Division: Worldwide Development
Retention Category: GRS019
Information Type: Clinical Pharmacology Reporting and Analysis Plan

Title:	Phase I Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Doses of Topical GSK1278863 in Healthy Volunteers and Diabetic Patients, and Repeat Doses of GSK1278863 in Diabetic Patients for the Treatment of Diabetic Foot Ulcer

Compound Number:	GSK1278863
Effective Date:	18-10-2017

Description:

The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in the Clinical Pharmacology Study Report for Protocol PWH115760. This RAP is intended to describe the safety, pharmacokinetic, and pharmacodynamic analyses required for the study. This document will be provided to the study team members to convey the content of Statistical Analysis Complete (SAC) deliverables.

Identifier/Version Number: [CM2009/00071/00]

Subject:

Author's Name and Functional Area:

PPD	Clinical Statistics, MPC

Approved by:

The Clinical Statistics Director (or designee) will give final approval

PPD	Senior Statistics Director PCPS, Statistics, Programming and Data Strategy	DD-MMM-YY

TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
ANCOVA	Analysis of Co-variance
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
%AUCex	Percentage of AUC(0-∞) obtained by extrapolation
AUC(0-x)	Area under the concentration-time curve from zero (pre-dose) to some fixed nominal time x
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
β-HCG	Beta-Human Chorionic Gonadotropin
BA	Bioavailability
BE	Bioequivalence
BMI	Body mass index
BP	Blood pressure
BPM	Beat Per Minute
BQL	Below the quantification limit
BUN	Blood urea nitrogen
CBC	Complete blood count
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CIB	Clinical Investigator's Brochure
CLr	Renal clearance
CL	Systemic clearance of parent drug
CL/F	Apparent clearance following oral dosing
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
Ct	Last observed quantifiable concentration
CDMP	Clinical Document Management and Publishing
CO_2	Carbon dioxide
CPDM	Clinical Pharmacology and Discovery Medicine
CPK	Creatine phosphokinase
CPKMS	Clinical Pharmacokinetics Modelling & Simulation
CPSR	Clinical Pharmacology Study Report
CP-RAP	Clinical Pharmacology Reporting and Analysis Plan

CRF	Case Report Form
CRO	Contract Research Organization
CRU	Clinical Research Unit
CV	Coefficient of variance
DBP	Diastolic blood pressure
DDS	Drug Development Sciences
DMPK	Discovery Medicine Pharmacokinetics
ECG	Electrocardiogram
ECP	Endothelial Progenitor Cell
EDC	Electronic data capture
EISR	Expedited Investigator Safety Report
EPO	Erythropoietin
Fabs	Absolute bioavailability of drug determined following extravascular and intravascular dosing
FDA	Food and Drug Administration
Frel	Relative bioavailability of drug determined between two formulations of the same drug following similar or different extravascular route of administration
FSH	Follicle Stimulating Hormone
FTIH	First time in humans
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilence
GGT	Gamma glutamyltransferase
GLS	Geometric Least-Squares
GSK	GlaxoSmithKline
HARP	GSK system designed to aid the statistical analysis of clinical trials data (Phases I to IV).
hCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
HR	Heart rate
IB	Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IU	International Unit
IV	Intravenous
Kg	Kilogram

λz	Terminal phase rate constant
L	Liter
LFTs	Liver function tests
Ln	Naperian (natural) logarithm
LOQ	Limit of quantification
LLQ	Lower limit of quantification
µg	Microgram
µL	Microliter
MAT	Mean absorption time
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
MRT	Mean residence time
MSDS	Material Safety Data Sheet
Msec	Milliseconds
NQ	Non-quantifiable concentration measured as below LLQ
PAH	Pulmonary Artery Hypertension
PASP	Pulmonary Artery Systolic Pressure
PHD	HIF- proly hydroxylases
PD	Pharmacodynamic
PGx	Pharmacogenetics
PK	Pharmacokinetic
PSRI	Periodic Safety Reports for Investigators
QC	Quality control
QD	Once daily
RAP	Reporting and Analysis Plan
RBA	Relative Bioavailability
RBC	Red blood cells
RV	Right Ventricular
SAE	Serious adverse event(s)
SAS	Statistical Analysis Software
SD	Standard deviation
SDTM	Study Data Tabulation Model
SOP	Standard Operating Procedure
SPM	Study Procedures Manual
SUSAR	Suspected, Unexpected, Serious Adverse drug Reaction
T	Infusion duration
T	Time of last observed quantifiable concentration
t½	Terminal phase half-life
T	Dosing interval
Tlag	Lag time before observation of drug concentrations in sampled matrix
Tlast	Time of last quantifiable concentration

Tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
UK	United Kingdom
US	United States
Vd/F	Apparent volume of distribution after extravascular (e.g., oral) administration
WBC	White blood cells

Trademark Information

Trademarks of the GlaxoSmithKline group of companies

Trademarks not owned by the GlaxoSmithKline group of companies

1. INTRODUCTION

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

Revision Chronology:		
2011N121462_00	2012-Mar-20	Original
2011N130130_01	2012-NOV-21	Amendment No.:01 This amendment reflects changes to the patient eligibility criteria, stopping criteria and sampling time points per regulatory feedback.
2011N130130_02	2013-FEB-14	Amendment No.: 02 This amendment reflects changes to DFU patient eligibility criteria number 7 and screening procedures in Part A as well as minor edits for clarity.
2011N130130_03	2013-JUN-06	Amendment No.: 03 This amendment clarifies an eligibility criterion and DFU clinical assessments as well as minor edits for clarity.
2011N130130_04	2014-JAN-29	Amendment No.: 04 This amendment reflects changes in the container type used to supply the bulk ointment. Minor edits are also included for clarity.
2011N130130_05	2014-JUN-02	Amendment No.: 05 This amendment reflects modifications to the DFU inclusion and exclusion criteria, hemoglobin stopping criteria and a change in biopsy collection expectations. Minor edits are also included for clarity. Amendment 5 was republished before distribution, with the DNG number of 2011N130130_06, in order to correct an error.
2011N130130_07	2014-NOV-19	Amendment No. 06: Due to emerging data, specific areas of Part B of the protocol were redesigned to better meet the needs of the study. To date Part A GSK1278863 systemic exposure is below analytical limits of quantification and therefore the stand alone single dose

		assessment in Part B is no longer required. Eclusion criteria number 10 was adjusted to better reflect the patient population. Other minor edits were also included for clarity.
PWH115760 RAP_V11	2017-SEP-19	Amendment No. 07 Due to the termination of this indication some TLF's were deleted in order to streamline outputs
PWH115760 RAP_V13	2017-OCT-1	Amendment No. 08 Text revisions to correspond with the TLF revisions in the prior amendments. Additional TLF's added in order to comply with data disclosure.

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

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

2.1. Study Objectives

2.1.1. Primary Objectives

- To evaluate the safety and tolerability of the topical application of GSK1278863 in healthy volunteers and patients with diabetic foot ulcer following single dose (SD) and repeat dose (RD) administration.
- To determine the pharmacokinetics of single and repeat doses of GSK1278863 and its metabolites following SD and RD administration.

2.1.2. Exploratory Objectives

To evaluate the effect of single and repeated doses of GSK1278863 on:

- Gene expression for HIF targets and genes associated with wound healing in the DFU.
- Local levels of biomarkers (e.g. inflammatory panel for cytokines, proteases).
- Bioburden in the wound (e.g. rtPCR for bacterial load).
- Physical characteristics of the wound (e.g. rate of healing, wound volume).
- Clinical characteristics of the wound (e.g., exudate, granulation tissue, color).

To evaluate the effect of repeat doses of GSK1278863 on:

- Gene expression for HIF targets and genes associated with wound healing in the DFU.
- Local levels of biomarkers (e.g., inflammatory panel for cytokines, proteases, inflammatory cell counts, collagen turnover).
- Bioburden in the wound (e.g., rtPCR for bacterial load).
- Biomarkers of angiogenesis via blood flow and oxygen availability [e.g., skin perfusion pressure (SPP) and pulse volume (PV), hyperspectral imaging].
- Tissue concentrations of GSK1278863 after repeat dosing in selected subjects, as site capabilities to perform the assessment permit.
- Circulating biomarkers for HIF activation (e.g., hemoglobin, hepcidin, EPO).
- Physical characteristics of the wound (e.g. rate of healing, wound volume).
- Clinical characteristics of the wound (e.g., exudate, granulation tissue, color)
- The dose-response and/or exposure-response relationships of repeat doses of GSK1278863 using PK/PD modeling for selected primary and exploratory endpoints (as data permit).

