

Note: P(ratio) > 1 is the probability that the posterior ratio of group means exceeds 1 based on 5,000 simulated posterior predicted values
Ratio of PAH patients to Healthy Volunteers.
Mean SUV is calculated over a xx minute period

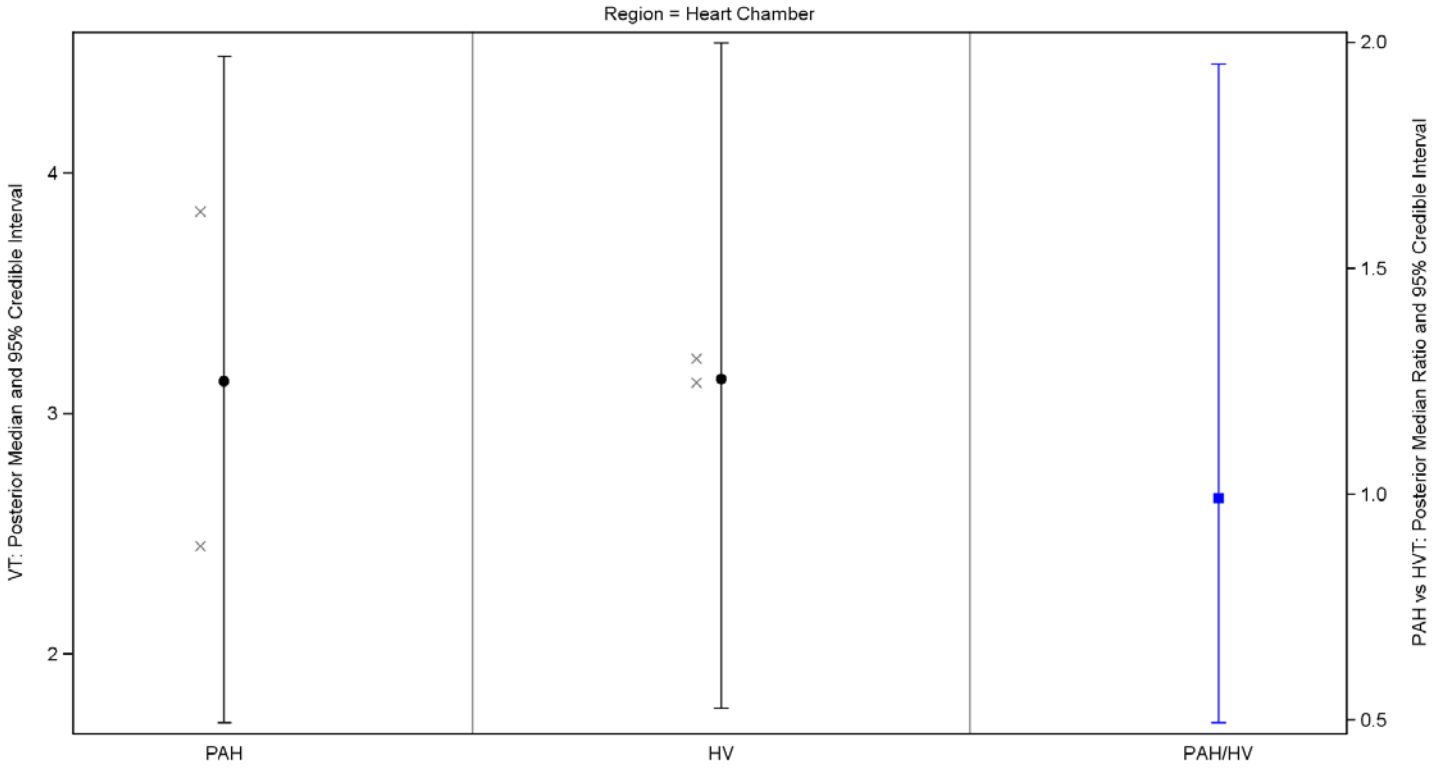
Source: Listing 16.2.xx

Programming notes: *Continued with all variables. Replace xx with the time period in the footnote .*

