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

Title	:	Reporting and Analysis Plan for A Phase I, Randomized, Placebo-Controlled, Double-Blind (sponsor unblind), Three Part Study to Evaluate the Safety, Tolerability, Preliminary PK and PD of Single and Repeat Oral Doses of GSK3008356 in Healthy Subjects and Obese Subjects
Compound Number	:	GSK3008356
Effective Date	:	03-AUG-2017

Description:

The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 204856.

This RAP is intended to describe the Safety, Pharmacokinetic (PK), and Pharmacodynamic (PD) analyses required for the study.

This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	The purpose of this report and analysis plan (RAP) is to describe the analyses to be included in the Clinical Pharmacology Study Report (CPSR) for Study 204856
Protocol	This RAP is based on Protocol Amendment 2, dated: 07-Feb-2017 of study 204856 for GSK204856 and eCRF Version 1.3 (22-May-2017).
	Part 1
Primary Objective	To characterize the safety, and tolerability of single doses of GSK3008356 in healthy subjects.
Primary Endpoint	Safety parameters including physical examination findings, vital signs, 12-lead ECGs, continuous lead II cardiac monitoring, clinical laboratory tests and clinical monitoring/observation for adverse events.
Study Design	Single Dose Tolerability and PK: this part was a randomized, placebo-controlled, double blind (sponsor unblind), single-dose, dose-rising study in healthy subjects. There are 5 cohorts with 8 subjects each (6 are on the active drug and 2 are on a matching placebo) while receiving a standard 30% fat meal. Based on emerging PK data, the original planned Part 1 doses were adjusted due to a much shorter observed half-life. Further details are shown in Figure 1: Schematic of Study Design.
Analysis Populations	Screened: Comprised of all subjects screened which also includes subjects with screen failure. Enrolled: Comprised of all subjects who consented and screened with eligibility verified. Safety (Primary): Comprised of subjects who received at least one dose of study medication. PKC (PK Concentration) (Secondary): Comprised of subjects for whom a pharmacokinetic sample was obtained and analysed. PKP (PK Parameter) (Secondary): Comprised of all subjects in the PKC population who receive at least one active dose of GSK3008356 and provide pharmacokinetic parameters. PD: Comprised of subjects in the Safety population for whom at least one a postprandial Triglyceride sample was obtained and analysed at baseline and post baseline.
Hypothesis	There are no formal hypotheses being tested.
Primary Analyses	Safety data will be presented either in tabular and/or graphical format and summarised descriptively. GSK's Integrated Data Standards Library (IDSL) standards for the displays are being used.

Overview	Key Elements of the RAP
Secondary Analyses	Pharmacokinetic: • Summary Statistics for AUC0-t, AUC0-∞, AUC0-24, Cmax, Tmax, t1/2, Ae, and CLr as data permit; Dose Proportionality: • Assessment of dose proportionality by AUC0-t, AUC0-∞, and Cmax; Pharmacodynamic (TG): • Summary statistics for absolute for TG values by treatment and day and Time Point • Summary statistics for Corrected TG by treatment day and time point • Summary statistics for AUC [AUC(1-12), AUC(2-5), Corrected AUC(1-12), Corrected AUC(2-5)] of TG by treatment and day • Summary statistics for percent (%) change from baseline in AUC AUC [AUC(1-12), AUC(2-5), Corrected AUC(1-12), Corrected AUC(2-5)] by treatment and day. Pharmacodynamic (BSFS): • Summary of number of subjects and number of BSFS by type, day, and treatment • Summary of total number of BSFS by day and treatment Pharmacokinetic / Pharmacodynamic • PK / PD analyses including correlation and Emax model will not be performed but are recorded in Appendix 9 due to the lack of a repeat dose regimen that was both active for TG suppression and tolerated from a GI perspective.
Part 2	
Primary Objective	To characterize the safety, and tolerability of 14 daily repeat doses of GSK3008356 in healthy subjects.
Primary Endpoint	Safety parameters including physical examination findings, vital signs, 12-lead ECGs, continuous lead II cardiac monitoring, clinical laboratory tests and clinical monitoring/observation for adverse events.
Study Design	Repeat Dose Tolerability and PK: this part was a randomized, placebo-controlled, double blind (sponsor unblind), 14-day, repeat-dose, dose-rising study in healthy subjects. There are 3 cohorts with 8 subjects each (6 are on the active drug and 2 are on a matching placebo) while they received a standard 30% fat meal on day -1, day 1, and day 14, respectively.
Analysis Populations	Screened: Comprised of all subjects who screened which included subjects with screen failure.

Overview	Key Elements of the RAP
	Enrolled: Comprised of all subjects who consented and screened with eligibility verified. Safety (Primary): Comprised of subjects who received at least one dose of study medication and had at least one safety evaluation. PKC (PK Concentration) (Secondary): Comprised of subjects who received at least one dose of GSK3008356 and for whom at least one sample was obtained which yielded a valid concentration value upon bioassay. PKP (PK Parameter) (Secondary): Comprised of all subjects in the PKC population who receive at least one active dose of GSK3008356 and provide pharmacokinetic parameters. PD: Comprised of subjects in the Safety population for whom at least one a postprandial Triglyceride sample was obtained and analysed at baseline and post baseline.
Hypothesis	There are no formal hypotheses being tested.
Primary Analyses	Safety data will be presented either in tabular and/or graphical format and summarised descriptively. GSK's Integrated Data Standards Library (IDSL) standards for the displays are being used
Secondary Analyses	Pharmacokinetic: • Summary Statistics for AUC(0-∞) on Day 1, $AUC_{0-\tau}$, Cmax, Tmax on Day 1 and Day 14, and t1/2, Ae, and CLr on Day 14 of GSK3008356 as data permit. Dose Proportionality: • Assessment of dose proportionality by AUC(0-∞) on Day 1, AUC_{0-tau} and C_{max} on Day 1 and Day 14; Accumulation Ratio: • Assessment of observed accumulation ratio by AUC(0-tau), (Ro), and C_{max} (R_{cmax}) on Day 14 vs. Day 1 as data permit. • Assessment of steady-state accumulation ratio (Rs) by AUC(0-tau) on Day 14 vs. AUC(0-∞) on Day 1 as data permit. Steady State: • Assessment of steady state after repeat dosing by trough plasma concentration on Days 2, 4, 5, 6, 12, 13, 14 (pre-dose), 15 (24 h post-dose on Day 14). Pharmacodynamic (TG): • Summary statistics for absolute for TG values by treatment and day and time point

Overview	Key Elements of the RAP
	• Summary statistics for corrected TG by treatment, day and time • Summary statistics for AUC of TG by treatment and day • Summary statistics for percent (%) change from baseline in AUC of TG Pharmacodynamic (BSFS): • Summary of number of subjects and number of BSFS by type, day, and treatment • Summary of total number of BSFS by day and treatment Pharmacokinetic / Pharmacodynamic • PK / PD analyses including correction and Emax model will not be performed but are in Appendix 9 due to the lack of a repeat dose regimen that was both active for TG suppression and tolerated from a GI perspective.
Exploratory Analyses	Serum Lipid Levels and Weight • Summary Statistics for the change in serum lipid levels and weight after 14 daily repeat doses of GSK3008356 in healthy subjects Skin Biopsy: • Assessment of skin biopsy and analyses will be performed under the management of PTS IVIVT BIB and details will not be included in this RAP.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were changes or deviations to the originally planned statistical analysis which are specified in protocol amendment 02 (Dated: 07-FEB-2017). The details of previous protocols are as follows:

- The original protocol was created on 02 March 2016.
- Protocol amendment 01 was created on 22 July 2016. Adds additional Part 1 cohorts which dose the compound in a way that provides a more appropriate exposure profile. This is to obtain better PK/PD data to inform progression into Part 2 of the study.
- Protocol amendment 02 was created on 22 January 2017. Clarifies dosing regimens for Part 2, adds skin biopsy assessment for drug level and activity, and adds information to the Benefit:Risk table based on 13 week dog and 13 week rat toxicity study findings and the addition of skin biopsy to procedures.

Further Rationale for Amendment 1 and Amendment 2:

Amendment 1 was based on preliminary pharmacokinetic data indicating a much shorter observed half-life compared to the predicted half-life (1.5-3h observed versus 14.1h predicted). While the adjusted doses in the first 5 cohorts did allow observation of a PD response in Cohort 5, the overall single dose data to date are limited and could not adequately inform a PK/PD model or support informed progression into Part 2 of the study.

Amendment 2 clarified the Part 2 regimens and added a skin biopsy. The former change provided specific regimens and noted evening dosing was no longer indicated. Addition of skin biopsy was to further define if the short observed half-life is in part based on distribution to tissue. Pharmacodynamics has been observed in the skin in preclinical studies.

2.2. Study disposition: Termination after Part 2

Dose escalation within a study **Part** was based on review of data from prior cohorts as outlined in Section 9.8.1 of the protocol. Across cohorts, a combination of tolerability, particularly in the GI organ system class, and pharmacodynamic (PD) activity (as identified through postprandial TG suppression) would be used to identify doses to progress across study **Parts** (see Section 3.3 in the protocol).

Specifically, **Part 1** doses with PD activity would be progressed into **Part 2**. GI tolerability was not expected to be an issue in **Part 1** and not expected to impact progression into **Part 2**. **Part 2** doses with PD activity and which had tolerability from a GI AE perspective were to be progressed into **Part 3**.

Part 1 data indicated that single doses of 125 mg or greater were tolerated and had postprandial TG suppression. Divided doses of 45 mg GSK3008356 or greater were tolerated and had postprandial TG suppression. The dose of 45 mg (5 mg hourly for 9 hours) had complete suppression. Divided doses below 45 mg GSK3008356 were not evaluated and exploration of lower divided doses was planned for **Part 2**.

Based on **Part 1** data, the short observed GSK3008356 half-life and future NOAEL identified from a 13 week repeat dose dog toxicology study, **Part 2** initially evaluated placebo or 20 mg GSK3008356 as 10 mg at time 0h and 16h.

Blinded data indicate that 20 mg GSK3008356 divided dosing was not tolerated with 6 of 8 subjects withdrawn early due to GI issues. Dosing was stopped for all subjects before Day 7 of a planned 14 days: 6 due to the GI issues and 2 as the remaining subjects in the cohort were discontinued following discussions between GSK and the Principle Investigator. No PD (postprandial TG suppression) was observed on Day 1; Day 14 could not be evaluated.

Subsequently, placebo or 2 mg GSK3008356 as 1 mg at time 0h and 16h and placebo or 6 mg GSK3008356 as 3 mg at time 0h and 16h were evaluated in Cohorts 2 and 3. All subjects except for 1 in the placebo or 6mg cohort completed the 14 days of dosing, indicating that the doses were tolerated. However, no postprandial TG suppression was observed in either the 2mg or 6mg GSK3008356 divided dosing cohorts.

Based on these data, **Part 2** did not identify a tolerated dose with PD activity and **Part 3** was not initiated.

For the purposes of the 204856 RAP, all sections and references pertaining to **Part 3** will be redacted. For any information pertaining to **Part 3** design, objectives and endpoints, please refer to the relevant sections in the protocol. Analysis for **Part 3** is therefore not included in the RAP.