2.2. Study Endpoints

2.2.1. Primary Endpoints

- Clinical safety and tolerability data including spontaneous AE reporting, ECGs, vital signs, nurse/physician observation and clinical laboratory values after single and/or repeat doses of GSK1278863.

- Pharmacokinetic parameters of GSK1278863: SD: Cmax, tmax, terminal t½, tlag, AUC(0-∞), AUC(0-t), (AUC(0-∞) and RD: Cmax, tmax, terminal t½, AUC(0-t), (AUC(0-∞) and accumulation ratio), after single and/or repeat doses of GSK1278863, as data permit.

2.2.2. Exploratory Endpoints

After single doses of GSK1278863 (as data permit based on sampling feasibility):

- Change from baseline in gene expression (mRNA) in the DFU tissue.
- Change from baseline in biomarkers in the DFU (e.g., cytokine panel, protease panel).
- Change from baseline on bioburden in the DFU (e.g., rtPCR for bacterial load).
- Physical parameters of the wound (e.g., rate of healing, wound volume).
- Clinical characteristics of the wound (e.g., exudate, granulation tissue, color).

After repeat doses of GSK1278863 (as data permit based on sampling feasibility):

- Change from baseline in gene expression (mRNA) in the DFU tissue.
- Change from baseline in biomarkers of angiogenesis and blood flow and oxygen availability [e.g., skin perfusion pressure (SPP) and pulse volume (PV), hyperspectral imaging].
- Change from baseline in biomarkers in the DFU (e.g., cytokine panel, protease panel, macrophage quantification)
    a. If the methodology can be validated at the site(s) cell proliferation and collagen turnover will be assessed.
- Change from baseline on bioburden in the DFU (e.g., rtPCR for bacterial load).

- Tissue concentrations of GSK1278863 in selected subjects as determined from micro-dialysis during RD, if feasible to conduct the assessment.
- Change from baseline on circulating biomarkers of systemic HIF activation in the blood (e.g., hemoglobin, hepcidin, EPO).
- Physical parameters of the wound following repeat doses of GSK1278863, for example:
    a. Rate of wound healing (via planimetry).
    b. Change in wound volume (Silhouette software).
    c. Percentage of subjects with closure of the study DFU.
    d. Time to DFU closure.
    e. Time required to achieve a certain percent of wound closure.
    f. Incidence of DFU closure.
- Clinical characteristics of the wound (e.g., exudate, granulation tissue, color).
- Correlation between GSK1278863 dose and/or exposure and parameters of pharmacodynamic activity, safety, and tolerability, as data permit.

Due to the termination of this project and the limitations of the data some of the exploratory endpoints have been modified for reporting as follows:

- Gene expression and qPCR data will be analysed by Target Sciences and the results will be summarized in a separate report.
- Instead of change from baseline, descriptive summaries will be created for the angiogenesis and blood flow and oxygen availability, the biomarkers in the DFU, the bioburden in the DFU, and biomarkers of systemic HIF activation in the blood.
- The only physical parameter to be evaluated is change in wound volume and area
- Correlation between GSK1278863 and PD and safety will not investigated further, unless multiple safety issues make is necessary

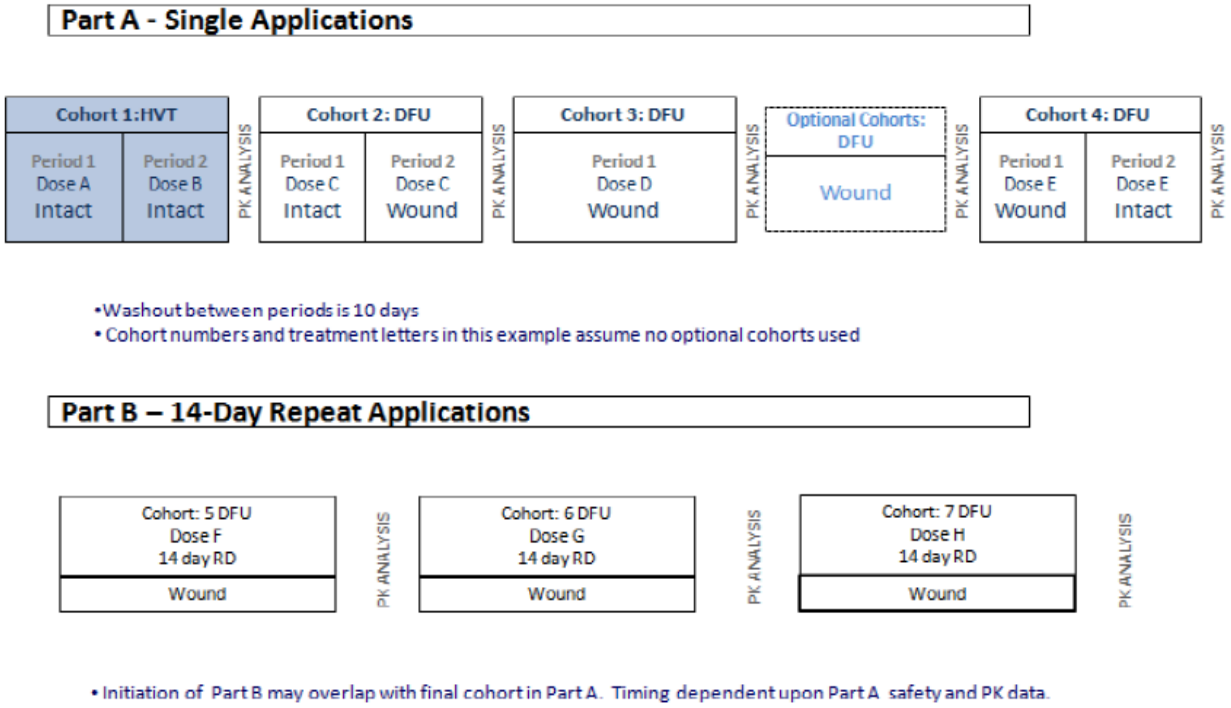
Given the time it takes to process the assay, the histology data will not be available for inclusion in the final data base at the time of database freeze. Therefore, this data will be analysed when it becomes available. If the results are available before CSR, then they will be included in the study report; otherwise, they will be included in an addendum to the study report or separate study report.

3. STUDY DESIGN

This first-time-in-human study of the topical formulation of GSK1278863 is designed as an initial exploration of the safety, tolerability, pharmacokinetic and pharmacodynamic effects. The study will be performed in a cohort of healthy volunteers and then in diabetics, including application both to healthy, intact skin, as well as to diabetic foot ulcers directly. This study includes two parts (Part A and Part B). Part A is designed to evaluate single applications of GSK1278863. Part A will include one cohort of healthy volunteers (intact skin) and approximately 3 cohorts of diabetic subjects with foot ulcer. Part B is designed to evaluate repeat applications of GSK1278863 in diabetics, both in the clinic and by subjects at home. Part B will include approximately 3 cohorts in which the concentration of drug applied will be determined by pharmacokinetic data from Part A and earlier cohorts in Part B. For both parts of the protocol, additional cohorts may be added as necessary to obtain relevant safety, pharmacokinetic or pharmacodynamic data.

Furthermore, for both Parts A and B, there will be at least one week between cohorts for review of safety, tolerability and PK data by the GSK study team (unblinded) and the Investigator (blinded). Pharmacodynamic data, where available, may be obtained for review. Enrollment to each cohort may be staggered (i.e., cohorts do not have to be enrolled as one group). However, all enrollments should occur within ~4 weeks for each cohort. Diabetic subjects, in either Part A or B, will require a two week run in period in which standard of care is given before treatment of the DFU with GSK1278863 or placebo in order to ensure the wound does not show a greater than 30% reduction in size.

Figure 1 Study Design/Schematic



Subjects will be assigned to receive GSK1278863A or vehicle (placebo) in Part A and GSK1278863A or vehicle or SOC only (moist occlusion) in Part B in accordance with the randomization schedule generated by GSK, prior to the start of the study, using validated internal software.

Based on data from Part A it was decided that there would only be one cohort in part B.

3.1. Sample Size

There is no formal calculation of power or sample size in this study. Sample sizes are based on feasibility. A sample size of six subjects per active single dose (Part A), and twelve subjects per active repeated dose (Part B) completing the study are feasible sample sizes to provide sufficient safety and PK data for this FTIH study. The target sample size is set at 8 subjects per cohort in Part A, (6 on active treatment and 2 on placebo), and 16 per cohort in Part B, (12 on active treatment, 2 on placebo and 2 receiving standard of care). The sample size for the placebo at each dose level is set at two to avoid subject bias in safety assessment.

4. PLANNED ANALYSES

4.1. Interim Analyses

There will be no formal interim analysis; however, all preliminary safety, tolerability, and available pharmacokinetic data will be reviewed internally at GSK prior to each dose escalation (GSK study staff are unblinded).