16.3.2 Figure Outlines

Template F_PT1_GK

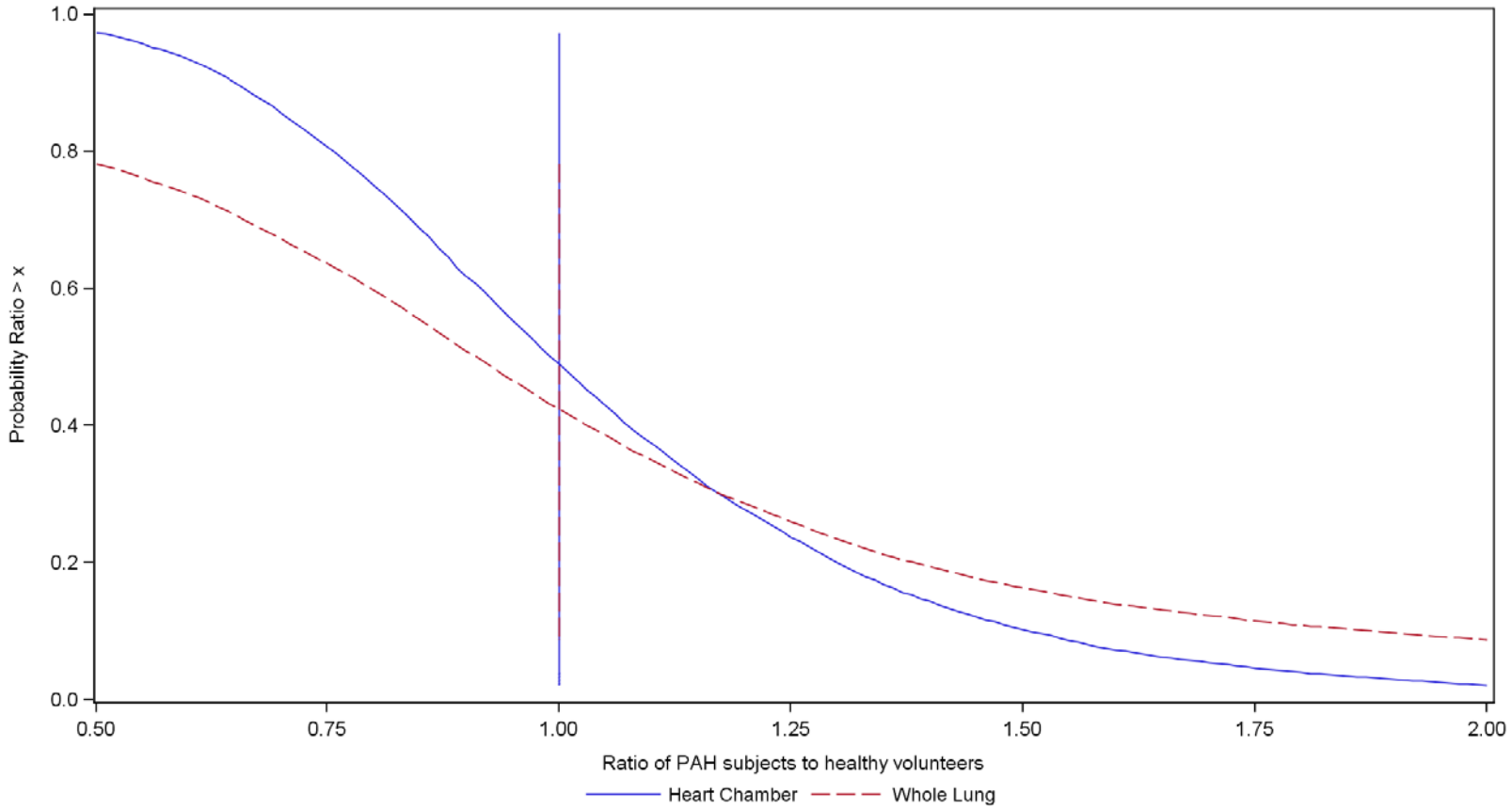
Figure 14.3.6.xx Plot of the Posterior Distribution of the Volume of Distribution (V_T) for the Group Means and the Ratio of the Group Means, by Region



95% credible intervals based on the highest posterior density interval.
Programming note: use the same symbols for each of the matched pairs

Template F_PT2_GK

Figure 14.3.6.xx Plot of the Posterior Probability that the Ratio of the Group Means Exceeds a Certain Value for the Volume of Distribution (V_T), by Region



16.3.3 Listing Outlines

Template L_SD1_PG

Listing 16.2.x.xx Listing of Study Dates

Group	Subject	Screening	Scanning visit	Follow Up

Template L_SD2_PG

Listing 16.2.x.xx Listing of Reasons for Withdrawal

Group	Subject	Date of Withdrawal	Study Day	Reason

Template L_DV1_PG

Listing 16.2.x.xx Listing of Subjects with Inclusion/Exclusion Criteria Deviations