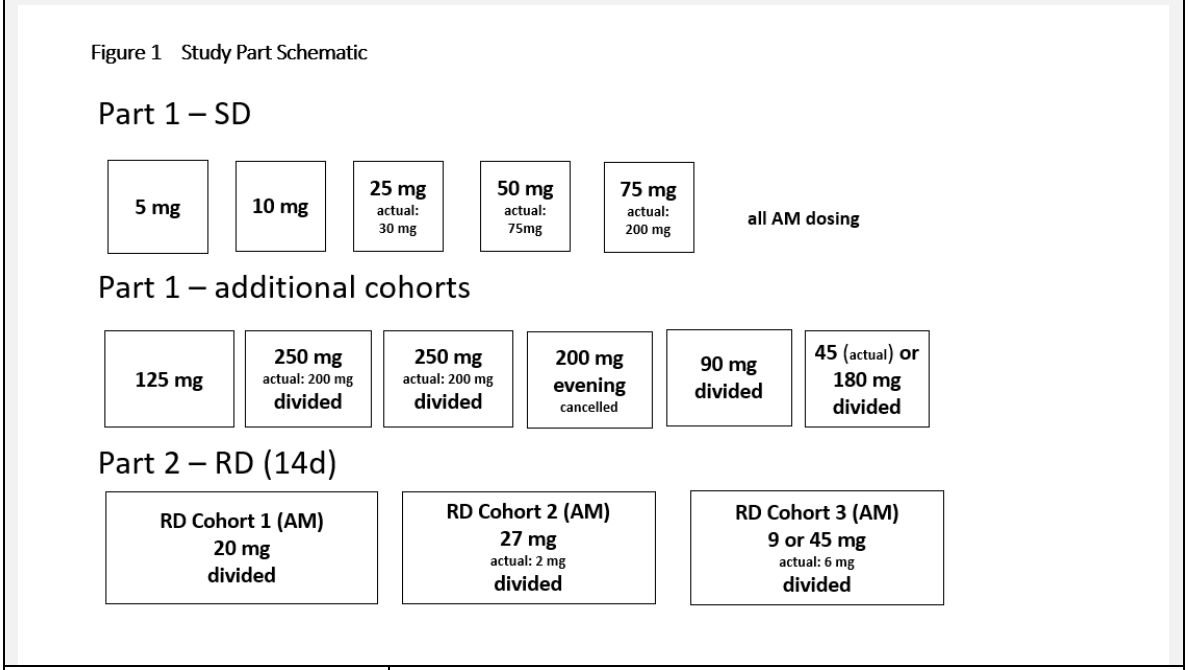
2.3. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary	
Part 1 Single Dose To characterize the safety, and tolerability of single doses of GSK3008356 in healthy subjects.	**Part 1 Single Dose** Safety parameters including physical examination findings, vital signs, 12-lead ECGs, continuous lead II cardiac monitoring, clinical laboratory tests and clinical monitoring/observation for adverse events.
Part 2 14d Repeat Dose To characterize the safety, and tolerability of 14 daily repeat doses of GSK3008356 in healthy subjects.	**Part 2 14d Repeat Dose** Safety parameters including physical examination findings, vital signs, 12-lead ECGs, continuous lead II cardiac monitoring, clinical laboratory tests and clinical monitoring/observation for adverse events.

Objectives	Endpoints
Secondary	
Part 1 Single Dose To determine the pharmacokinetics of GSK3008356 after a single dose in healthy subjects; To assess dose proportionality of GSK3008356 after a single dose in healthy subjects; To evaluate the preliminary pharmacodynamics after a single dose of GSK3008356 in healthy subjects.	**Part 1 Single Dose** PK endpoints include the AUC(0-t), AUC(0-24), Cmax, tmax, AUC(0-∞), t1/2, Ae, and CLr of GSK3008356 as data permit; AUC(0-t), AUC(0-∞), and Cmax for the assessment of dose proportionality as data permit; Fat challenge meal postprandial triglyceride levels.
Part 2 14d Repeat Dose To determine the pharmacokinetics of GSK3008356 after 14 daily doses in healthy subjects; To assess dose proportionality of GSK3008356 after 14 daily doses in healthy subjects; To examine the extent of accumulation and achievement of steady-state following 14 daily doses of GSK3008356 in healthy subjects; To evaluate the preliminary pharmacodynamics after 14 daily repeat doses of GSK3008356 in healthy subjects.	**Part 2 14d Repeat Dose** PK endpoints include the AUC(0-∞) on Day 1, AUC(0-τ), Cmax, and tmax on Day 1 and 14, and t1/2, Ae, and CLr on Day 14 of GSK3008356 as data permit; AUC(0-∞) in Day 1, AUC(0-τ) and Cmax on Day 1 and 14 for the assessment of dose proportionality as data permit; Observed accumulation ratio based on AUC(0-τ), (Ro), and Cmax (RCmax) on Day 14 versus Day 1 as data permit. The steady-state accumulation ratio (Rs) by AUC(0-tau) on Day 14 vs. AUC(0-∞) on Day 1 as data permit. Trough plasma concentrations (Ctrough) to assess steady state after repeat dosing, as data permit; Fat challenge meal postprandial triglyceride levels.
Exploratory	
Part 2 14d Repeat Dose To evaluate the change in serum lipid levels and weight after 14 daily repeat doses of GSK3008356 in healthy subjects To evaluate the impact of evening dosing on tolerability. To evaluate partitioning of GSK3008356 into skin.	**Part 2 14d Repeat Dose** Serum Lipid panel, weight; Clinical monitoring/observation for adverse events with a focus on gastrointestinal findings and a stool scale. Skin biopsy for drug concentration and activity.

2.4. Study Design

Figure 1 Schematic of Study Design adapted from Protocol Amendment 2



Design Features	• This is a randomized, double-blind (sponsor unblind), placebo controlled trial in three Parts, but Part 3 was cancelled. For the schematic of the study design for Part 3, please refer to the relevant sections in the protocol (see the schematic in Figure 1 for further details on Part 1 and Part 2). • Part 1, is a single-dose (SD), dose-rising study in healthy subjects. • Part 2, is a 14-day, repeat-dose (RD), dosing-rising study in healthy subjects.
Dosing	• Part 1, subjects were screened within 28 days before dosing, and morning dosing began on day 1. Subjects were only dosed on Day 1 in the morning. Doses were adjusted based on protocol amendment 02. The figure above includes the planned and actual doses which were used. • Part 2, subjects were screened within 28 days before doing, dosed over 14 days in the morning and twice a day. Doses were adjusted during the study, to 10 mg BID in Cohort 1, 1 mg BID in Cohort 2, and 3mg BID in Cohort 3. The figure above includes the planned and actual dosing which were used.
Treatment Assignment	• Part 1, 8 subjects receive GSK3008356 (or matching placebo), at a treatment allocation ratio of 6:2 in each of 10 cohorts. The actual dosing received are 5mg, 10mg, 30mg,

	75mg, 200mg, 125mg, 200mg divided into 0 hour and 4 hour, 200mg divided into 0 hour and 16 hour, 90mg divided hourly by 9, and 45mg divided hourly by 9, respectively. • Part 2, 8 subjects receive GSK3008356 (or matching placebo), at a treatment allocation ratio of 6:2, with repeat doses in each of 3 cohorts. The actual doing received are 10mg BID in cohort 1, 1mg BID in cohort 2, and 3mg BID in Cohort 3.

Note: All actual doses start from the morning regardless of the treatment group description.

2.5. Statistical Hypotheses

The primary objectives of this study are to evaluate the safety, tolerability and pharmacokinetics of single and repeat doses of GSK300835. No formal hypotheses will be tested.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analysis was planned for this study. However, preliminary safety, tolerability, and available pharmacokinetic and pharmacodynamic data was reviewed internally at GSK prior to dose escalation.

3.2. Final Analyses

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

1. All subjects have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met.
4. Randomisation codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• Comprised of all subjects who were screened including subjects with screen failure.	• Study Disposition
Enrolled	• Comprised of all subjects who consented and were screened with eligibility verified.	• Study Population
Safety:	• Comprised of all subjects who receive at least one dose of study medication. • This population will be based on the treatment/dose the subject actually received.	• Study Population • Safety • Bristol Stool Form Scale • Exploratory PD Markers
PKC: PK Concentration	• Comprised of subjects for whom a pharmacokinetic sample was obtained and analysed. • This population will be based on the treatment/dose the subject actually received.	• Analysis of PK Concentrations
PKP: PK Parameter	• Comprised of all subjects in the PKC population who receive at least one active dose of GSK3008356 and provide pharmacokinetic parameters. • This population will be based on the treatment/dose the subject actually received.	• Analysis of PK Parameters • PK/PD
PD	• Comprised of subjects in the Safety population for whom at least one postprandial Triglyceride sample was obtained and analysed at baseline and post baseline.	• Postprandial TG

NOTES:

- Please refer to Appendix 12: List of Data Displays which details the population to be used for each display generated.

4.1. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset. This includes deviations which may lead to exclusion of data from the analysis, specifically those which invalidate laboratory measurements/assays.

- This dataset will be the basis for the summaries and listings of protocol deviations.

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

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 below lists the appendices which describe various rules, conventions, and considerations for data analyses and data handling.

Table 1 Overview of Appendices

Section	Component
11.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
11.2	Appendix 2: Time & Events
11.3	Appendix 3: Assessment Windows
11.4	Appendix 4: Treatment States & Phases
11.5	Appendix 5 Data Display Standards & Handling Conventions
11.6	Appendix 6: Derived and Transformed Data
11.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
11.8	Appendix 8: Values of Potential Clinical Importance
11.9	Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses
11.10	Appendix 10: Model Checking and Diagnostics for Statistical Analysis
11.11	Appendix 11: Abbreviations
11.12	Appendix 12: List of Data Displays
11.13	Appendix 13: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

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

In general, summary tables will be presented in sets, with separate tables for Part 1 and Part 2 of the study. Listings will include all subjects, showing part /dosing regimen. For placebo group, pooling of placebo subjects within each part is considered a general report rule, unless otherwise specified. Exceptions to pooling may occur when meals might impact assessment, like PD (see Section 8.2). Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 12: List of Data Displays: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Endpoint / Parameter / Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Status and Reason for Study Withdrawal	Y		
Reasons for Subject Withdrawal			Y
Treatment Status and Reasons for Discontinuation of Study Treatment [2]	Y		Y
Screening Status and Reasons for Screen Failure	Y		Y
Subjects for Whom the Treatment Blind was Broken			Y
Planned and Actual Treatments			Y
Protocol Deviations			
Important Protocol Deviations	Y		Y
Subjects with Inclusion/Exclusion Criteria Deviations			Y
Populations Analysed			
Study Populations [1]	Y		
Demographic and Baseline Characteristics			
Demographic Characteristics	Y		Y
Race and Racial Combinations	Y		Y [3]
Prior and Concomitant Medications			
Current Medical Conditions	Y		
Past Medical Conditions	Y		
Concomitant Medications			Y
Exposure and Treatment Compliance			
Exposure to Study Treatment	Y		Y

NOTES:

- Y = Yes display generated.

[1] For Part 1, Including the differently pooled placebo: first, pooling of placebo in all cohorts; secondarily, pooling of all

placebo except for cohort 8.
[2] Part 2 Only
[3] Listing of Race

6.1.1. Subject Disposition

Subject disposition will summarize all subjects.

The number of subjects screened, failed screening, randomized, in each population (Safety, PKC, PKP, and PD), completing and withdrawing from the study (along with reasons for withdrawal) will be summarized and listed.

The details can be found at Appendix 12: List of Data Displays as well as at the file of the mock shell.

6.1.2. Demographics and Baseline Characteristics

Subject age, gender, race, ethnicity, and baseline weight/height/BMI will be summarized and listed.

The details can be found at Appendix 12: List of Data Displays as well as in the file of the mock shell.

6.1.3. Concomitant Medications

Concomitant medications are defined as all non-study medications, excluding those known to be discontinued prior to study enrolment.

The GSKDrug dictionary will be used to code all verbatim medication terms.

Concomitant medications will be listed and summarized by class.

The details can be found at Appendix 12: List of Data Displays as well as at the file of the mock shell.

6.1.4. Drug Exposure

Exposure will be assessed for Part 1 and Part 2 separately.

For Part 1, the dose received by each subject will be summarized descriptively by cohort of the active treatment.

In Part 2, for each subject, the number of doses, total dose, and the duration (in days) of dosing with the study drug (GSK3008356) will be calculated. These will be listed by subject and summarized descriptively by the cohort active treatment.

The details can be found at Appendix 12: List of Data Displays as well as at the file of the mock shell.

6.1.5. Medical History

Medical history will be listed by subject.

The details can be found at Appendix 12: List of Data Displays as well as at the file of the mock shell.

6.1.6. Protocol Deviation

All important protocol deviations will be summarised and listed.

The details can be found at Appendix 2: Time & Events as well as at the file of the mock shell.