4.2. Final Analyses

The final planned SAC analyses will be performed after all subjects have completed or withdrawn from the study and after the database freeze/unblinding is declared.

5. ANALYSIS POPULATIONS

All Subject Population: All subjects who receive at least one dose of study drug (including GSK1278863, placebo and standard care) will be included in the All Subject Population. Randomized subjects will only be excluded if there is clear documented evidence of failure to take any study medication. Subjects in the All Subject Population will be analyzed according to the treatment received and will be used for the reporting of safety and study population.

Enrolled: All participants who sign informed consent and for whom a record exists on the study database. This population will be used for the tables/listings of reasons for withdrawal before randomization and listings of AEs and SAEs for non-randomized participants.

Pharmacodynamic (PD) Population: All subjects who provide pharmacodynamic (PD) data will be included in the PD population. This population will be used in the evaluation of PD. For the change from baseline assessment, only those providing both evaluable baseline and post-dose values (so that the change can be calculated) will be included in the analysis. All subjects in the PD Population will be analyzed according to the treatment they actually received.

Pharmacokinetic (PK) Population: All subjects from whom a pharmacokinetic (PK) sample has been obtained and analyzed will be included in the PK population. This population will be used for reporting of PK concentration and the PK parameters.

6. HYPOTHESES AND TREATMENT COMPARISONS

This study is designed to evaluate the safety and tolerability of topical application of GSK1278863 in healthy volunteers and patients with diabetic foot ulcer following single dose (SD) and repeat dose (RD) administration. No formal hypothesis will be tested. For each primary pharmacokinetic endpoint, point estimates and corresponding

95% confidence intervals will be constructed for GSK1278863 and it metabolites for SD and RD respectively. Comparison of PD endpoints, including physical parameters of the wound, clinical characteristics of the wound, gene expression, biomarkers, bioburden, etc, will be performed with GSK1278863 versus placebo or standard care as data permit.

7. TREATMENT AND OTHER SUB-GROUP DESCRIPTIONS FOR DATA DISPLAYS

Randomisation		**Final Data Display (i.e. HARP / other)**
Code	**Treatment Description**	**Treatment Description***
A	0.3 mg GSK1278863	300mg of 0.1% ointment to deliver 300µg of GSK1278863- SD
B	GSK1278863 Single Dose B	300mg of 1% ointment to deliver 3000µg of GSK1278863- SD
C	GSK1278863 Single Dose C	0.1% of GSK1278863 ointment at 25 mg/cm^2 SD
D	GSK1278863 Single Dose D	1% of GSK1278863 ointment at 25 mg/cm^2 SD
E	GSK1278863 Single Dose E	1% of GSK1278863 ointment at 100 mg/cm^2 SD
R1r	GSK1278863 Repeat Dose R1r	1% of GSK1278863 ointment at 100 mg/cm^2 RD
PR1r	Placebo	Placebo RD
P	Placebo	Placebo SD
Sr	Standard of Care	Standard of Care RD

* for dose applies to DFU patients, since the actual dose depends on the size of the wound, the treatment description should use a volume measure similar as used for Doses C and D once the actual dose formulation becomes available.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

Data will be listed and summarized according to GlaxoSmithKline reporting standards, where applicable.

8.1. Reporting Conventions

- All the data will be listed for clinical safety and tolerability evaluation.
- Missing data will not be imputed.
- Actual times relative to study drug dosing will be used in data listings. Planned times relative to study drug dosing will be used in data summaries.
- Any changes from the analyses within this reporting and analysis plan will be stated in the final study report
- Analyses are performed using the SAS/STAT® module of the SAS® System, Version 9.3 (SAS and SAS/STAT are registered trademarks of the SAS Institute Inc., Cary, NC, USA). Programs will be imported into HARP and the final output will be produced by running drivers in HARP.
- Sections 10 to 13 contain the details regarding the planned analyses and see Section 15.2 for the data displays for decision critical results.

- For subjects who entered multiple cohorts, the subject number of the very first entry will be used as the subject ID for reporting purpose.

8.2. Data Management

The data collection tool for this study will be GSK-defined electronic case report forms (CRFs). In all cases, subject initials will not be collected nor transmitted to GSK. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures. Original CRFs will be retained by GSK, while the investigator will retain a copy.

Data Type	Source	Format of Data	Planned Date of Final File[1]	Responsibility
Study population, Safety, PD sampling	Inform Database	IDSL data	DBR	CPSSO
Safety Laboratory Data	Quest Central Laboratory	IDSL data	DBR	CPSSO/External Vendor
PK Concentration	SMS2000 data files	data file	DBR	DMPK
Biomarker/bio burden	External Vendor Forsyth files through external alliance portal	.xlsx and. cel files	DBR	CPSSO/ External Vendor/Target Sciences
PD	CRO CPC – files through external alliance portal	IDSL data	DBR	CPSSO/External Vendor

[1]This is for study teams to determine upfront if there is a possibility of not meeting the completion of the CPSR within 6 months of LSLV (i.e. novel data that may not be available until several months after LSLV).

8.3. Premature Withdrawal and Missing Data

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

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

No imputations will be made for missing data.

8.4. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with. Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations are captured and categorized on the protocol deviations dataset. This dataset will be the basis for listings of protocol deviations.

A separate listing of all inclusion/exclusion deviations will also be provided. This listing will be based on data as recorded on the inclusion/exclusion page of the eCRF.

8.5. Baseline Definition

Baseline values for safety and PD parameters will be calculated for each subject as defined in the following table:

The following table indicates the baseline observations to be used in the analyses:

Parameter	**Visit of Baseline Observation**
Safety:	
ECG	Day 1 pre-dose
Laboratory	Day 1 pre-dose
Vital Signs	Day1 pre-dose (weight/height at screening)
Demographics	Screening
PD:	
Gene expression	Day 1 pre-dose
Biomarkers	Day 1 pre-dose
Physical characteristics	Day 1 pre-dose
Clinical characteristics	Day 1 pre-dose
PK parameters	Day 1

Note for cohort 2, baseline should be Day1 predose on Period 2.

For those without baseline run in, screening visit should come from baseline run in for reporting purpose.

If, for any parameter, the baseline has a missing value or blow LLQ, then the most-recent non-missing value obtained before dosing will be used as the baseline value for that parameter.

8.6. Derived and Transformed Data

8.6.1. Change from Baseline

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

8.6.2. Multiple Measurements at One Time-point

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

8.6.3. Derived parameters for EPO

Cmax, tmax and AUC of EPO concentration will be derived for each subject by the study day (Part A: Day 1; Part B: Day 1, Day 8, Day14 or Day21) .

The maximum observed concentration (Cmax) and the first time of its occurrence (tmax) will be obtained directly from the EPO concentration-time data for each subject by study day.

AUC will be calculated using linear trapezoidal rules. Let C1 and C2 be two adjacent concentration point and T1 and T2 be corresponding two adjacent time points, then according to the trapezoidal rule, the partial AUC between T1 and T2, AUC[T1, T2]= (C1+C2)*(T2-T1)/2, and total AUC is the sum of all partial AUC's within the defined time window.

8.6.4. Derived parameters for time to event measures

Time to events for wound healing will be derived using a first occurrence approach as follows:

x% healed: the x% healing event is recorded when percent change from baseline of area of wound (or volume of wound) is -x% or lower; the time of first occurrence is the event time, x can be 30, 50 or 75;

The full closure event is recorded when the wound is fully healed, the event time is the first occurrence time of the event.