Group	Subject	Type	Criterion
		Inclusion	
		Exclusion	

Template L_DV2_PG

Listing 16.2.2.3 Listing of Subjects with Important Protocol Deviations

Group	Subject	Protocol Deviation

Template L_AN1_PG

Listing 16.2.x.xx Listing of Analysis Populations

Group	Subject	Screened Population	Safety Population

Template L_DM1_PG

Listing 16.2.x.xx Listing of Demographic Characteristics

Group	Subject	Date of visit	Year of birth	Age (y)	Gender	Race	Ethnicity	Height (cm)	Weight (kg)	BMI (kg/m2)
PAH Patients Healthy Volunteers										

Group	Subject	Smoking Status	Date Last Smoked	Cigarettes (daily)	Number Years Smoked	Cigarettes (Pack Years)	Allen's Test	INR (units)
PAH Patients Healthy Volunteers								

Template L_CM1_PG

Listing 16.2.x.xx Listing of Concomitant Medications

Group	Subject	Drug Name/ Indication	Dose/ Units/ Freq/ Route	Date/time Started/ Date Stopped	Time Since Last Dose	Started Pre-Trial?	Ongoing Medication?

Template L_EX1_PG

Listing 16.2.x.xx Listing of Exposure Data

Group	Subject	Start Date/ Start Time of Dose	Stop Date/ Stop Time of Dose	Dur-ation (days)	Dose	Dose Unit	Formulation/ Route	Frequency
PAH Patients	PPD	PPD	PPD	46	25	mg	Tablet/ Oral	2xday

Template L_AE1_PG

Listing 16.2.x.xx Listing of All Adverse Events

Group	Subject	System Organ Class/ Preferred Term/ Verbatim Text	Outcome/ Onset Date/Time/ Resolved Date/Time/ Duration	Time Since Last Dose	Severity/ Serious/ Withdrawal	Frequency/ Action Taken (1)/ Other Action Taken	Related to Study Treatment/ Treatment Emergent?
PAH Patients	PPD	Gastrointestinal disorders / Intestinal spasm/ Entero-spasm	Resolved/ PPD 13:05/ PPD 7:50/ 34d 4h 5m	10d 7h 3m	Mild/ No/ Yes	Intermittent/ Dose not changed/ None	Possibly/ Yes

(1) Action Taken with Study Treatment

Template L_AE1_GSK

16.2.7.4 Listing of Subject Numbers for Specified Adverse Events

System Organ Class/ Preferred Term	Group	No. with Event	Unique Subject Id.
Gastrointestinal disorders/ Dyspepsia	PAH Patients	x	PPD

Template L_AE2_GSK

16.2.7.6 Listing of Relationship between System Organ Class and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Blood and lymphatic system disorders	Lymphadenopathy	ENLARGED LYMPH NODE
Cardiac disorders	Palpitations	HEART PALPITATION
	Tachycardia nos	TACHYCARDIA

Template L_AE3_GSK

16.2.7.5 Listing of Reasons for Considering a Serious Adverse Event

Site Id./ Unique Subject Id.	Age(YEARS)/ Sex/ Race Detail/ Weight (kg)	Preferred Term/ VERBATIM TEXT	Outcome/ Onset Date/ Date of Resolution/ Duration	Death [1]	Life [2]	Hosp [3]	Disab [4]	Birth Dfect [5]	Med Imp [6]	Prot [7]
PPD	57/ M/ ASIAN - JAPANESE HERITAGE/ 62.0	Abnormal liver function tests/ AST INCREASED	FATAL/ PPD 1999PPD / 120 d	Y	Y	Y				Y
	65/ F/ MULTIPLE/ 75.0	Candidiasis mouth/throat/ ORAL CANDIDIASIS	RECOVERED/RESOLVED / PPD 85 d			Y			Y	

[1] Resulted in death.
[2] Was life-threatening.
[3] Required hospitalization or prolongation of existing hospitalization.
[4] Resulted in persistent or significant disability/incapacity.
[5] Congenital anomaly/birth defect.
[6] Other medically important serious event.
[7] Protocol specified serious event.