7. PRIMARY STATISTICAL ANALYSES

7.1. Safety Analyses

The primary analyses will be based on the "Safety" population, unless otherwise specified. For placebo group, pooling of placebo subjects within each part is considered a general report rule, unless otherwise specified. All summary tables and figures are for each part separately and all listings are for both parts combined into one, unless otherwise specified.

7.1.1. Overview of Planned Adverse Events Analyses

The safety analyses will be based on the Safety population unless otherwise specified. Table 3 provides an overview of the planned analyses, with full details of data displays being presented in Appendix 12: List of Data Displays.

Table 3 Overview of Planned Safety Analyses

Endpoint / Parameter/ Display Type	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AEs by SOC and PT	Y		Y
AEs by GI SOC and PT	Y		
Most Frequent Adverse Events by Overall Frequency	Y		
Drug-Related AEs by SOC and PT	Y		
Subject Numbers for Individual AEs			Y
Relationship Between AE SOCs, PT and Verbatim Text			Y
Serious and Other Significant Events			
All SAEs	Y		Y
Reasons for Considering as a Serious AE			Y
AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by SOC and PT	Y		Y
Pregnancy			Y

NOTES:

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

7.1.1.1. Adverse Events

Adverse events will be assessed for Part 1 and Part 2 separately. Adverse events will be summarized by the cohort of active treatments and pooling of placebo subjects within each part.

An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

No distinction will be made between pre-treatment AEs and treatment emergent AEs in this study, as AE collection is scheduled to start after first dose of study medication.

AE verbatim text will be coded and classified by system organ class (SOC) (body system) and preferred term (PT) using MedDRA (current version 19.0).

AEs will be summarized by number of subjects and percentage of total subjects, by SOC and PT. Summaries and listings will be provided for all AEs, AEs by severity, drug-related AEs, serious AEs, and AEs leading to drug withdrawal.

The details can be found at Appendix 12: List of Data Displays as well as at the file of the mock shell.

7.1.1.2. Adverse Event Incidence Rates for All Subjects

The primary presentation of AE data is prepared without regard to causality or relationship to study medication. Subjects will be counted only once at each level of summarization, by SOC and by PT.

7.1.1.3. Severity of Adverse Events

The investigator makes assessment of intensity for each AE reported during the study and assigns it to one of the following categories:

- **Mild**: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.

AEs will be summarized by severity. If a subject has multiple occurrences of the same SOC or PT, then it will be counted as the maximum severity among them.

7.1.1.4. Relationship to Study Treatment

For each AE, the investigator will assess the relationship between study treatment and the AE occurrence, using clinical judgment. The investigator will provide a YES / NO answer to the question "Is there a reasonable possibility that the AE may have been caused by the study treatment? Use best judgment at initial entry. May be amended when additional information becomes available."

The subset of AEs which are classified as "related" (answer = YES) will be summarized in the same way as all AEs (Section 7.1.1).

The details can be found at Appendix 12: List of Data Displays as well as at the file of the mock shell.

7.1.1.5. Serious Adverse Events (SAE), Adverse Events Leading to Drug Discontinuation, and Death

The subset of AEs which are serious (SAEs) and/or lead to discontinuation of study drug, withdrawal from the study, or death will be summarized in the same way as all AEs (Section 7.1.1.2). These AEs will be listed, indicating "serious" and/or the outcome.

The results of pregnancy testing will be listed. The details can be found at Appendix 12- List of Data Display as well as the file of the mock shell.

7.1.2. Overview of Planned Clinical Laboratory Analysis

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

Table 4 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 12: List of Data Displays.

Table 4 Overview of Planned Clinical Laboratory Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Chemistry						
Chemistry Changes from Baseline				Y		
Hematology						
Hematology Changes from Baseline				Y		
Urinalysis						
Urine Concentration Changes from Baseline				Y		
Urinalysis Dipstick Results	Y					
Hepatobiliary (Liver)						
Liver Monitoring/Stopping Event Reporting	Y		Y			
Matrix Display of Maximum LFT (ALT, AST, ALP, and Total Bilirubin) Values		Y				
Individual LFT (ALT, AST, ALP, and Total Bilirubin) Values versus Study Time by Treatment Group and Test		Y				
All Laboratory						
All Laboratory Data for Subjects with any Value of Potential Clinical Concern/PCI			Y			

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Laboratory Values of PCI			Y			

NOTES:

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

7.1.2.1. Clinical Laboratory

Clinical laboratory results will be assessed for Part 1 and Part 2 separately. Laboratory evaluations will be summarized by the cohort of active treatments and pooling of placebo subjects within each part.

Clinical laboratory evaluations are divided into:

- **Haematology**: Platelet Count, RBC Count, WBC Count (absolute), Reticulocyte Count, Hemoglobin, Hematocrit, MCV, MCH, MCHC, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils;

- **Clinical Chemistry:** BUN, Creatinine, Glucose, Sodium, Bile Acids, Potassium, Chloride, bicarbonate, Calcium, AST (SGOT), ALT (SGPT), GGT, Alkaline phosphatase, Total and direct bilirubin, Uric Acid, Albumin, Total Protein;

- **Urinalysis**: Specific gravity, pH, glucose, protein, blood, ketones, Microscopic examination;

- **Liver Function Tests** (LFTs): total bilirubin, ALT.

Tables with descriptive statistics of change from baseline will be produced for all numerical tests for subjects with non-missing assessments. For categorical tests the number and percent of subjects for each category will be produced. Prior to analysis, all applicable numeric assessments will be converted to standard units.

Listing of all laboratory data for subjects with any value of PCI will be produced.

Listings of laboratory data with any value of PCI will be produced, too.

A listing will be created for subjects with any post baseline Liver Function Test (LFTs) with other Laboratory parameters, i.e. one of ALT and total bilirubin, classified as PCI..

Special figures, “matrix displays”, will be produced showing pairwise plots of the LFT values. To create these plots, the maximum value (over time) for each subject for each LFT will be calculated. Then for each pair of tests (e.g., total bilirubin vs ALT), each

subject will be plotted on the chart according to the maximum value of each. The subject markers (color and symbol) will be coded according to part /treatment.

7.1.3. Overview of Planned Other Safety Analyses

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

Table 5 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 12: List of Data Displays.

Table 5 Overview of Planned Other Safety Analyses

Endpoint / Parameter/ Display Type	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
ECG						
ECG Findings	Y					
Change from Baseline in ECG Values by Visit				Y		
All ECG Data for Subjects with any Value of PCI			Y			
ECG Values of PCI			Y			
Abnormal ECG Findings			Y			
Vital Signs						
Change from Baseline in Vital Signs by Visit				Y		
Vital Signs Results by PCI Criteria	Y					
All Vital Signs for Subjects with any Value of PCI			Y			
Vital Signs of PCI			Y			
Other Exams						
Physical Exam			Y			

NOTES:

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

7.1.3.1. Vital Signs

Vital signs will be assessed for Part 1 and Part 2 separately. The assessment results will be summarized by the cohort of active treatments and pooling of placebo subjects within each part.

Tables with descriptive statistics of changes from baseline in vital signs (systolic blood pressure, diastolic blood pressure, pulse rate, heart rate, etc.) will be produced. Number and percent of subjects with any post baseline vital sign results of PCI will be produced.

A listing of vital signs data will be produced, including flagging for PCI.

7.1.3.2. ECG

Electrocardiograms (ECGs) will be assessed for Part 1 and Part 2 separately. The assessment results will be summarized by the cohort of active treatments and pooling of placebo subjects within each part.

Tables with descriptive statistics of changes from baseline will be produced for all numerical ECG tests of heart rate, PR interval, QRS interval, QT interval, QT with correction (Fridericia's formula), and number and percent of subjects will be produced for all categorical tests (ECG finding). Number and percent of subjects with any post baseline ECG results of PCI will be produced.

A listing of ECG data will be produced, including flagging for PCI.

7.1.3.3. Other Exams

Physical exam data will be listed, showing exam dates and any abnormalities found.

8. SECONDARY STATISTICAL ANALYSES

8.1. Pharmacokinetic Analyses

8.1.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses described below will be based on the PKC and PKP populations, unless otherwise specified. All summary tables and figures are for each part separately and all listings are for both parts combined into one, unless otherwise specified.

Table 6 below provides an overview of the planned analyses, with full details being presented in Appendix 12: Listing of Data Display.

Table 6 Overview of Planned Pharmacokinetic Analyses

Endpoint / Parameter/ Display Type	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Concentration of GSK3008356														
PK Plasma Drug Concentration-time (Part 1 and Part 2 on Days 1 and 14)				Y	Y	Y	Y					Y	Y	
PK Trough Plasma Concentration-time (Part 2)				Y			Y							
PK Parameters														
Part 1: AUC_{0-t} AUC_{0-24}, $AUC_{0-\infty}$, C_{max}				Y			Y*				Y			
Part 2: $AUC_{0-\infty}$, on Day 1, $AUC_{(0-tau)}$, Cmax on Days 1 and 2. Accumulation Ratio (R_o, R_s and R_{cmax}),				Y			Y*				Y			
Parts 1 & 2: t_{max}, $t_{1/2}$, Ae, CLr				Y			Y*							
Part 1: Dose Proportionality (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}) AUC_{0-t}, $AUC_{0-\infty}$, C_{max}: Only applied for the single dosing. $AUC_{0-\infty}$: Applied for								Y		Y**				

Endpoint / Parameter/ Display Type	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
for all other cohorts with multiple dosing.														
Part 2: Dose Proportionality (AUC(0-∞) on Day 1, $AUC_{(0\text{-}tau)}$, C_{max} on Day 1 and Day 14								Y		Y**				
Part 2: Accumulation Ratio (R_o, R_{cmax})								Y		Y**				
Part 2: Steady State (C_{trough})								Y		Y**				

NOTES :

- T = Table, F = Figure, L = Listings, Y = Display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- * Listing of All derived PK parameters will be produced in one listing by part.
- ** SAS Output of the Statistical Analyses from the statistical model.

8.1.2. Drug Concentration Measures

Concentrations of plasma GSK3008356 will be listed by Part, Treatment Subject, Day and time, and summarised by Part, Treatment, Day and nominal time for the active treatment groups. Standard summary statistics will be calculated (i.e. n, mean, standard deviation, median, minimum and maximum).

Trough plasma concentration (Ctrough) collected at pre-dose on Days 2, 4, 5, 6, 12, 13, 14 together with the 24h post-dose on Day 14 from Part 2 will be listed, and summarized by Active Treatment and Day.

Individual plasma concentration-time profiles and median/mean profiles by treatment group (i.e., by Part, and then Treatment) will be plotted for Part 1 and Part 2 at Day 1 and Day 1 and Day 14 respectively. 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. semi log plot).

8.1.3. Pharmacokinetic Parameters

8.1.3.1. Deriving Pharmacokinetic Parameters

Deriving Pharmacokinetic Parameters:

- Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 11.5.3 Reporting Process & Standards).

- The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using Phoenix WinNonlin Version 6.2.1 or higher.
- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in Table 7 will be determined from the plasma concentration-time data, as data permits.