The event time (number of days) = date of event occurrence – date of Randomization +1

8.6.5. Derived Parameters for Metabolite:Plasma Exposure Ratios

If data permit, Metabolite : Parent drug systemic exposure ratios (corrected for molecular weight) will be calculated for plasma AUC and Cmax parameters as follows:

$$\text{M: P AUC ratio} = \frac{\text{Metabolite AUC}/\text{Metabolite MW}}{\text{GSK1278863 AUC}/\text{GSK1278863 MW}}$$

$$\text{M: P Cmax ratio} = \frac{\text{Metabolite Cmax}/\text{Metabolite MW}}{\text{GSK1278863 Cmax}/\text{GSK1278863 MW}}$$

Compound	Molecular Weight (MW)
GSK1278863 (parent)	393.442
GSK2391220 (metabolite)	425.442
GSK2531403 (metabolite)	425.442
GSK2487818 (metabolite)	425.442
GSK2506102 (metabolite)	425.442
GSK2531398 (metabolite)	425.442
GSK2531401 (metabolite)	441.442

8.6.6. Derived Parameters for Actual Drug Administered

In Part A, the difference of syringe weights will be calculated for determination of amount of dose administered. Predose syringe weight will reflect the empty syringe weight plus amount of drug to be administered; postdose syringe weight will reflect the empty syringe weight plus any residual drug remaining in syringe after dosing.

$$\text{Amount of Dose Administered} = \text{Syringe weight predose} - \text{Syringe weight postdose}$$

In Part B, the difference in ointment tube weights will be calculated for a general assessment of patient compliance by determining the average amount of dose administered in the repeat dose portion of the study. Predose tube weight will reflect the tube weight prior to dosing; postdose tube weight will reflect the tube weight when the patient returns for their office visits throughout the repeat dose portion of the study.

$$\text{Average Amount of Dose Administered} = \frac{\text{Tube weight predose} - \text{Tube weight postdose}}{\text{Number of days}}$$

8.7. Values of Potential Clinical Importance

Laboratory Values of Potential Clinical Importance (Healthy Volunteers)

Hematology Analyte	Effect	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
White Blood Cell Count (x10^9/ L)		0.5	2
Neutrophil Count (x10^9/ L)		0.75	
Hemoglobin (g/L)	Low	< -25 decrease from baseline	
	Male		1.1
	Female		1.1
Hematocrit (Ratio of 1)	Low	< -0.1 decrease from baseline	
	Male		1.1
	Female		1.1
Platelet Count (x10^9/ L)		0.5	1.75
Lymphocytes (x10^9/ L)		0.75	

Chemistry Analyte	Effect	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
Albumin (g/L)			
Calcium (mmol/L)		0.85	1.1
Creatinine (μmol/L)			
	High	≥ 22 increase from baseline (Note 22 μmol/L ≈ 0.25 mg/dL)	
Glucose (mmol/L)		0.71	1.41
Potassium (mmol/L)		0.86	1.1

Liver Function Test Analyte	Effect	Potential Clinical Importance (PCI) Range	Unit
ALT/SGPT	High	≥ 2x ULN	U/L
AST/SGOT	High	≥ 2x ULN	U/L
AlkPhos	High	≥ 2x ULN	U/L
T Bilirubin	High	≥ 1.5xULN	µmol/L
T. Bilirubin + ALT	High	≥ 1.5xULN T. Bilirubin + ≥ 2x ULN ALT	µmol/L U/L

ECG Values of Potential Clinical Importance (Healthy Volunteers)

ECG Parameter	Potential Clinical Importance Range (PCI)	Unit
Absolute QTc interval	>450	msec
Increase from baseline QTc	>60	msec
QRS interval	>110	msec

Vital Sign Values of Potential Clinical Importance (Healthy Volunteers)

Vital Sign Parameter	Potential Clinical Importance Range (PCI)	Unit
Systolic Blood Pressure	< 85 or > 160	mmHg
Diastolic Blood Pressure	< 45 or > 100	mmHg
Heart Rate	< 40 or > 110	bpm

PCI for patients

Hematology Analyte	Effect	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
White Blood Cell Count (x10^9/ L)		0.5	2
Neutrophil Count (x10^9/ L)		0.75	
Hemoglobin (g/L)	Low	< -25 decrease from baseline	
	Male		1.1
	Female		1.1
Hematocrit (Ratio of 1)	Low	< -0.1 decrease from baseline	
	Male		1.1
	Female		1.1
Platelet Count (x10^9/ L)		0.5	1.75
Lymphocytes (x10^9/ L)		0.75	

Chemistry Analyte	Effect	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
Calcium (mmol/L)		0.85	1.1
Creatinine (μmol/L)			
	High	≥ 22 increase from baseline (Note 22 μmol/L ≈ 0.25 mg/dL)	
Glucose (mmol/L)		0.5	2
Potassium (mmol/L)		.75	1.25
Sodium (mmol/L)		.9	1.1

Liver Function Test Analyte	Effect	Potential Clinical Importance (PCI) Range	Unit
ALT/SGPT	High	≥ 2x ULN	U/L
AST/SGOT	High	≥ 2x ULN	U/L
AlkPhos	High	≥ 2x ULN	U/L
T Bilirubin	High	≥ 1.5xULN	µmol/L
T. Bilirubin + ALT	High	≥ 1.5xULN T. Bilirubin + ≥ 2x ULN ALT	µmol/L U/L

ECG Values of Potential Clinical Importance (DFU Patients)

ECG Parameter	Potential Clinical Importance Range (PCI)	Unit
Absolute QTc interval	>500 for patients with baseline bundle branch block (BBB) and >450 for patient without a baseline BBB	msec
Increase from baseline QTc	>60	msec
QRS interval	>110	msec

Vital Sign Values of Potential Clinical Importance (DFU Patients)

Vital Sign Parameter	Potential Clinical Importance Range (PCI)	Unit
Systolic Blood Pressure	< 85 or > 160	mmHg
Diastolic Blood Pressure	< 45 or > 100	mmHg
Heart Rate	< 40 or > 110	bpm

9. STUDY POPULATION

Study population data will be summarised by, or under the direct auspices of Clinical Statistics GlaxoSmithKline.
The precise format and content of Study Population tables are shown in Section 15.1.1 of this RAP.
The study population tables will use the "All Subjects" population unless otherwise specified.

10. SAFETY ANALYSES

Safety analysis will be based on the All Subject Population. Safety parameters include adverse events, clinical laboratory evaluations, vital signs, ECGs, and physical examinations if data permit.

Clinical monitoring and laboratory safety will be reviewed by the Investigator but will not be formally analyzed. Vital signs and ECG data will be summarized by dose and time point.

The following safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's IDSL standards by, or under the direct auspices of Clinical Statistics, Quantitative Science, GSK.

- Exposure data
- Adverse events (AEs)
- Laboratory data, including hematology, clinical chemistry, routine urinalysis, lipase, amylase,
- Vital signs (systolic BP, diastolic BP,and pulse rate), weight/height
- ECG data

11. 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 (programmer), GlaxoSmithKline.

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

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

Listings will be generated and summary statistics (n, arithmetic mean, standard deviation, minimum, median, maximum) will be calculated for each derived plasma pharmacokinetic (PK) parameter by regimen and time. PK parameters are listed in Section 2.1.1.

11.1. Drug Concentration Measures

Concentrations of GSK1278863 in plasma and its metabolites [M2, M3, M4, M5, M6 and M13] will be listed and summarised by treatment group and nominal time. Standard summary statistics will be calculated (i.e. mean and associated 95% confidence interval, standard deviation, median, minimum and maximum). Refer to the standard operating procedure, SOP-CPK-0001, and the guidance document, GUI-CPK-3001, for more information regarding the treatment of plasma concentrations below the assay's lower limit of quantification (NQ). For this study, when there is

more than one embedded NQ, NQ will be treated as zero rather than missing or truncated. Leading and tailing NQ will be treated per SOP.

Individual plasma concentration-time profiles and median/mean profiles by treatment group will be plotted. Each of the figures will contain one plot on the untransformed scale (i.e. a linear plot) and one plot on the log transformed scale (i.e. log-linear plot).

Plasma drug concentrations excluded from the PK analysis (i.e. PK parameter calculation) will be excluded from the summaries and figures. These concentrations will be flagged in the listing of PK concentration data.

11.2. Deriving and Summarizing Pharmacokinetic Parameters

For subjects in each active treatment group the following pharmacokinetic parameters will be determined from the plasma concentration-time data for GSK1278863 and its metabolites [M2, M3, M4, M5, M6 and M13]. The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using WinNonlin Version 5.2 or higher. All calculations of non-compartmental parameters will be based on actual sampling times.

1. The first occurrence of the maximum observed plasma concentration determined directly from the raw concentration-time data (Cmax).
2. The time at which Cmax is observed will be determined directly from the raw concentration-time data (tmax).
3. The area under the plasma concentration-time curve to the last quantifiable concentration (AUC(0-t)), will be determined using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations.
4. The AUC extrapolated to infinity ($AUC_{(0-\infty)}$) will be calculated, where data permit, as the sum of $AUC_{(0-t)}$ and $C_{t/z}$, where C_t is the observed plasma concentration obtained from the log-linear regression analysis of the last quantifiable time-point and z is the terminal phase rate constant. The percentage of the $AUC_{(0-\infty)}$ that is extrapolated will be calculated as the ratio of [$AUC_{(0-\infty)}$ minus $AUC_{(0-t)}$] to $AUC_{(0-\infty)}$.
5. The apparent terminal elimination half-life (t1/2) obtained as the ratio of $\ln 2/\lambda z$, where λz is the terminal elimination phase rate constant estimated by linear regression analysis of the log transformed concentration-time data (if data permits)
6. Trough concentration (C_τ) will be measured as the lowest concentration prior to dosing on Day 18 in Part B. Summary statistics of trough concentration will be used as an informal assessment of the attainment of steady state.