Template L_LB1_PG

Listing 16.2.x.xx Listing of Clinical Chemistry Abnormalities of Potential Clinical Importance

Group	Subject	Lab test (units)	Planned Relative Time	Date/Time	Value	Range	NR
	PPD	Alk Phos (U/L)					L
							H
		ALT (U/L)					

NR = Normal Range flag
H = Above reference interval, L = Below reference interval,

Template L_VS1_PG

Listing 16.2.x.xx Listing of Vital Signs of Potential Clinical Importance

Group	Subject	Planned Relative Time	Date/Time	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	Etc (units)
PAH Patients		24 H	26SEP2012:09:57	63	148*	

* Value of potential clinical importance

Template L_EG1_PG

Listing 16.2.x.xx Listing of ECG Values

Treatment	Subject	Planned Relative Time	Date/Time	Heart Rate (bpm)	PR Int. (msec)	QRS Dur. (msec)	QRS Axis (deg)	QT int (msec)	QTcB (msec)	QTcF (msec)

Programming notes:

Template L_EG2_PG

Listing 16.2.x.xx Listing of Abnormal ECG Findings

Treatment	Subject	Planned Relative Time	Date/Time	ECG Finding	Comment on Clinical Significance

Programming notes: *Lists only values with Normal variant='No' or with comment on ECG result*
ECG Finding contains Physician's Opinion from CRF and relates to whole trace (not individual parameters), e.g. Normal, Abnormal - NCS or Abnormal - CS

Template L_PE1_PG

Listing 16.2.x.xx Listing of Abnormal Physical Examination Findings

Group	Subject	Planned Relative Time	Date/Time	Site	Details

Programming Notes: *List only findings with an 'abnormal' result.*
If subjects have multiple abnormal sites at a given time, create a separate row for each site.

Template L_PET_GK

Listing 16.2.x.xx Listing of Volume of Distribution (V_T) and Mean Standardised Uptake Values (SUV)

Group	Subject	Date/Start Time / Stop Time	Region	Mean Standardised Uptake Value (SUV)	Volume of Distribution (V_T) (mL/cm^3)

Programming Notes: *Add the footnote Mean SUV is calculated over a xx minute period . Note xx in the footnote will be replaced by the time period*

Appendix A: Laboratory Ranges

Laboratory Assessments Parameters		Sex	Max age	Normal Range	Range for potential clinical concern	
	Unit				Low	High
Haematology						
Platelet Count	10^9/L	F	NA	163 - 376	100	600
Platelet Count	10^9/L	M	NA	129-346	100	600
Red blood cell count	10^12/L	F	NA	3.7-5.1	NA	NA
Red blood cell count	10^12/L	M	NA	4.4-6.0	NA	NA
Neutrophils	10^9/L	Both	NA	1.57-6.81	1.2	13
Hemoglobin	pg	F	NA	114-153	110	175
Hemoglobin	pg	M	NA	133-170	125	185
Lymphocytes	10^9/L	Both	NA	0.89-2.88	0.5	4
Hematocrit	L/L	F	NA	0.338-0.445	0.3	0.55
Hematocrit	L/L	M	NA	0.386-0.489	0.35	0.65
MCV					NA	NA
MCH					NA	NA
MCHC					NA	NA
Monocytes	10^9/L	Both	NA	0.09-0.90	NA	NA
Eosinophils	10^9/L	Both	NA	0.05-0.55	NA	0.55
Basophils	10^9/L	Both	NA	0.00-0.14	NA	NA
Cinical Chemistry						
BUN (Urea)	mmol /L	F	54	2.2- 6.7	NA	12
BUN (Urea)	mmol /L	F	120	3.0-8.6	NA	12
BUN (Urea)	mmol /L	M	54	2.7-7.6	NA	12
BUN (Urea)	mmol /L	M	120	3.0-8.6	NA	12
Potassium	mmol/L	Both	NA	3.5-5.3	3	5.5
AST (SGOT)	lU/L	F	NA	<=30	NA	200
AST (SGOT)	lU/L	M	NA	<=62	NA	200
Total bilirubin		F	NA	<= 19.7	NA	40
Total bilirubin		M	NA	<=29.3	NA	40
Direct Bilirubin		F	NA	<=3.9	NA	NA
Direct Bilirubin		M	NA	<=6.2	NA	NA
Creatinine		F	NA	42-72	NA	150
Creatinine		M	NA	53-102	NA	150
Sodium	mmol/L	Both	NA	133-146	125	160
ALT (SGPT)	lU/L	F	NA	<=33	NA	200
ALT (SGPT)	lU/L	M	NA	<=70	NA	200

Total Protein	g/L	Both	NA	60-80	NA	NA
Glucose	mmol/L	Both	NA	2.8-5.8	2	10
Calcium	mmol/L	Both	NA	2.2-2.6	2	2.6
Albumin	g/L	Both	NA	35-50	30	60

Appendix B: Sample Page Layout

GlaxoSmithKline Ltd : 204746 Page x of y*

Population: [Pop]

Table [number] [title]

Column headers

Main body of output

Source:Listing[16.2.xx]

Footnotes about the table or listing text go here.

Program: [Prog Name] [Date] HMR 15-505

Produced By:[Username]

*y = last page of individual output