Table 7 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
$AUC_{(0-t)}$ (Part 1)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
$AUC_{(0-\tau)}$ (Part 2)	Area under the concentration-time curve from time zero to the time of the end of dosing interval (C(T)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
$AUC_{(0-24)}$ (Part 1)	Area under the concentration-time curve from time zero to the time of the 24 hour concentration (C(24h)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
$AUC_{0-\infty}$ (Part 1 + Part 2 day 1)	Area under the concentration-time curve extrapolated to infinity will be calculated as: **AUC(0-inf) = AUC(0-t) + C(t) / lambda_z** This parameter will only be calculated for the single-dose profiles in Part 1 and Day 1 in Part 2.
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
Ct	Last quantified observed concentration, determined directly from the concentration-time data.
Tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: **t½ = ln2 / lambda_z**
Ae	Cumulative amount of drug excreted in urine. $Ae = \sum C_{ur} * V_{ur}$ Where C_{ur} is the concentration in urine and V_{ur} is the volume of urine
CLr	Renal Clearance [1] Single Dose: CLr = Ae/AUCinf [2] Repeat Dose: $CLr = Ae_{\tau} / AUC_{\tau}$ Where Ae_{τ} is cumulative amount of drug excreted in urine over a dosing interval.
C_{trough} (Part 2)	Observed Concentration at the end of a dosing interval, immediately before next administration. Directly obtained from the observed concentration vs. time curves. They are the pre-dose concentration on Days 2, 4, 5, 6, 12, 13, 14 and the 24 h post dose on Day 14.
R_O (Part 2)	Accumulation Ratio, calculated in the multi-dose regimens, as the ratio [$AUC_{0-\tau}$ on the final day (Day 14)]/[$AUC_{0-\tau}$ on Day 1]

Parameter	Parameter Description
R_{cmax} (Part 2)	Accumulation Ratio, calculated in the multi-dose regimens, as the ratio [Cmax on the final day (Day 14)]/[Cmax on Day 1]
R_s (Part 2)	Steady-state Accumulation Ratio, calculated in the multi-dose regimens, as the ratio [AUC(0-tau) on final day (Day 14)]/[$AUC_{0-\infty}$ on Day 1]

NOTES:

- Additional parameters may be included as required.
- Lambda_z is the terminal phase rate constant (also known as the constant of elimination or K_{el}). This is determined for each concentration*time profile by fitting a log-linear curve through the concentration*time points in the terminal phase as data permits. The determination of which points are included in the terminal phase is made according to pre-specified rules.
- R_O, Rcmax and Rs will be calculated as Day 14 / Day 1 for Part 2 (14-day dosing).

All the derived PK parameters described in the Table 7 will be listed, as data permits. The PK parameters will be displayed by dose and then by Day (Day 1 in Part 1, Days 1 and 14 in Part 2), of each active treatment within each part. For each of these parameters except t_{max}, Ae, and CLr, the following summary statistics will be calculated for the active treatment group: median, maximum, minimum, arithmetic mean, standard deviation, CVb, geometric mean, 95% confidence interval for the geometric mean and standard deviation of logarithmically transformed data. For t_{max}, Ae, and CLr, median, maximum, minimum, arithmetic mean and standard deviation will be calculated.

8.1.3.2. Statistical Analysis of Pharmacokinetic Parameters

Statistical analysis of the pharmacokinetic parameters data will be the responsibility of Accenture with oversight by Clinical Statistics GlaxoSmithKline. Once the plasma has been analysed for GSK3008356 any remaining plasma may be analysed qualitatively for other compound-related metabolites and the results reported under a separate PTS-DMPK protocol. The urine samples will also be analysed for compound-related metabolites and the results reported under a separate PTS-DMPK protocol.

The following pharmacokinetic statistical analyses will only be performed, if sufficient data is available (i.e. if subjects have well defined plasma profiles).

Dose Proportionality in Part 1 and Part 2

Planned Statistical Analyses
Endpoint(s)

• Part 1:
  ○ AUC(0-t), AUC(0-∞), and C_{max} applied to all single dosing active treatments
  ○ AUC(0-∞) applied to multiple dosing active treatments
• Part 2: AUC(0-∞) on Day 1, AUC_{0-tau} and C_{max} on Day 1 and Day 14

Model Specification
• **The Power Model can be described below:** $y = \alpha * dose^{\beta}$ or $y = \alpha * surface\ area^{\beta}$

Planned Statistical Analyses

where y denotes the PK parameter being analysed (endpoints specified above) and α depends on the random error in the single dose and repeat dose parts where subjects take the study drug in a parallel-group fashion.

Dose proportionality implies that β=1 and will be assessed by estimating β along with its 90% CI. The exponent, β, in the power model will be estimated by regressing the loge-transformed PK parameter on loge-transformed dose.
An example of the SAS code that will be used for this analysis:

```
Part 1:   Proc Mixed;
              model logPKparm = logdose / solution ddfm=kr cl alpha=0.1 outp=pred;
          run;
```

Note: logPKparm is the log of the following PK parameters: AUC(0-t), AUC(0-∞), and Cmax for all single dosing active treatments. AUC(0-∞) for multiple dosing active treatments. We will compare the highest dose to the lowest dose for these parameters in single dosing active treatments and multiple dosing active treatments, respectively.

```
Part 2:   Proc Mixed;
              by day;
              model logPKparm = logdose / solution ddfm=kr cl alpha=0.1 outp=pred
          run;
```

Note: logPKparm is the log of the following PK parameters: AUC(0-∞) on Day 1, AUC(0-tau) and Cmax on Day 1 and Day 14. We will compare the highest dose to the lowest dose for these parameters.

Model Checking

- Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- Point estimates of comparison the highest dose to the lowest dose for the mean slopes of PK parameters with associated 90% CIs will be presented.

Accumulation Ratio in Part 2

Planned Statistical Analyses
Endpoint(s)
• AUC(0-tau) and C_{max} on Day 14 and Day 1 in Part 2;
Model Specification

• **The Mixed Model for Ro and Rcmax can be described below:**
Endpoint = treatment + day + treatment*day + subject (treatment) + random error
 	
Where endpoint is the loge-transformation of AUC(0-tau) and Cmax.
Fixed effects: treatment, day, and treatment*day interaction
Random effect: subject within treatment.
Treatments will be ordered according to Appendix 5.
 	
For accumulation ratio based on parameters in the endpoint(s) above, following loge-transformation, endpoints will be analyzed using a mixed model, fitting fixed effect terms and random effect as specified above. The accumulation ratio of GSK300836 will be estimated by calculating the ratios of AUC(0-tau) and Cmax on Day 14 to Day 1 and the corresponding 90% CI for each cohort in Part 2.
 	
An example of the SAS code that will be used for this analysis:
Part 2: Proc Mixed;
class treatment day subjid;
model logPKparm = treatment day treatment*day/ s ddfm=kr cl alpha=0.1
outp=pred;
random subjid (treatment) / type = un;
run;
 	
Note: PKparm is PK parameters: AUC(0-tau) and Cmax on Day 1 and Day 14 in Part 2.

Model Checking
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Point estimates of accumulation ratio with associated 90% CIs will be presented.

Steady State Assessment in Part 2

Planned Statistical Analyses
Endpoint(s)
• C_{trough} in Part 2
Model Specification
• **The Mixed Model can be described below:** Endpoint = day + subject + random error Where endpoint is the log_e-transformation of C_{trough} which were collected at pre-dose on Days 2, 4-6, 12-14, 15 (or 24 h post-dose on Day 14) in Part 2. Fixed effect: day Random effect: subject Trough plasma concentration (C_{trough}) following log_e-transformation will be analysed using a mixed model, fitting fixed effects and random effects as specified above. Day will be treated as a continuous variable in the model. The 90% CI of the slope of the linear regression will be calculated for each cohort. An example of the SAS code that will be used for this analysis: Part 2: Proc Mixed; class subjid; by treatment; model logC_{trough} = day / ddfm=kr cl alpha=0.1 outp=pred; random subjid; run;
Model Checking
• Refer to Appendix 10: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Point estimates of slope of the collection day for each active treatment with associated 90% CIs will be presented.

8.2. Biomarker/Pharmacodynamic Markers Analyses

8.2.1. Overview of Planned Biomarker/Pharmacodynamic Analyses

The pharmacodynamic analyses for Postprandial Triglyceride will be based on the "Pharmacodynamic" population, while exploratory pharmacodynamics lab test and the Bristol stool Form Scale will be based on "Safety Population", unless otherwise specified. For placebo group, pooling of placebo subjects within each part is considered a general report rule, except for Postprandial Triglyceride (TG) in part 1, where placebo is pooled without cohort 8.

All summary tables and figures are for each part separately and all listings are for both parts combined into one, unless otherwise specified.

Table 8 below provides an overview of the planned pharmacodynamic analyses with full details of data displays being presented in Appendix 12: List of Data Displays.

Table 8 Overview of Planned Pharmacodynamic Analyses

	Absolute			
	Summary		Individual	
Endpoint / Parameter/ Display Type	T	F	L	F
Postprandial Triglyceride (TG)				
Absolute TG Values by Treatment, Day, and Time Point	Y	Y	Y	Y
Corrected TG Post Dose Values by Treatment, Day and Time Point	Y	Y	Y	Y
TG AUC (1-12), TG AUC(2-5), Corrected TG AUC(1-12), and Corrected TG AUC(2-5) by Treatment and Day	Y		Y	
Percent (%) Change from Baseline TG AUC by Treatment and Day	Y	Y		
Bristol Stool Form Scale (BSFS)				
BSFS	Y	Y	Y	
Exploratory PD Labs (Serum Lipid Levels)				
Exploratory PD Labs Data in Serum Lipid (Total Cholesterol HDL LDL VLDL-TG (if feasible) Spot TG) by Treatment and the Nominal Sampling Time Point	Y		Y	

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- HDL = High / LDL = Low Density Lipoproteins, VLDL-TG = Very Low Density Lipoprotein Triglycerides
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- Figures will show both baseline (Day -1) and post-treatment TG levels plotted together over time (from meal).

8.2.1.1. Postprandial Triglyceride Evaluation

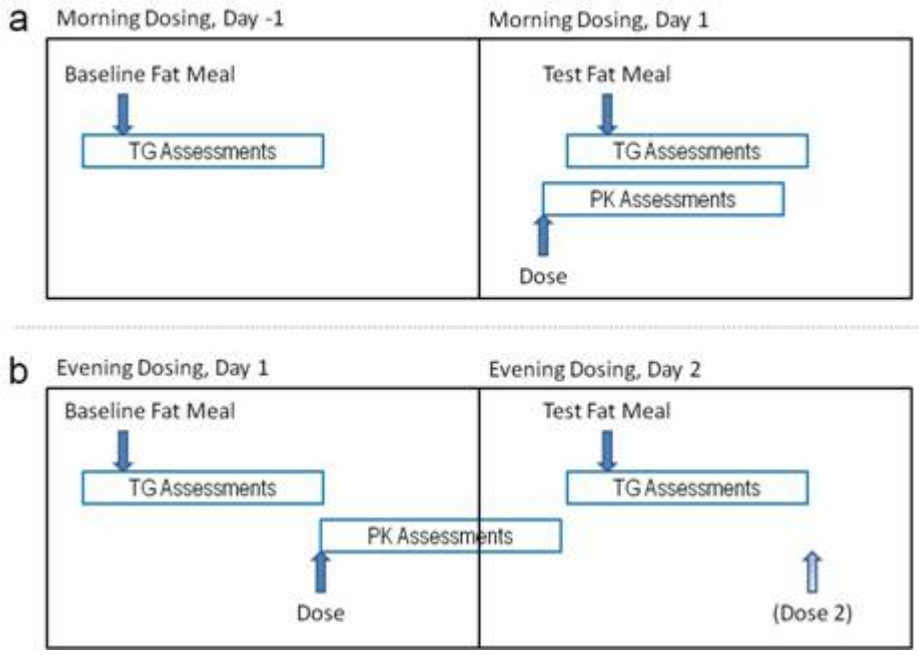
Each subject will undergo, at pre-dose and post-dose, a fat meal challenge, consisting of 30% fat by calories, to be consumed within 15 min (±10 min). Triglyceride (TG) measurements will be collected from 1 hour prior to the meal through 10 hours after the meal (at meal time and 1, 2, 3, 4, 5, 6, 7, 10 hours post-meal).

The following will be taken into consideration when pooling placebo data. For all dosing with only a single dose administered at 0h, two doses at 0h and 4h, and hourly dosing starting 0h x 9 doses, only one meal was provided within the TG assessment period (Part 1, Cohorts 1, 2, 3, 4, 5, 6, 7, 10, and 11). For all dosing with two doses administered at 0h and 16h, a second meal with 20% fat was provided at 6h post-dose (Part 1, Cohort 8, and Part 2, Cohorts 1, 2, and 3). The second meal will impact the TG data beyond 6h and these cohorts data should be pooled separately from the single-meal placebo data. For only the TG analysis the pooled placebo in Part 1 will not include Cohort 8; placebo data in cohort 8 will be displayed separately.

For subjects undergoing a dosing regimen, the post-dose meal will start 2 hours post-dose. The first TG measurement will be collected 1 hour post-dose which is 1 hour pre-meal, and TG collections will run through 12 hours post-dose.