7. If data permit, the metabolite:parent AUC and Cmax ratios (corrected for molecular weight) will be calculated.

Time profile for PK concentration for individual subjects will be plotted by dose regimen and study day. Mean (SD) plot for PK concentration will be generated by dose regimen and day.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D. Statistical analyses of the pharmacokinetic parameter data will be the responsibility of Clinical Statistics, Quantitative Science, GlaxoSmithKline.

12. PHARMACODYNAMIC AND BIOMARKERS ANALYSES

12.1. Pharmacodynamic Analyses for DFU

12.1.1. Physical parameters of the wound

Wound volume/area, after log-e transformation if appropriate, will be analyzed using a repeat measures ANOVA model, fitting terms for regimen, visit, interaction of regimen and visit, and with compound symmetry variance-covariance structure, for Part B as data permit. The repeat measures ANOVA model will be used to produce least squares means, point estimates, and 95% confidence intervals for each post-dose time point vs Day 1 predose, , each post-repeat-dose time point vs Day 8 predose, as well as for the baseline corrected active versus placebo and active vs standard care (Part B) for each post-dose visiting time point(see Exhibit A)

Physical parameters of the wound will be summarized (for continuous measures) or tabulated (for categorical measures) by regimen and visit for Part A and Part B respectively. Descriptive summary stats include n, arithmetic mean and corresponding 95% confidence interval, standard deviation, minimum, median, maximum.

Mean (SE) plots will be produced by regimen, including part A and part B across study day (day 1, day 4 and follow-up for part A, Day 1 and Day 8 for part B), as well as for Part B alone, by regimen and study days (Exhibit H)

Physical parameters of the wound will be analyzed and summarized separately by methods (Acetate or photo).

12.1.2. Clinical parameters of the wound

Clinical parameters of the wound will be summarized (for continuous measures) or tabulated (for categorical measures) by regimen and visit for Part A and Part B respectively. Descriptive summary stats include n, arithmetic mean and corresponding 95% confidence interval, standard deviation, minimum, median, maximum. Tabulation for categorical endpoints will be presented in a frequency table (n, % by regimen and visiting time).

Similar ANCOVA model as 12.1.1, as well as Mean (SE) plot, may apply to (continuous) clinical parameters of the wound as data permit.

12.2. Biomarker Analyses

12.2.1. Wound fluid biomarkers: Cytokines

Change from baseline wound fluid biomarkers, including cytokines, growth factors and proteases, after log-e transformation if appropriate (i.e. change from baseline becomes log ratio on the loge transformed data), will be analyzed separately for Part A DFU and Part B.

Descriptive statistics (n, arithmetic mean and corresponding 95% confidence interval, standard deviation, minimum, median, maximum) will be calculated by regimen and visiting time points. In addition, in cases that $\log_e$ transformed data are used in the analysis, geometric means (and corresponding 95% confidence interval) and between subject coefficients of variation (CVb) will be calculated by regimen and visit time points, where Geometric mean = exp (mean on $\log_e$-scale) CVb(%) = sqrt[exp(sd2)-1]x100 where sd is the standard deviation of the $\log_e$-transformed data.

Mean (SE) plots will be produced by regimen agent across visit.

12.2.2. Wound fluid biomarkers: Bioburden

Similar summary descriptive statistics and mean SE plot by regimen and visit will be produced (see Section 12.2.1).

12.2.3. Gene expression in the DFU tissue

The qPCR data from the forsyth vendor will be analysed by target science and the finding will be summarized in a separate report.

12.2.4. Biomarkers of angiogenesis and blood flow and oxygen

Similar summary descriptive statistics and mean SE plot by regimen and visit will be produced (see Section 12.2.1).

12.2.5. Circulating biomarkers of systemic HIF activation

Summary descriptive statistics and mean SE plot by regimen and visit will be produced (see Section 12.2.1).

13. REFERENCES

14. ATTACHMENTS

14.1. Table of Contents for Data Display Specifications

14.1.1. Study Population

Table No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Deliverable Priority
1.01	All Subjects	DM1	Summary of Demographic Characteristics		SAC, in stream
1.02	Enrolled	DM11	Summary of Age Ranges		
1.03	All Subjects	IE1	Summary of Inclusion/Exclusion Criteria Deviations		SAC
1.04	All Subjects	DM5	Summary of Race and Racial Combinations		SAC
1.05	All Subjects	ES1	Summary of Subject Disposition		SAC, in stream
1.06	All Subjects	*ES6*	Summary of Reasons for Run-In Failure		SAC, in stream
1.07	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID		SAC

14.1.2. Safety Figures & Tables

Tables

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable Priority
10.xx	*All Subjects*	Ex1	Summary of Exposure data for Part A		SAC, in stream
10.xx	*All Subjects*	Ex1	Summary of Exposure data for Part B		SAC, in stream
10.xx	*All Subjects*	AE1	Summary of All Adverse Events		SAC, in stream
10.xx	*All Subjects*	AE1	Summary of Drug Related Adverse Events		SAC, in stream
10.xx	*All Subjects*	AE1	Summary of AEs Leading to Withdrawal		SAC, in stream
10.xx	*All Subjects*	AE5	Summary of Adverse Events by Maximum Intensity		SAC, in stream
10.xx	*All Subjects*	LB1	Summary of Chemistry Data		SAC
10.xx	*All Subjects*	LB1	Summary of Hematology Data		SAC
10.xx	*All Subjects*	VS1	Summary of Vital Signs		SAC, in stream
10.xx	*All Subjects*	EG2	Summary of ECG Values		SAC, in stream
10.xx	*All Subjects*	LB2	Summary of Hematology Data Outside the Reference Range		SAC
10.xx	*All Subjects*	LB2	Summary of Chemistry Data Outside the Reference Range		SAC
10.xx	*All Subjects*	VS2	Summary of Vital Sign Data Outside Clinical Concern Range		SAC
10.xx	*All Subjects*	EG2	Summary of Change from baseline ECG Values		SAC, in stream
10.xx	*All Subjects*	EG1	Summary of ECG Findings		SAC, in stream
10.xx	*All Subjects*	Exhibit F	Summary of raw EPO data by treatment		SAC, in stream
10.xx	*All Subjects*	AE15	Summary of Common Non-Serious Adverse Events by System Organ Class and Preferred Term	AE is considered common if more than one subject experiences it regardless of treatment	SAC
10.xx	*All Subjects*	AE16	Summary of Serious Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)		SAC

Figures

Figure No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable Priority
10.xx	All Subjects	Exhibit E	The Time course of EPO values of treatment period		SAC, in stream

14.1.3. Pharmacokinetic Figures and Tables

Tables

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable Priority
11.xx	*PK*	PKCT1	Summary of {Matrix} GSK1278863 Pharmacokinetic Concentration-Time Data	By treatment and visit time	*SAC*, in stream
11.xx	PK	PKCF6	Individual Subject Plasma GSK1278863A Concentration-Time Plots – by Treatment Regimen	1. X-axis displays actual relative time. 2. Include line for LLQ along with footnote defining LLQ value.	SAC

14.1.4. Pharmacodynamic Figures and Tables

Figures

Figure No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable Priority
12.xx	PD	Exhibit H	Plot of Mean(SE) PD Endpoints - Skin Perfusion Pressure(mmHg) and Pulse Volume Recording(mmHg)		SAC, in stream
12.xx	PD	Exhibit H	Plot of Mean(SE) PD Endpoints - Wound Area(cm2)		SAC, in stream
12.xx	PD	Exhibit H	Plot of Mean(SE) PD Endpoints - Wound Depth(mm)		SAC, in stream
12.xx	PD	Exhibit H	Plot of Mean(SE) PD Endpoints - Wound Volume(mm3)		SAC, in stream
12.xx	PD	Exhibit H	Plot of Mean(SE) Exploratory Biomarker Parameters	One plot per endpoint.	SAC
12.xx	PD	Exhibit Y	Spline Plot of Percent Change from Baseline of Wound Area	A plot for photo and for acetate	SAC

Tables

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable Priority
12.xx	PD	Exhibit A	Point Estimate and 95% Confidence Interval for the Comparison of wound size changes in part B (unit)	Results may report in one single table for all the physical parameters of wound	SAC, in stream
12.xx	PD	Exhibit G	Summary Statistics of PD Endpoints - Skin Perfusion Pressure(mmHg) and Pulse Volume Recording(mmHg)		SAC, in stream
12.xx	PD	Exhibit G	Summary Statistics of PD Endpoints - Wound Area(cm2)	for wound area and wound volume. Wound area is done by photo and acetate	SAC, in stream
12.xx	PD	Exhibit G	Summary Statistics of PD Endpoints - Wound Depth(mm)		SAC, in stream