To serve as a baseline comparator, the same TG profile will be collected prior to dosing, also in the morning. This will be the day prior to morning dosing, for subjects undergoing a morning dosing regimen. Please see the following figure for further information on the exact dosing:

Figure 2 Postprandial Triglyceride Assessment Schematic



Tables and Figures will be produced for absolute TG values by Part/Treatment/Day and the nominal sampling time points.

Post dose values of TG will be adjusted so that baseline day and post dose day pre-meal values are as close as possible. Post dose values (i.e. Part 1: Day 1; Part 2: Days 1 and 14) at each nominal sampling time point will be adjusted by adding the following value:

- Part 1 Day 1 Correction:
    - (Day -1 (1hr + 2hr)/2) – (Day 1 (1hr + 2hr)/2)
- Part 2:
    - Day 1 Correction:
        - ❖ (Day -1 (1hr + 2hr)/2) – (Day 1 (1hr + 2hr)/2)
    - Day 14 Correction:
        - ❖ (Day -1 (1hr + 2hr)/2) – (Day 14 (1hr + 2hr)/2)

Table and Figure will be also produced for the pre-meal corrected TG post dose values by Part/Treatment/Day and the nominal sampling time points.

8.2.1.2. Postprandial Triglyceride AUC

Postprandial triglyceride AUC(1-12) and AUC(2-5) (on day -1 and day 1 in part 1; day -1 day 1, and day 14 in part 2) will be calculated using trapezoidal rule.

Postprandial triglyceride AUC(1-12) and AUC(2-5) (on day 1 in part 1; day 1 and day 14 in part 2) will be calculated by adding the correction value in Section 8.2.1.1 to each time point after post-dose, but these adjustments/transformations will not apply to TG value at baseline day -1. Corrected TG AUC values will be also calculated using the linear trapezoidal rule.

Table and Figure will be produced for TG AUC and corrected TG AUC above of postprandial triglyceride by part, treatment, and day.

Table and Figure will be also produced for percent (%) change from baseline (e.g. Part 1: (Day 1 and Day -1 difference) /TG AUC on Day -1 ; Part 2: (Day 1 and Day -1 difference) / TG AUC on Day -1 as well as (Day 14 and Day -1 difference) / TG AUC on Day -1) in AUC and correct AUC of postprandial triglyceride by part and treatment.

Listing of individual change from baseline in AUC and Corrected AUC of postprandial triglyceride will be produced for both parts combined together.

8.2.1.3. Bristol Stool Form Scale (BSFS)

The Bristol Stool Form Scale (BSFS) which describes 7 types of stool, will be used by the subjects and verified by the staff in real time in all parts of the study. The number of each type of stool will be collected across the 24h calendar day.

The BSFS data will be summarized for Part 1 and Part 2 separately.

Summary of number of subjects and number of BSFS by type, day, and treatment

Summary of total number of BSFS by day and treatment.

A listing will also be produced showing study day and BSFS score for each entry.

A histogram and a line plot will also be produced by part, treatment and BSFS type.

8.2.2. Exploratory Pharmacodynamic Markers

Descriptive statistics for serum lipid levels will be tabulated for the time points collected, by Part/treatment/Dose. A listing will also be produced. The exploratory PD markers are Cholesterol, high density lipoproteins (HDL), low density lipoproteins (LDL), very-low density lipoprotein triglycerides (VLDL-TG) and spot TG labs will be collected. Spot TG are defined as not collected as part of the fat meal challenge postprandial TG assessment.

8.3. Pharmacokinetic / Pharmacodynamic Analyses

The PK/PD analyses in this section will be outside of the scope of this RAP. However, a road map of how these analyses can be done are described below.

Based on the lack of a repeat dose regimen that was both active for TG suppression and tolerated from a GI perspective, it has been decided not to perform a detailed PK/PD model analysis. However, for documentation, the approach we had previously planned on taking is in Appendix 9.

8.3.1. Population Pharmacokinetic / Pharmacodynamic Analyses

A separate RAP will be created for the Population PK/PD analysis for publication purpose as data permit that will completed by CPMS, GSK.

The reporting will be separate from this CSR.

9. OTHER STATISTICAL ANALYSES

9.1. Exploratory Analysis

9.1.1. Skin Biopsy in Part 2

Details of the skin biopsy sample collection, including collection procedures, sample preparation, sample storage, and shipping procedures are provided in the Study Reference Manual.

Drug concentration analysis of the skin sample will be performed under the management of PTS-DMPK. Concentrations of GSK3008356 may be determined through standard Liquid Chromatography Tandem Mass Spectrometry (LC MS/MS) in homogenate and/or using Matrix Assisted Laser Desorption/Ionization (MALDI) analysis through approved analytical methodology. Analysis of pharmacology (if feasible) may also be performed potentially including lipodomics/metabolomics for lipid levels, including TG, in the skin.

Additional target engagement studies may also be performed (if feasible) including thermal shift assay and/or human skin lipogenesis (SLiP) assay. Raw data will be archived at the bioanalytical site. All skin biopsy analysis results will be reported under a separate PTS-DMPK protocol.

10. REFERENCES

GlaxoSmithKline Document Number 2015N242776_02 Study ID Protocol Amendment 02. A Phase I, Randomized, Placebo-Controlled, Double-Blind(sponsor unblind), Three Part Study to Evaluate the Safety, Tolerability, Preliminary PK and PD of Single and Repeat Oral Doses of GSK3008356 in healthy Subjects and Obese Subjects'. Report Date January 22, 2017.

Lewis SJ and Heaton KW. "Stool form as a useful guide to intestinal transit time." Scandinavian Journal of Gastroenterology, 1997, 32(9): 920-924.

11. APPENDICES

Section	Appendix
11.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
11.2	Appendix 2: Time & Events
11.3	Appendix 3: Assessment Windows
11.4	Appendix 4: Treatment States & Phases
11.5	Appendix 5 Data Display Standards & Handling Conventions
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11.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

11.1.1. Protocol Deviation Definition

Please refer to the exclusion criteria in Section 4.2 of Protocol Amendment02.

11.1.2. Per Protocol Population

Per Protocol Population will not be applied for this study.

11.2. Appendix 2: Time & Events

11.2.1. Protocol Defined Time & Events

11.2.1.1. Part 1 – Single Dose

	Screening (within 28d)	Day -2, Day -1 [9]	Day 1													Day 2	Day 3	Day 4	Follow Up (Day 6-8)
			Pre-dose	0h	0.25h	0.5h	1h	1.5h	2h	4h	6h	8h	12h	18h	24h	36h	48h	72h	
Informed Consent	X																		
Medical/medication/drug/alcohol history	X	X																	X
Complete Physical Exam, Weight	X	X[1]																X[1]	X
HIV, Hep B, Hep C	X																		
Pregnancy Test[2]	X	X																	X
Estradiol/FSH[3]	X																		
Urine Drug, Cotinine & Alcohol Screen[4]	X	X																	
Fat Meal[5]		X							X										
Triglyceride Assessment[5]		←→					X		←==========→										
Study Drug Dose[10]				X[10]															
Vital Signs (BP, HR, pulse, Temp)[6]	X	X	X				X			X			X		X		X	X	X
12-Lead ECG	X		X				X			X			X		X			X	
Telemetry			←==========→																
Hematology, Chemistry	X	X									X				X		X	X	X
UA	X	X													X			X	X
Exploratory PD Labs	X		X												X			X	X
Plasma PK and Metabolite Sampling[5, 7]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine PK and Metabolite Sampling[7]			←→	←==========→										←→					
Adverse Event Review		←==========→																	

	Screening (within 28d)	Day -2, Day -1 [9]	Day 1												Day 2	Day 3	Day 4	Follow Up (Day 6-8)
			Pre-dose	0h	0.25h	0.5h	1h	1.5h	2h	4h	6h	8h	12h	18h	24h	36h	48h	72h	
BSFS[8]			←==========→																
Concomitant Medication Review		←==========→																	
Outpatient Visits	X																		X
Inpatient Check-in		X																	
Inpatient Check-out																		X	

1. Brief physical exam, weight.
2. Serum hCG at screening and follow up, urine hCG pre-dose on Day -1 – all females.
3. If indicated.
4. An alcohol breath test is acceptable.
5. Detailed Fat Meal and Triglyceride Assessment relative to Dose and Plasma PK Sampling can be found in Section 6.1.1.1 in Protocol Amendment 2.
6. Temperature Screening and Day -1 only.
7. Plasma analysis for circulating metabolite profile; Urine analysis to aid structural identification. Urine samples for parent and metabolite structure will be collected pre-dose and over the post-dose intervals 0-12 hours and 12-24 hours. Plasma and urine samples for metabolites will be analyzed from only the highest dose cohort.
8. The number of BSFS stool types will be collected in real time for each 24h period (Section.11.5 in Protocol Amendment 2).
9. Based on logistics, check-in and all Day -1 assessments may occur on Day -2 with the exception of the Fat Meal and TG Assessment, both of which must be done on Day -1.
10. For cohorts where multiple doses are to be administered either q1h, q4h or q16h, Time 0 is the first dose and subsequent doses are per regimen (q1h, q4h or q16) and the subsequent doses are not noted on the T&E Table. For the single evening cohort, the dose will be at hour 16 and not noted on the T&E Table.

11.2.1.2. Part 1 – Single Dose, Fat Meal Challenge and Triglyceride Assessment Relative to Dose and PK Sampling

	Day -1, Day 1															
	Pre-dose	0h	0.25h	0.5h	1h	1.5h	2h	3h	4h	5h	6h	7h	8h	9h	12h	18h
Study Drug Dose[1, 3]		X[3]														
Fat Meal							X									
Triglyceride Assessment					X		X	X	X	X	X	X	X	X	X	
Plasma Pharmacokinetic Sampling[1, 2]	X		X	X	X	X	X		X		X		X		X	X

1. Day 1 only
2. PK Samples included in table to provide relative time to dosing, fat meal and triglyceride assessment.
   The full PK time points are found in Section.6.1.1 in Protocol Amendment 2
3. For cohorts where multiple doses are to be administered either q1h, q4h or q16h, Time 0 is the first dose and subsequent doses are per regimen

(q1h, q4h or q16) and the subsequent doses are not noted on the T&E Table. For the single evening cohort, the dose will be at hour 16 and not noted on the T&E Table

11.2.1.3. Part 2 – Repeat Dose, Morning Dose Administration, Screening, Day -1, Day 1

	Screening (within 28d)	Day -2, Day -1 [9]	Day 1												
			Pre-dose	0h	0.25h	0.5h	1h	1.5h	2h	4h	6h	8h	12h	18h	24h
Informed Consent	X														
Medical/medication/drug/alcohol history	X	X													
Complete Physical Exam, Weight	X	X[1]													
HIV, Hep B, Hep C	X														
Pregnancy Test[2]	X	X													
Estradiol/FSH[3]	X														
Urine Drug, Cotinine & Alcohol Screen[4]	X	X													
Fat Meal[5]		X							X						
Triglyceride Assessment[5]		←→					X		←==========				→		
Study Drug Dose[10]				X[10]											
Vital Signs (BP, HR, pulse, Temp)[6]	X	X	X				X			X			X		X
12-Lead ECG	X		X				X			X			X		X
Telemetry			←==========												
Hematology, Chemistry	X	X									X				X
UA	X	X													X
Exploratory PD Labs	X		X												X
Plasma PK and Metabolite Sampling[5, 7]			X		X	X	X	X	X	X	X	X	X	X	X
Skin biopsy [11]							X[11]				X[11]				X[11]
Adverse Event Review		←==========													→
BSFS[8]			←==========												→
Concomitant Medication Review		←==========													→
Outpatient Visits	X														

	Screening (within 28d)	Day -2, Day -1 [9]	Day 1											
			Pre-dose	0h	0.25h	0.5h	1h	1.5h	2h	4h	6h	8h	12h	18h	24h
Inpatient Check-in		X													