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable Priority
12.xx	PD	Exhibit G	Summary Statistics of PD Endpoints - Wound Volume(mm3)	for wound area and wound volume. Wound area is done by photo and acetate	SAC, in stream
12.xx	PD	Exhibit Z	Summary of Exploratory Biomarker Parameters		SAC

14.1.5. ICH Listings

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable Priority
1	All Subjects	DM4	Listing of Demographic Characteristics		SAC, in stream
2	All Subjects		Listing of all Clinical Chemistry Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance		SAC
3	All Subjects	IE3	Listing of Subjects with Inclusion/exclusion Criteria Deviations		SAC
4	All Subjects	DM10	Listing of Race		SAC
5	All Subjects	CM3	Listing of Concomitant Medications by Generic Term		SAC
6	All Subjects	ES3	Listing of Reason for Withdrawal		SAC, in stream
7	All Subjects	DV1A	Listing of Subjects with study protocol Deviations		SAC
8	*All Subjects*	EX3	Listing of Exposure Data		SAC
9	*All Subjects*	AE7	Listing of Subject Numbers for Individual Adverse Events		SAC
10	*All Subjects*	AE8	Listing of all Adverse Events		SAC
11	*All Subjects*	AE9a	Listing of AEs with No Resolution Date		SAC
12	*All Subjects*	LB5	Listing of Clinical Chemistry of Potential Clinical Importance		SAC
13	*All Subjects*	LB12	Listing of all Clinical Hematology Laboratory Data for Subjects with Abnormalities of Potential Clinical Importance		SAC
14	*All Subjects*	CP_VS4	Listing of All Vital Signs for Subjects with Values of Potential Clinical Importance		SAC

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable Priority
15	*All Subjects*	CP_VS4	Listing of Vital Signs of Potential Clinical Importance		SAC
16	*All Subjects*	CP_EG6a	Listing of All ECG Values for Subjects with a Value of Potential Clinical Importance		SAC
17	*All Subjects*	CP_EG3	Listing of ECG Values of Potential Clinical Importance		SAC
18	*All Subjects*	CP_EG5	Listing of Abnormal ECG Findings		SAC
19	*All Subjects*	IE4 (XO)	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
20	Enrolled	*ES7*	Listing of Reasons for Run-In Failure		SAC
21	All Subjects	Exhibit Q	Listing of prior Medications		SAC
22	*All Subjects*	AE8	Listing of Serious Adverse Events		SAC, in stream

14.1.6. Other Listings

Table No.	Population	IDSL No. / Example Shell	Title	Programming Notes	Deliverable Priority
1	PD	Exhibit N	Listing PD Endpoints by Treatment and Time Points for Part A and Part B Respectively - Skin Perfusion Pressure and Pulse Volume Recording		SAC
2	PD	Exhibit N	Listing PD Endpoints by Treatment and Time Points for Part A and Part B Respectively - Wound Area(cm2)		SAC
3	PD	Exhibit N	Listing PD Endpoints by Treatment and Time Points for Part A and Part B Respectively - Wound Depth(mm)		SAC
4	PD	Exhibit N	Listing PD Endpoints by Treatment and Time Points for Part A and Part B Respectively - Wound Volume(mm3)		SAC
5	PD		SAS output for mixed effects models Analysis of physical characteristics of wound healing		SAC, in stream
6	*All Subjects*	AE2	Listing of Relationship Between System Organ Class and Verbatim Text		SAC, in stream
7	PD	LB12	Listing of Exploratory Biomarker Parameters	List all data, flag if out of range	SAC

15.2 Data Display Specifications (Example Shells)

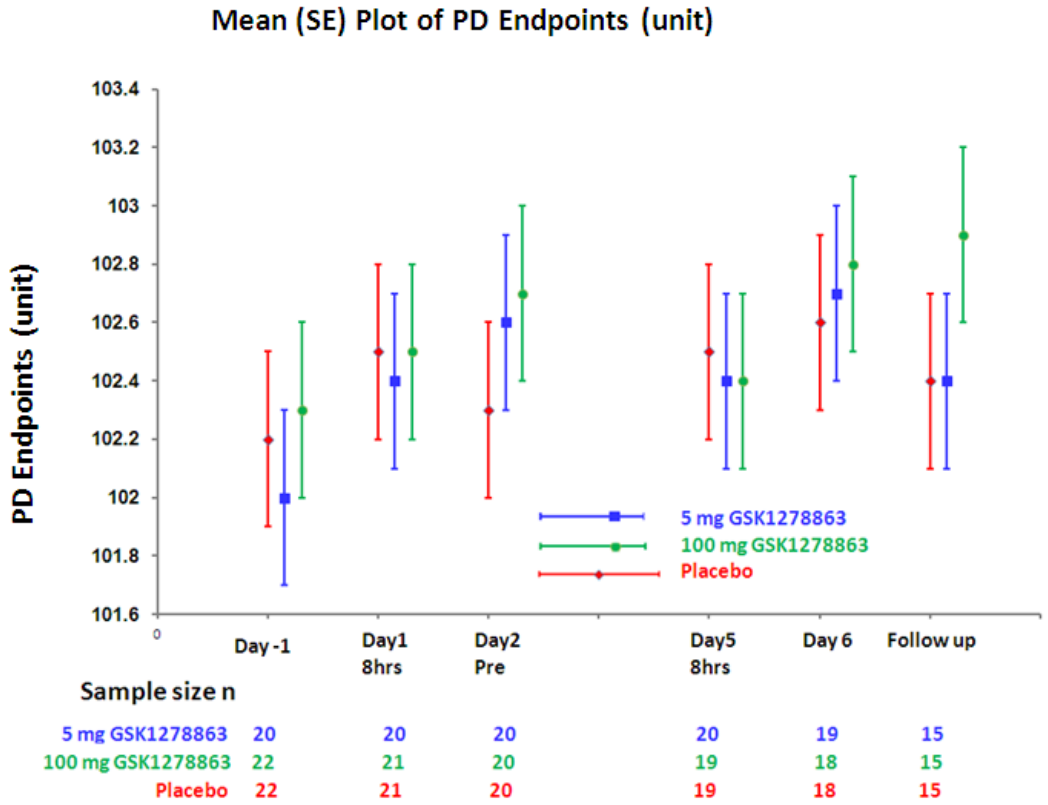
Exhibit A Point Estimate and 95% Confidence Interval for the Comparison of change of wound volume/Area (unit) in Part B

Parameter	Comparison	Group	Estimates (units)	95% CI	P value
Wound volume (unit)	Day 7 vs Day 1	Active	xx.xx	(xx.xx, xx.xx)	0.xxx
		Placebo / Standard of Care	xx.xx	(xx.xx, xx.xx)	0.xxx
	Day 15 vs Day 1	Active	xx.xx	(xx.xx, xx.xx)	0.xxx
		Placebo / Standard of Care	xx.xx	(xx.xx, xx.xx)	0.xxx
	Follow-Up vs Day 1	Active	xx.xx	(xx.xx, xx.xx)	0.xxx
		Placebo / Standard of Care	xx.xx	(xx.xx, xx.xx)	0.xxx
	Active vs Placebo/SoC	Day 7–Day 1	xx.xx	(xx.xx, xx.xx)	0.xxx
		Day 15–Day 1	xx.xx	(xx.xx, xx.xx)	0.xxx
		Follow-Up– Day 1	xx.xx	(xx.xx, xx.xx)	0.xxx

This is a mock-up table, in addition to the end of treatment, estimates of other visits vs day 1 should also be produced in this analysis. Similar table will be generated for other physical and clinical characteristics including healing rate, as data permit

Protocol : *[PWH115760]*
Population : *[PD Population]*

Exhibit H



Note: This is a mock up, visiting time schedule will vary for different pd endpoints. One endpoint per plot.