11.2.1.4. Part 2 – Repeat Dose, Morning Dose Administration, Days 2-13

	Days 2-13	
	Pre-dose	0h
Study Drug Dose[6]		X[6]
Vital Signs (BP, HR, pulse)	X	
12-Lead ECG[1]	X	
Hematology, Chemistry[2]	X	
UA[3]	X	
Exploratory PD Labs[3]	X	
Plasma PK and Metabolite Sampling[4]	X	
Skin biopsy[7]	X	
Adverse Event Review	←==========→	
BSFS[5]	←==========→	
Concomitant Medication Review	←==========→	

1. Day 2 (equal to Day 1 24h time point), 7, 12, and 13 only.
2. Day 2 (equal to Day 1 24h time point), 4, and Day 7 only
3. Day 2 (equal to Day 1 24h time point) and Day 7 only
4. Day 2 (equal to Day 1 24h time point), 4, 5, 6, 12, and 13 only
5. The number of BSFS stool types will be collected in real time for each 24h period (Section11.5. in Protocol Amendment 2).
6. For cohorts where multiple doses are to be administered either q1h or q16h, Time 0 is the first dose and subsequent doses are per regimen (q1h or q16) and the subsequent doses are not noted on the T&E Table.
7. Day 2 (equal to Day 1 24h time point) only

11.2.1.5. Part 2 – Repeat Dose, Morning Dose Administration, Days 14-17, Follow-up

	Day 14													Day 15	Day 16	Day 17	Follow Up (Day 20-22)
	Pre-dose	0h	0.25h	0.5h	1h	1.5h	2h	4h	6h	8h	12h	18h	24h	36h	48h	72h	
Medical/medication/drug/alcohol history																	X
Complete Physical Exam, Weight																X[1]	X
Pregnancy Test[2]																	X
Fat Meal[3]							X										
Triglyceride Assessment[3]					X		←==========				→						
Study Drug Dose[6]		X[6]															
Vital Signs (BP, HR, pulse)	X				X			X			X		X		X	X	X
12-Lead ECG	X				X			X			X		X			X	
Hematology, Chemistry	X								X				X		X	X	X
UA	X												X			X	X
Exploratory PD Labs	X												X			X	X
Plasma PK and Metabolite Sampling[3, 4]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Skin Biopsy[7]					X[7]				X[7]				X[7]				
Adverse Event Review	←==========																→
BSFS[5]	←==========																→
Concomitant Medication Review	←==========																→
Outpatient Visits																	X
Inpatient Check-out																X	

1. Brief physical exam and weight Day 17 only
2. Serum hCG at follow up, all females.
3. Detailed Fat Meal, Triglyceride Assessment, Plasma PK Sampling and Plasma Metabolite Sampling can be found in Section 6.1.8.1 in Protocol Amendment 2
4. Plasma analysis for circulating metabolite profile; Plasma samples for metabolites will be analyzed from only the highest dose cohort.
5. The number of BSFS stool types will be collected in real time for each 24h period (Section 11.5. in Protocol Amendment 2).
6. For cohorts where multiple doses are to be administered either q1h or q16h, Time 0 is the first dose and subsequent doses are per regimen (q1h or q16) and the subsequent doses are not noted on the T&E Table.
7. Cohort 1 (10mg q16) collect only at 1h and 24h Day 14; Cohorts 2 & 3 (3mg, 1mg or 5mg q1h) collect only at 6h and 24h Day 14

11.2.1.6. Part 2 – Repeat Dose, Fat Meal Challenge and Triglyceride Assessment Relative to Dose and PK Sampling--Morning Dose Administration, Day -1, Day 1, and Day 14

	Day -1, Day 1, Day 14															
	Pre-dose	0h	0.25h	0.5h	1h	1.5h	2h	3h	4h	5h	6h	7h	8h	9h	12h	18h
Study Drug Dose[1]		X														
Fat Meal							X									
Triglyceride Assessment					X		X	X	X	X	X	X	X	X	X	
Plasma Pharmacokinetic Sampling[1, 2]	X		X	X	X	X	X		X		X		X		X	X

1. Day 1 and 14 only. For cohorts where multiple doses are to be administered either q1h or q16h, Time 0 is the first dose and subsequent doses are per regimen (q1h or q16) and the subsequent doses are not noted on the T&E Table.
2. PK Samples included in table to provide relative time to dosing, fat meal and triglyceride assessment. The full PK time points are found in Section 11.2.1.3, Section 11.2.1.4, and Section 11.2.1.5.

11.3. Appendix 3: Assessment Windows

11.3.1. Definitions of PK Assessment Windows

Analysis Set / Domain	Target / nominal time	Target Window		Analysis Timepoint
		Beginning Timepoint	Ending Timepoint	
PK Concentration (analyte is GSK3008356)	Pre-Dose	within 30 mins of dosing	dosing time	0 Hours
	0.25 hour	00:13	00:17	Actual draw time
	0.5 hour	00:27	00:33	Actual draw time
	1 hour	00:57	01:03	Actual draw time
	1.5 hours	01:27	01:33	Actual draw time
	All Subsequent draws between 2 hours – 24 hours*	Target – 00:10	Target + 00:10	Actual draw time
	All Subsequent draws between 36 hours – 72 hours*	Target – 00:30	Target + 00:30	Actual draw time

NOTES :

- Any actual draws outside of these time windows will be listed as deviations (not necessarily "important"), but will still be used in the concentration assay and determination of PK parameters according to the actual draw time.
- Any concentrations determined from blood draws inside or outside these windows may still be excluded from PK determinations for other reasons, such as sample handling or other protocol deviations.
- * All Subsequent draws after 2 hour will be at hours 4, 6, 8, 12, 18, 24, 36, 48, and 72 in Part 1.
- In Part 2, All Subsequent draws after 2 hour will be at hours 4, 6, 8, 12, and 18 on Day 1; then PK Samples will be taken at Pre-Dose on Days 2, 4, 5, 6, 12, and 13 only during period Days 2-13 Morning Dose; and starting on Day 14, PK Samples will be taken at Pre-dose, hours at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 36, 48, and 72.

11.3.2. Definitions of Triglyceride (Postprandial) Assessment Windows

Analysis Set / Domain	Target / nominal time		Target Window		Analysis Timepoint
	Rel to Dosing	Rel to Meal	Beginning Timepoint	Ending Timepoint	
Triglyceride	+01:00	-01:00	Target – 00:15	Target + 00:15	-01:00
	+02:00	00:00	Target – 00:15	Target + 00:15	00:00
	+03:00	+01:00	Target – 00:15	Target + 00:15	+01:00
	+04:00	+02:00	Target – 00:15	Target + 00:15	+02:00
	+05:00	+03:00	Target – 00:15	Target + 00:15	+03:00
	+06:00	+04:00	Target – 00:15	Target + 00:15	+04:00
	All Subsequent assessments (7, 8, 9, 12 hours post-dose or 5, 6, 7, 10 hours post-meal)		Target – 00:15	Target + 00:15	Nominal Time relative to meal

NOTES :

- For evening dosing regimens, triglyceride assessments will be at the same times relative to the meal, but the meal will be the following morning (not at 2 hours post-dose as with morning dosing).
- Any triglyceride assessments outside of these time windows will be listed as deviations (not necessarily "important"), but will still be used in the analysis. However, any evaluation which is closer to an adjacent (nominal) time than to its own nominal sampling will not be used.
- Any triglyceride assessments inside or outside these windows may still be excluded for other reasons, such as sample handling or other protocol deviations.
- Part 1: The assessment will be on Day -1 and Day 1; Part 2: The assessment will be on Day -1, Day 1 and Day 14. On Day -1, Target/nominal time is only relative to fat meal.

11.3.3. Definitions of Vital Signs and ECG Assessment Windows

Analysis Set / Domain	Target / nominal time	Target Window		Analysis Timepoint
		Beginning Timepoint	Ending Timepoint	
Vital Signs (BP, HR, pulse, Temp.)* and 12-Lead ECG	Screening	Within 28 day	Day -1	Screening
	Checking in	Day -1	Day -1	Day -1
	Pre-Dose	Within 12 hours before dosing	dosing time	00:00
	1 Hour Post-Dose	Target – 00:15	Target + 00:15	+01:00
	4 Hours Post-Dose	Target – 00:15	Target + 00:15	+04:00
	12 Hours Post-Dose	Target – 00:15	Target + 00:15	+12:00

NOTES :

- There are also 24-hour assessments of these shown in the protocol. In cases of repeat dose (Part 2), these serve as the pre-dose assessment on the next day. In other cases, they (and 48 and 72 hours) are follow-up assessments on subsequent days, in which case, the target window will be ± 6 hours, but the assessments will be used if they occur on that day.
- *: Temperature Screening and Day -1 only.

- ECG: Assessment windows are same as those of Vital Signs excluding time points at Checking in (Day -1), 48 hours, and follow-up (Days 6-8) for Part 1
- Any assessments outside of these time windows will be listed as deviations (not necessarily "important"), but will still be used in the analysis. However, any evaluation which is closer to an adjacent (nominal) time than to its own nominal sampling will not be used

11.4. Appendix 4: Treatment States and Phases

11.4.1. Treatment Phases

Assessments and events will be classified according to the time of occurrence relative to start and/or stop date of the study treatment in double-blind phase I study.

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

11.4.2. Treatment States

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

11.4.2.1. Treatment States for AE Data

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

NOTES:

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

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Study Treatment & Sub-group Display Descriptors

Part 1: All treatments are dosed in the morning; some regimens are single morning dosing while other regimens are multiple dosing.

Part 2: All treatments are dosed in the morning repeated over 14 days. All doses are BID.

Consistent with the treatment group code shown in the randomization schedules, parts, cohorts, actual doses, and treatment regimens will appear as follows in data displays produced:

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
Part 1			
A1	SD Cohort 1 GSK3008356 Active	5mg	2
A2	SD Cohort 2 GSK3008356 Active	10mg	3
A3	SD Cohort 3 GSK3008356 Active	30mg	4
A4	SD Cohort 4 GSK3008356 Active	75mg	5
A5	SD Cohort 5 GSK3008356 Active	200mg	6
A6	SD Cohort 6 GSK3008356 Active	125mg	7
A7	MD Cohort 7 GSK3008356 Active	100mg t0, t4	8
A8	MD Cohort 8 GSK3008356 Active	100mg t0, t16	9
A9	SD Cohort 9 GSK3008356 Active	cancelled	n/a
A10	MD Cohort 10 GSK3008356 Active	10mg q1h x 9	10
A11	MD Cohort 11 GSK3008356 Active	5mg q1h x 9	11
P1	Placebo	Placebo	1
Part 2			
B1	RD Cohort 1 GSK3008356 Active (AM) 14 days dosing	10mg BID	2
B2	RD Cohort 2 GSK3008356 Active (PM) 14 days dosing	1mg BID	3

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
B3	RD Cohort 3 GSK3008356 Active (PM) 14 days dosing	3mg BID	4
P2	RD Placebo 14 days dosing	Placebo	1

NOTES:

1. General order (left-right or top-down) of treatments being presented in TFLs, as appropriate. Since displays will be separate for the 2 parts of the study, outputs will contain only those doses/regimens used in that part.

11.5.2. Baseline Definition & Derivations

11.5.2.1. Baseline Definitions

Parameter				Baseline Used in Data Display
	Screening (within 28 days)	Day -2, Day -1 [1]	Day 1 (Pre-Dose)	
Part 1 – Single Dose				
Vital Signs (BP, HR, pulse)	X	X	X	Day 1 (Pre-Dose)
Hematology, Chemistry	X	X		Day -2, Day -1
UA	X	X		Day -2, Day -1
12-Lead ECG	X		X	Day 1 (Pre-Dose)
Exploratory PD Labs (Serum Lipid Levels)	X		X	Day 1 (Pre-Dose)
Part 2 – Repeat Dose				
Vital Signs (BP, HR, pulse)	X	X	X	Day 1 (Pre-Dose)
Hematology, Chemistry	X	X		Day -2, Day -1
UA	X	X		Day -2, Day -1
12-Lead ECG	X		X	Day 1 (Pre-Dose)
Exploratory PD Labs (Serum Lipid Levels)	X		X	Day 1 (Pre-Dose)

NOTES :

- Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.
- [1]: Based on logistics, Day -1 assessments may occur on Day -2.

All TG collection is relative to nominal or actual dose time 0h. For postprandial TG assessments, Day -1 is the Baseline TG Excursion since no study drug was administered. Day 1 and Day 14 are Post-Dose TG Excursion responses. Within these TG Excursions, times 1h and 2h are pre-meal. The challenge meal is administered at 2h (after lab collection). Times 3h onward are post-meal (postprandial) TG Excursion. See the Tables in Section 11.2.1.2 and Section 11.2.1.6.

Keep in mind that the 3h (post dose) TG collection is 1h post-meal (postprandial) whether on Baseline Day or Post-Dose Day. However, the labelling of the data point should remain relative to dosing (3h) and not changed to be relative to meal.

As noted in Section 8.2, one Part 1 and all three Part 2 cohorts had a second (20% fat) meal provided at 6h post-dose.

11.5.2.2. Derivations and Handling of Missing Baseline Data

Derivation	How Derived	Handling of Missing Data
Change from Baseline	= Post-Dose Visit Value – Baseline	Missing if either baseline or post is missing
%Change from Baseline	= (Post-Dose Visit Value – Baseline)/Baseline	Missing if either baseline or post is missing
Log Transformation	= [natural] log (PK Parameter)	Missing if PK parameter is missing
Back-Transformation	= EXP(estimate or confidence limit)	Missing if estimate or CL is missing
Maximum LFT	= maximum of that LFT (e.g., ALT) value for that subject over time	Missing only if all values of that LFT are missing for that subject
%AUCex	= [AUC(0-inf) – AUC(0-t)] / AUC(0-inf) x 100	Missing if AUC(0-inf) is missing
Accumulation Ratio (Ro)	=[$AUC_{0-\tau}$ on the final day (steady state)]/[$AUC_{0-\tau}$ on Day 1]	Missing if AUC_{0-tau} is missing for either Day 1 or final day
Accumulation Ratio (Rs)	=[$AUC_{0-\tau}$ on the final day (steady state)]/[AUC_{0-inf} on Day 1]	Missing if either AUC_{0-tau} on final day or AUC(0-inf) on Day 1 is missing.
Corrected by adding the adjusting value to post dose TG values	• Part 1 Day 1 Correction: ○ (Day -1 (1hr + 2hr)/2) – (Day 1 (1hr + 2hr)/2) • Part 2: ○ Day 1 Correction: ❖ (Day -1 (1hr + 2hr)/2) –	Missing if any TG value is missing for either post dose or pre-dose at any time point

Derivation	How Derived	Handling of Missing Data
	(Day 1 (1hr + 2hr)/2) ○ Day 14 Correction: ❖ (Day -1 (1hr + 2hr)/2) – (Day 14 (1hr + 2hr)/2)	

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 11.5.2.1. Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

11.5.3. Reporting Process & Standards

Reporting Process
Software
• Version 6.2.1 (or higher) of WinNonlin will be used to determine PK parameters. • Version 9.4 of SAS software will be used to create output displays (TLFs).
Analysis Dataset
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.1 or higher & AdaM IG Version 1.1.) • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.
Generation of RTF Files
• RTF files will be generated for outputs (TLFs).

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: ○ 4.03 to 4.23: General Principles ○ 5.01 to 5.08: Principles Related to Data Listings ○ 6.01 to 6.11: Principles Related to Summary Tables ○ 7.01 to 7.13: Principles Related to Graphics • For placebo group, pooling of placebo subjects with each part is considered a general report rule, unless otherwise specified. All summary tables are for each part and all listings are for both parts combined into one, unless otherwise specified.
Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for

Reporting Standards	
reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF and laboratory reports.	
Planned and Actual Time	

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses of concentration and lab data unless otherwise stated.
  • Actual time relative to dosing will be used to determine PK parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.
  • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but may be omitted from figures, summaries and statistical analyses if the deviation is great enough, according to Section 11.1.	

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables or figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ (BLQ) values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive Summary Statistics (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and [between and or within] geometric coefficient of variation (CVb/w (%)) will be reported, based on one-sample analysis: [1] CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (SD = SD of log transformed data) [2] CV_w (%) = $\sqrt{}$ (exp(MSE) - 1) * 100 (MSE = mean square error from mixed effect model of loge-transformed data).
Parameters Not Log Transformed	Parameters t_{max}, Ae, and CLr will not be transformed.
Summary Tables	All derived PK parameters which were listed in Table 7 in Section 8.1.3 above.
Listings	Will include, for each subject PK profile, the first point and number of points

Reporting Standards	
	used in the determination of lambda_z.
Figures	• Will include Plasma PK Concentration-Time Plots (Linear and Semi-log) o Individual (PK16a) o Mean (PK17) o Median (PK18) • Box plot of PK parameters vs. Treatment

11.6. Appendix 6: Derived and Transformed Data

11.6.1. General

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

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

11.6.2. Study Population

Demographics
Age

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

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

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

11.6.3. Safety

ECG Parameters

RR Interval

- IF RR interval (msec) is not provided directly, then RR can be derived as:
  [1] If QTcF is machine read and QTcF is not provided, then:

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

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

Corrected QT Intervals

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

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

Adverse Events

- GI AEs/SAEs as specified under SOC as Gastrointestinal (GI)

Laboratory Parameters

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

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

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion is defined in the protocol (Section 4.6) as completing all phases of the study including the follow-up visit. The end of the study is defined as the last subject's last visit. • A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. If applicable, the reason for withdrawal of consent. A withdrawn subject may be replaced with another subject who will be assigned to the same treatment randomization. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels. All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

11.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.7.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: o Missing Start Day: First of the month will be used unless this is before the

Element	Reporting Detail
	start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per: Appendix 4 −Treatment States and Phases. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

11.7.2.2. Handling of Partial Dates

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

11.7.2.3. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
Imputation	• No imputation will be carried out for any parameters

11.8. Appendix 8: Values of Potential Clinical Importance

11.8.1. Laboratory Values

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

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	mmol/L	Δ from BL		↑ 44.2
Glucose (Fasting)	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO2	mmol/L		18	32

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

11.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec	> 450 [1]	
		> 450 [2]	≤ 479 [2]
		≥ 480 [2]	≤ 499 [2]
		≥ 500 [2]	
Absolute PR Interval	msec	< 110 [1]	> 220 [1]
Absolute QRS Interval	msec	< 75 [1]	> 110 [1]
Change from Baseline			
Increase from Baseline QTc	msec	> 60 [1]	
	msec	> 30 [2]	≤ 59 [2]
	msec	≥ 60 [2]	

NOTES: [Remove footnotes for RAP development]

[2] Represent standard ECG values of PCI for HV studies

[3] Represent further subdivisions of ECG values for analysis whereby the RAP team needs to decide whether these need to be generated in addition to standard ECG values being flagged. IF not required, then delete.

11.8.3. Vital Signs

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

Vital Sign Parameter (Change from Baseline)	Units	Clinical Concern Range			
		Decrease		Increase	
		Lower	Upper	Lower	Upper
Systolic Blood Pressure	mmHg	≥ 20	≥ 40	≥ 20	≥ 40
Diastolic Blood Pressure	mmHg	≥ 10	≥ 20	≥ 10	≥ 20
Heart Rate	bpm	≥ 15	≥ 30	≥ 15	≥ 30

NOTES: [Remove footnotes for RAP development]

Represent further subdivisions of BP & HR for analysis whereby the RAP team needs to decide whether these need to be generated in addition to standard absolute BP & HR values being flagged. IF not required, then delete.

11.9. Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses

11.9.1. Overview of Planned Pharmacokientic (PK) / Pharamcodynamic (PD) Analyses

The PK/PD analyses described in this appendix is purely for documentation purpose only and report is outside of scope of this RAP/CSR.

The PK/PD analyses will be based on the PK/PD population, unless otherwise specified.

The relationship between drug pharmacokinetics and pharmacodynamic endpoints (e.g. TG AUC) will be explored.

The PK parameters are perhaps included AUC(0-∞), AUC(0-t), Cmax, and Cmin in Part 1, AUC(0-∞) on Day 1, AUC(0-tau), Cmax, and Cmin on Days 1 and 14 in Part 2. PD parameters are %change from baseline (Day -1) of TG AUC(1-12) and TG AUC(2-5) as well as with the adjusted post dose TG values calculated AUC(1-12) and TG AUC(2-5).

All summary tables and figures are for each part separately and all listings are for both parts combined into one, unless otherwise specified.

Exposure-Response Analysis between the PK parameters and PD parameter will be conducted separately for Part 1 and Part 2.

PK parameters are PK AUC and PK concentrations including Cmax and other concentrations as appropriate. The PD parameters are %change from baseline (Day -1) of TG AUC(1-12) and TG AUC(2-5) as well as with the adjusted post dose TG values calculated AUC(1-12) and TG AUC(2-5).

Table 9 below provides an overview of the planned PK/PD analyses with full details of data displays being presented in Appendix 12: List of Data Displays.

Table 9 Overview of Planned PK/PD Analyses

PK Parameter / PD Parameter	Untransformed Stats Analysis		
	T	F	L
PK Parameter / PD Parameter			
Correlation between PD Parameter TG AUC and PK Parameters by Treatment and Day (in Part 2)	Y	Y	
Emax Model Applied for PD Parameter TG AUC and PK Parameters by Treatment and Day (in Part 2)	Y	Y	Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.

11.9.2. Statistical Analyses of Postprandial Triglyceride

11.9.2.1. Correlation Analysis

The correlation between PK parameters and PD parameters will be analysed by spearman method.

Summary and Figures of correlation between percent (%) change from baseline of TG AUC [AUC(1-12), AUC(2-5), as well as Corrected AUC(1-12) and Corrected AUC(2-5)] and PK parameters [AUC(0-inf), Cmax, Cmin on day 1 in part 1, AUC(0-inf) on day 1 in part 2, Cmax and Cmin on days 1 and 14 in part 2] by treatment and day will be produced.

Figure of the TG Level vs. dose by day may be also produced.

Sample code can be used as follows:

```
Proc corr data=analy Spearman;
   Var parameter1;
   with parameter2;
run;
```

11.9.2.2. Exposure – Response Analysis

A 4 parameter Emax model will be applied between PD parameter and PK parameters.

The PK parameters are probably included AUC, Cmax, and other concentration as appropriate.

The PD parameter is percent (%) change from baseline in TG AUC.

The exposure-response analysis will be conducted separately for part 1 and part 2.

Analyses of percent (%) change from baseline in TG AUC data will be carried out using MIXED effect model.

Emax Model description:

Primary Statistical Analyses
Endpoint(s)
• Part 1: Percent change from baseline in TG AUC at Day 1 • Part 2: Percent change from baseline in TG AUC at Day 1 and Day 14
Model Specification
• First: A 4 parameter Emax model will be used as specified below: Endpoint = $E_0 - E_{max}$ [PK parameter^m / (IC_{50}^m + PK parameter^m)] + Subject + random error

Primary Statistical Analyses

where:

- PK parameter are the PK parameters we would investigate: AUCLast, Cmax, Cmin and Clast
- E_0 is the percent change from baseline in TG AUC when the PK parameter is 0
- E_{max} is the maximum achievable percent change from baseline in TG AUC
- IC_{50} is the PK parameter level which achieves 50% of the E_{max}
- m is the slope/hill constant

Sample SAS code will be provided later.

Depending upon the adequacy of model fitting some parameter may need to be analyzed on log scale (e.g. IC50, Emax).

If issues arise with the model fitting using a 4 parameter model then maybe made based on the data.

Model Checking & Diagnostics

- Refer to Appendix 1: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- The results of the Emax model will be tabulated by part and day (in part 2). Tables will include the point estimates of the parameters, their 95% confidence interval and p-value. The IC50, IC90 (PK parameter level which achieves 90% of the E_{max}) and model fit diagnostics such as the AIC and R^2 value will also be presented for each PK parameter.
- The results of the Emax model will be presented graphically by part and day (in part 2). Predictions will be plotted against the raw values of percent change from baseline in TG AUC against the relevant PK parameter.