Exhibit I

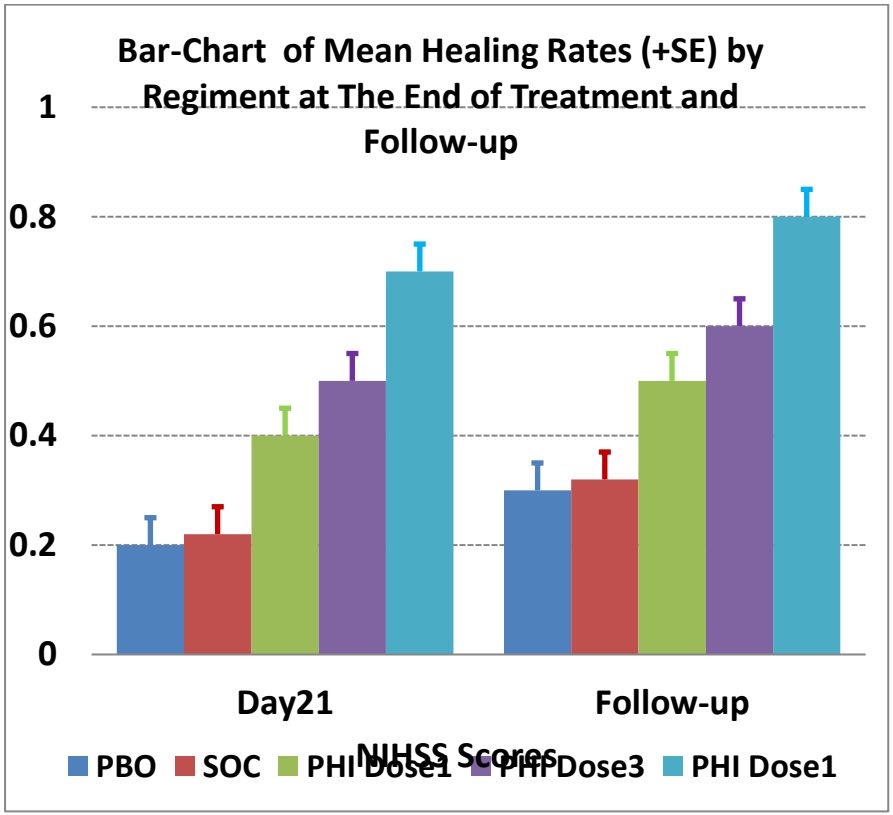
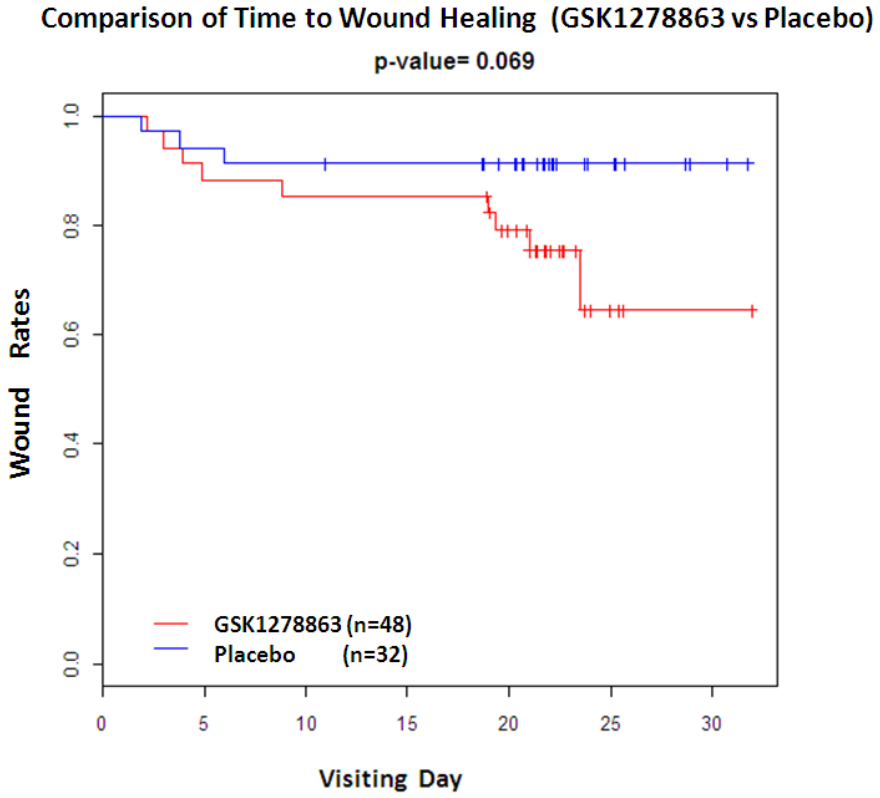

Bar-Chart of Mean Healing Rates (+SE) by Regiment at The End of Treatment and Follow-up
1
0.8
0.6
0.4
0.2
0
Day21
Follow-up
NIHSS Scores
PBO
SOC
PHI Dose1
PHI Dose3
PHI Dose1

Exhibit J Kaplan-Meier of comparisons of probability of wound healing



Note: this is a mock-up, this plot may be produced with individual active (GSK1278863) regimen vs placebo and soc or combined active doses vs placebo and soc as data permit and appropriate to the data.

Summary of Chemistry and PD Data

Parameter	Time points	Summary Statistics	GSK 1278863	Placebo
PD endpoint (units)	Day 1 predose	N	xxx	Xxx
		n	xxx	Xxx
		Arith. Mean	xxx.x	xxx.x
		95% CI	(xxx.x,xxx.x)	(xxx.x,xxx.x)
		SD(arith)	xxx.x	xxx.x
		Geo. Mean*	xxx.x	xxx.x
		95% CI*	(xxx.x,xxx.x)	(xxx.x,xxx.x)
		SD(log)*	xxx.x	xxx.x
		%CVb	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Min	xxx.x	xxx.x
		Max	xxx.x	xxx.x
		:::::::::::::::::::::::::::::		

* Only for the endpoints which are log transformed in statistical analysis.

Exhibit J

Figure 11.xx
Individual Plasma GSK1278863 concentration by dose regimen and Day

Protocol: HMA112795
Population: Pharmacokinetic

Figure 11.1
Individual Plasma GSK256073 Concentration Time Plots for 50 mg
Subject ID=P
P
D

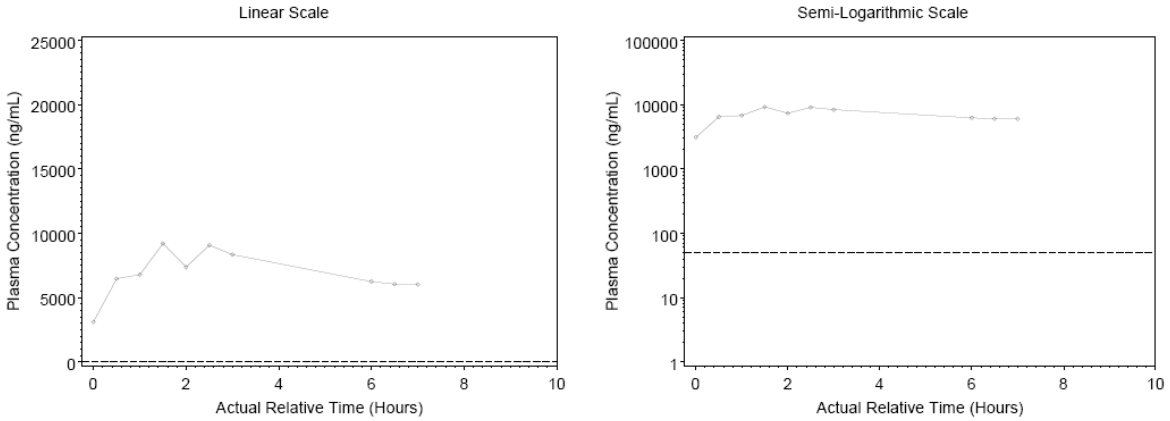


Exhibit G
Summary of Chemistry and PD Data

Period Treatment	Wound method	N	Visit	Planned Time point	n	Mean	SD	Median	Min.	Max.
Placebo DFU	Acetate	3	PART A PERIOD 1 DAY 1	PREDOSE	3	XX.X	XX.XX	XX.X	XX.X	XX.X
				72 H	2	XX.X	XX.XX	XX.X	XX.X	XX.X
			PART A PERIOD 1 DAY 2	PREDOSE	3	XX.X	XX.XX	XX.X	XX.X	XX.X
				72 H	2	XX.X	XX.XX	XX.X	XX.X	XX.X
	Photo	3	PART A PERIOD 1 DAY 1	PREDOSE	3	XX.X	XX.XX	XX.X	XX.X	XX.X
				72 H	2	XX.X	XX.XX	XX.X	XX.X	XX.X
			PART A PERIOD 1 DAY 2	PREDOSE	3	XX.X	XX.XX	XX.X	XX.X	XX.X
				72 H	2	XX.X	XX.XX	XX.X	XX.X	XX.X
0.1% of 25 mg/cm2 Active	Acetate	3	PART A PERIOD 1 DAY 1	PREDOSE	3	XX.X	XX.XX	XX.X	XX.X	XX.X
				72 H	2	XX.X	XX.XX	XX.X	XX.X	XX.X
			PART A PERIOD 1 DAY 2	PREDOSE	3	XX.X	XX.XX	XX.X	XX.X	XX.X
				72 H	2	XX.X	XX.XX	XX.X	XX.X	XX.X
	Photo	3	PART A PERIOD 1 DAY 1	PREDOSE	3	XX.X	XX.XX	XX.X	XX.X	XX.X
				72 H	2	XX.X	XX.XX	XX.X	XX.X	XX.X
			PART A PERIOD 1 DAY 2	PREDOSE	3	XX.X	XX.XX	XX.X	XX.X	XX.X
				72 H	2	XX.X	XX.XX	XX.X	XX.X	XX.X

Note: X-axis will include visit2 predose and visit6 end of treatment; label drug A as: GSK 1278863 and drug B as placebo; one box plot will generated for each PD protein marker (HIF-1, PDK4, COX4, etc.)

Exhibit K

Figure 11.xx
Mean (+SD) plasma GSK1278863 concentration by dose regimen and day

Protocol: HMA112795
Population: Pharmacokinetic

Figure 11.4
Mean(+SD) Plasma GSK256073 Concentration-Time Plots for 50 mg Group

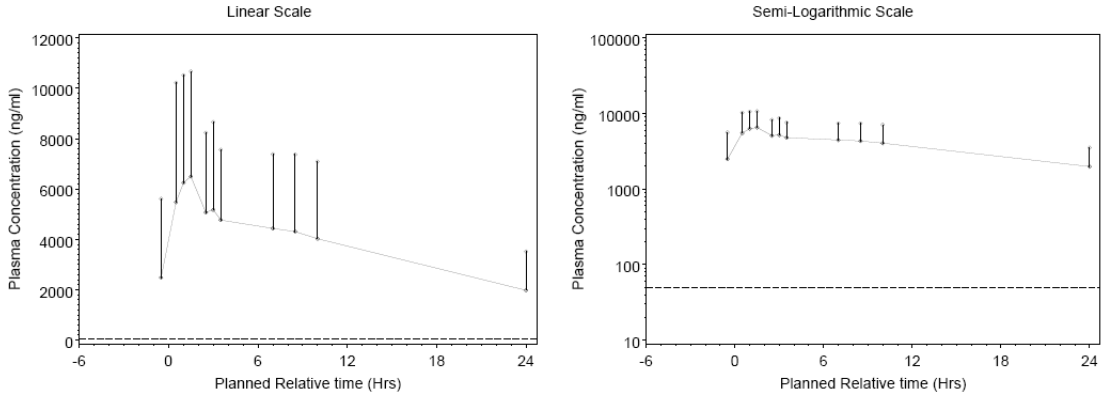


Exhibit L

Summary of Chemistry and PD Data

Parameter	Visit Time	Summary Statistics	5 mg GSK1278863	Placebo
PD parameter (unit)	Screening	n	Xxx	Xxx
		Arith. mean	xxx.x	xxx.x
		95% CI	(xxx.x,xxx.x)	(xxx.x,xxx.x)
		SD(arith)	xxx.x	xxx.x
		Geo. Mean*	xxx.x	xxx.x
		95% CI*	(xxx.x,xxx.x)	(xxx.x,xxx.x)
		SD(log)*	xxx.x	xxx.x
		%CVb	xxx.x	xxx.x
		Median	xxx.x	xxx.x
		Min	xxx.x	xxx.x
		Max	xxx.x	xxx.x
	:::::::::	:::::::::		
	:::::::::	:::::::::		
	:::::::::	:::::::::		
	:::::::::	n	Xxx	Xxx
	:::::::::			
	:::::::::			
	Day 6	Arith. mean	xxx.x	xxx.x
		95% CI	(xxx.x,xxx.x)	(xxx.x,xxx.x)
		SD(arith)	xxx.x	xxx.x
		Geo. Mean*	xxx.x	xxx.x
		95% CI*	(xxx.x,xxx.x)	(xxx.x,xxx.x)
		SD(log)*	xxx.x	xxx.x
		%CVb	xxx.x	xxx.x
		Median	xxx.x	xxx.x

Min	xxx.x	xxx.x
Max	xxx.x	xxx.x

Note :This is just a mock-up, The same type of summary table will be generated for other PD endpoints, LAB parameters and other Blood/Urine Biomarkers, protein transcriptional biomarkers. Parameters from the same type of test (e.g. physical characteristics of wound) may be summarized and reported in one table.

Change from baseline data will be summarized similarly by treatment and visiting timepoints (and simulation conditions if apply). GeoMean and 95% for the difference of log transformed should also be included in the change from baseline summary table, where Geomean will be a ratio estimate, i.e. exp[log(post) –log(baseline)] No other statistics (SD(log), %CVb, Median, Min and max) for log-transformed are needed in the change from baseline summary table.

* Only for the endpoints which are log transformed in statistical analysis.

Exhibit Q List of Prior Medication

Protocol: **PVD114272**
Population: sarety

Listing **9.xxx**
Listing of Prior Medications

Treatment	Inv./ Subj.	ATC Level 1/ Ingredient/ Verbatim Text/ Indication	Dose/ Units/ Freq/ Route	Date Started/ Time Started/ Study Day	Date Stopped/ Time Stopped	Strated Pre-Trial?	Ongoing Medication?
PPD - This section has been excluded to protect patient privacy.							

PPD

Exhibit Y Percent Area Change from Baseline of Wound Area

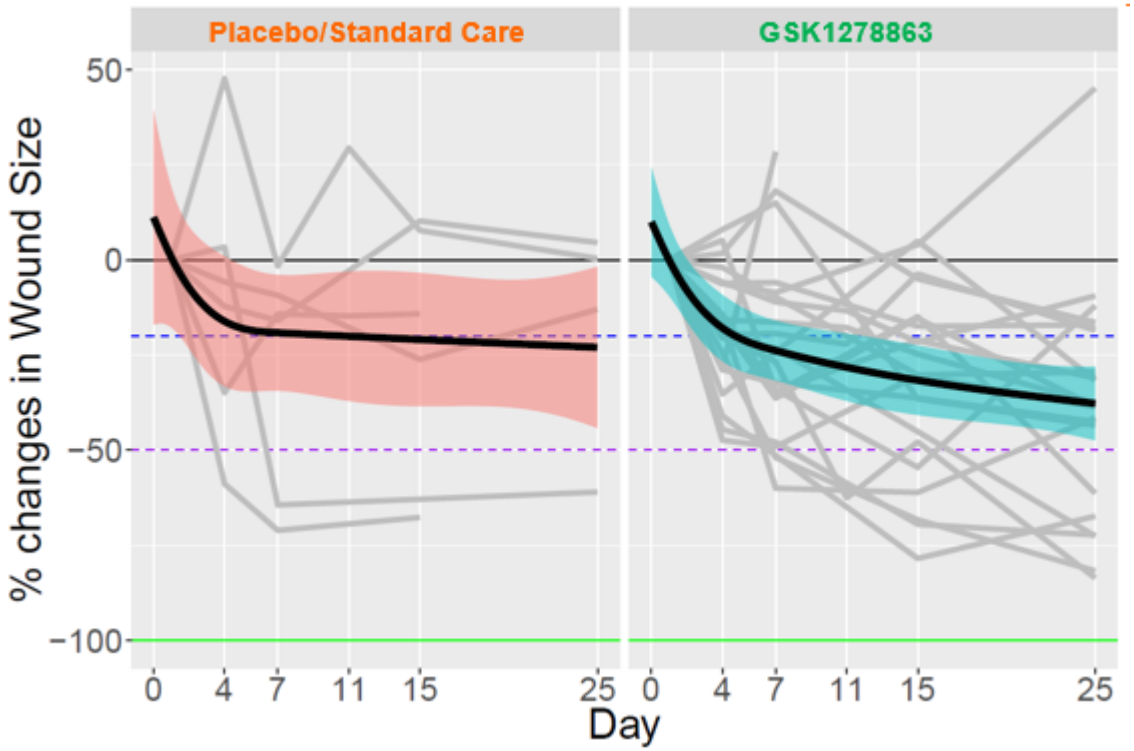


Exhibit Z Table of Forsyth Endpoints

Biomaker	Treatment	Day 1		Day 7		Day 15		Change from Day 1 to Day 15	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE
Angiopoietin-2	Active	x.x	x.xx	x.x	x.xx	x.x	x.xx	x.x	x.xx
	Placebo/SoC	x.x	x.xx	x.x	x.xx	x.x	x.xx	x.x	x.xx

Exhibit R Listing of subjects who entered multiple cohorts in the study

Inv	Initial Subjid	Sex/ Age/ Race	# of cohorts Entered	Initial Rand #/ cohort/ trt seq	Subseqent subjid/ Rand #/ cohort/ trt seq
PPD - This section has been excluded to protect patient privacy.					

Note: for those with multi-cohort entrances, the initial subject number, i.e. the very first number assigned to the subject when he/she first entered the study, will be used as the subject ID for the subject.