11.10. Appendix 10: Model Checking and Diagnostics for Statistical Analyses

11.10.1. Statistical Analysis Assumptions

Dose Proportionality (Part 1 and Part 2)

Endpoint(s)	• Part 1: ○ AUC(0-t), AUC(0-∞), and C_{max} applied to all single dosing active treatments ○ AUC(0-∞) applied to multiple dosing active treatments • Part 2: AUC(0-∞) on Day 1, AUC_{0-T} and C_{max} on Day 1 and Day 14
Analysis	• Power Model

- Model assumptions will be applied, but appropriate adjustments maybe made based on the data.
- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
- If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.

Accumulation Ratio (Part 2)

Endpoint(s)	• (R_o, R_{Cmax})
Analysis	• Mixed Model

- Model assumptions will be applied, but appropriate adjustments maybe made based on the data.
- When the G matrix does not converge, the alternative variance covariance structure will be used.
- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
- If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.

Steady State Assessment (Part 2)

Endpoint(s)	• C_{trough} in Part 2
Analysis	• Mixed Model
• Model assumptions will be applied, but appropriate adjustments maybe made based on the data. • When the G matrix does not converge, the alternative variance covariance structure will be used. • The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.] • Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. • If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.	

Emax model for PK/PD (Part 1 and Part 2)

Endpoint(s)	• Part 1: Percent change from baseline in TG AUC at Day 1 • Part 2: Percent change from baseline in TG AUC at Day 1 and Day 14
Analysis	• 4 parameter Emax Model
• Model assumptions will be applied, but appropriate adjustments maybe made based on the data. • Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable. • If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data	

11.11. Appendix 11 – Abbreviations

11.11.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
Ae	Cumulative amount of unchanged drug excreted into the urine
AE	Adverse Event
ALT	Alanine aminotransferase
AUC	Area under the curve
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to time t
AUC_{0-tau}	Area under the concentration-time curve from time zero (pre-dose) to the end of dosing interval
$AUC_{0-\infty}$	The area under the curve from time 0 extrapolated to infinite time
AUC_{0-24}	The area under the curve from time 0 to 24 hour
AUC_{incr}	Postprandial increase in triglyceride area under the curve
BCRP	Breast cancer resistance protein
BMI	Body mass index
BP	Blood pressure
BSFS	Bristol Stool Form Scale
BUN	Blood urea nitrogen
CI	Confidence Interval
Cmax	The maximum concentration
Clast	The last quantified concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DGAT	Diacylglycerol acyltransferase
DMPK	Drug Metabolism and Pharmacokinetics
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
GSK	GlaxoSmithKline
HDL	High-density lipoprotein
HR	Heart rate
IA	Interim Analysis
ICH	International Conference on Harmonisation
LDL	Low-density lipoprotein
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures

Abbreviation	Description
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PK	Pharmacokinetic
PKC	Pharmacokinetic Concentration (population)
PKP	Pharmacokinetic Parameter (population)
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RBC	Red blood cell
RD	Repeat-dose
R_O	Observed accumulation ratio based on AUC(0-τ)
R_{cmax}	Observed accumulation ratio based on Cmax
Rs	Steady-state accumulation ration based on AUC(0-τ) on Day 14 and $AUC_{0-\infty}$ on Day 1
SAE	Serious Adverse Event
SD	Single-dose
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
$t_{1/2}$	Elimination half-life
TA	Therapeutic Area
t_{max}	Time to maximum observed plasma concentration
TFL/TLF	Tables, Figures & Listings
VLDL	Very-low density lipoprotein
VLDL-TG	Very-low density lipoprotein triglycerides
WBC	White blood cell

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11.12. Appendix 12: List of Data Displays

11.12.1. General Data Display Numbering

The following general numbering convention will be applied for RAP displays:

Section	Tables	Figures
Study Population	1.x	N/A
Safety	3.x	3.x
Pharmacokinetic	4.x	4.x
Pharmacodynamic	5.x	5.x
Pharmacokinetic/Pharmacodynamic	6.x	6.x
Section	**Listing**	
ICH Listings	1 to x	
Other Listings	y to z	

11.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 13: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / TST ID / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

11.12.3. Deliverable [Priority]

Delivery	Description
Headline	Headline Results (Not applied for this study)
SAC	Final Statistical Analysis Complete

11.12.4. General Note for Display

General note:

For any display where information needs to be presented on one row, please see below for how we will handle the 11 treatments in Part 1 and 3 treatments in Part 2.

The column for part 1 is:

On first page:

	Single Dose					
P1 (N=x)	A1 (N=x)	A2 (N=x)	A3 (N=x)	A4 (N=x)	A5 (N=x)	A6 (N=x)

On second page:

	Multiple Dose			
P1 (N=x) [1]	A7 (N=x)	A8 (N=x)	A10 (N=x)	A11 (N=x)

Note: [1] Placebo is repeated on both pages.

The column for part 2 is:

P2 (N=x)	B1 (N=x)	B1 (N=x)	B1 (N=x)

The “Total” column will be added on a case by case basis.

Please note: For PD parameter TG, P1 = matched placebo in part 1 excluding cohort 8 (‘Placebo exl. Cohort 8’ would be displayed in TFL). Placebo in cohort 8 will be presented separately in the display (‘Cohort 8 Placebo’ would be displayed in TFL).

Please note: For mock shells and anywhere which list treatment codes, please replace actual treatment dosing regimens in the Appendix 5, please update/remove footnote accordingly.

11.12.5. Study Population

11.12.5.1. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
Subject Disposition					
1.1 1.2	Safety	ES8	Summary of Subject Status and Reason for Study Withdrawal (Part X)	ICH E3 (U)	SAC
1.3	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment (Part 2)	ICH E3 (U) Only for Part 2 since this table is required for all studies except single dose studies.	SAC
1.4	Screened Subjects	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements Used with Summary of Study Populations and Summary of Subject Disposition to create Consort diagram.	SAC
Protocol Deviation					
1.5 1.6	Safety	DV1	Summary of Important Protocol Deviations (Part X)	ICH E3 (U)	SAC
Populations Analysed					
1.8 1.9	Screened Subject	SP1	Summary of Study Population (Part X)	IDSL To display both pooling of subjects at placebo in part 1. (1) Pooling of subjects at placebo for all cohorts (2) Pooling of subjects at placebo	SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
				except in cohort 8. Placebo in cohort 8.	
Demographic and Baseline Characteristics					
1.10 1.11	Safety	DM1	Summary of Demographic Characteristics (Part X)	ICH E3 (U)	SAC
11.12 11.13	Safety	DM5	Summary of Race and Racial Combinations	ICH E3 (U)	SAC
Prior and Concomitant Medications					
1.14 1.15	Safety	MH1	Summary of Past Medical Conditions (Part X)	ICH E3 (U) Required if medical condition data is collected. MH1 depending on level of detail collected.	SAC
1.16 1.17	Safety	MH1	Summary of Current Medical Conditions (Part X)	ICH E3 (R) Required if medical condition data is collected. MH1 depending on level of detail collected.	SAC
1.18 1.19	Safety	CM1	Summary of Concomitant Medications (Part X)	ICH E3 (U)	SAC
Exposure and Treatment Compliance					

Study Population Tables					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
1.20 1.21	Safety	EX1	Summary of Exposure to Study Treatment (Part X)	ICH E3 (U)	SAC

11.12.5.2. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
Adverse Events (AEs)					
3.1 3.2	Safety	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term (Part X)	ICH E3 (U)	SAC
3.3 3.4	Safety	AE1	Summary of Adverse Events by System Organ Class Gastrointestinal (GI) and PT	ICH E3 (U) by SOC and PT term, where SOC=GI.	SAC
3.5 3.6	Safety	AE3	Summary of Most Frequent Adverse Events by Overall Frequency	Most frequent adverse events are the frequency greater than 3.	
3.7 3.8	Safety	AE1	Summary of All Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3 (R)	SAC
Serious Adverse Events (AEs)					
3.9 3.10	Safety	AE1	Summary of Serious Adverse Events by System Organ Class and	ICH E3 (U)	SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
			Preferred Term (Part X)		
3.11 3.12	Safety	AE1	Summary of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by System Organ Class and Preferred Term (Part X)	ICH E3 (R)	SAC
Laboratory: Chemistry					
3.13 3.14	Safety	LB1	Summary of Chemistry Changes from Baseline (Part X)	ICH E3 (U) Includes Baseline values. Includes pre-specified parameters repeated in conventional units.	SAC
Laboratory: Hematology					
3.15 3.16	Safety	LB1	Summary of Hematology Changes from Baseline (Part X)	ICH E3 (R) Includes Baseline values.	SAC
Laboratory: Urinalysis					
3.17 3.18	Safety	LB1	Summary of Urine Concentration Changes from Baseline	ICH E3 (R) Includes Baseline values.	SAC
3.19 3.20	Safety	LB2	Summary of Urinalysis Dipstick Results (Part X)	IDSL (U) As above for Chemistry, using dipstick categories.	SAC
Laboratory: Hepatobiliary (Liver)					
3.21 3.22	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event	IDSL	SAC

Safety: Tables					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
			Reporting (Part X)	(U)	
ECG					
3.23 3.24	Safety	EG1	Summary of ECG Findings (Part X)	IDSL (U) As above for Chemistry, using ECG findings categories (and change from baseline categories, if applicable).	SAC
3.25 3.26	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit (Part X)	IDSL (U) Includes Baseline values.	SAC
Vital Signs					
3.31 3.32	Safety	VS1	Summary of Change from Baseline in Vital Signs by Visit (Part X)	ICH E3 (U) Includes Baseline values.	SAC
3.33 3.34	Safety	VS3	Summary of Vital Signs Results by PCI Criteria (Part X)	IDSL (U) Recommended for studies with sufficiently large sample size or frequency of values of interest.	SAC

11.12.5.3. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
Laboratory					
3.1 3.2	Safety	LB8	Matrix Display of Maximum LFT (ALT, AST, ALP, and Total Bilirubin) Values	IDSL (U)	SAC
3.3 3.4	Safety	Non-Standard Mock SAFE_F1	Plot of Individual LFT (ALT, AST, ALP, and Total Bilirubin) Values vs. Study Time by Treatment Group and Test (Part X)	The name of X-axis is Days in Study. The name of Y-axis is the value of LFT (ALT, AST, ALP, and Total Bilirubin). One plot for each treatment group	SAC

11.12.5.4. Pharmacokinetic Tables

Pharmacokientic: Tables					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
Concentration-time					
4.1 4.2	PKC	PK01	Summary of Plasma Pharmacokinetic Concentration-Time Data by Treatment (Part X)	IDSL (U)	SAC
4.3	PKC	PK01	Summary of Pharmacokinetic Trough Plasma Concentration-Time Data by Treatment (Part 2)	IDSL (R)	SAC
Pharmacokinetic Parameters: Analyses					

Pharmacokientic: Tables					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
4.4 4.5	PKP	PK03	Summary of Derived Pharmacokinetic [units] by Treatment (Part X)	IDSL (U) All derived PK parameters were listed in Table 6 in the section. They are as follows: Part 1: AUC(0-t), AUC(0-24), AUC(0-inf). Part 2: AUC(0-tau), Ro and Rcmax, Rs, Ctrough. Part 1 + Part 2 on Day 1: AUC(0-inf) Part 1 + Part 2: Cmax on Day 1 in part 1 and Days 1, 14 in part 2. Tmax, t1/2, Ae, CLr on . on Day 1 in part 1 and Day 14 in part 2	SAC
4.6 4.7	PKP	PK03	Summary of Log-Transformed Derived Pharmacokinetic [units] by Treatment (Part X)	IDSL (U) All Log-Transformed derived PK parameters were listed in Table 6.	SAC
4.8 4.9	PKP	Non-standard Mock PK_T1	Summary of Statistical Analysis of Dose Proportionality (Part X)	(U) Please follow the sample code in the Section 8.1.3.2:.Statistical Analysis of Pharmacokintic Parameters.	SAC
4.10	PKP	Non-standard Mock PK_T2	Summary of Statistical Analysis of Accumulation Ratio (Part 2)	(U) For Ro, Rcmax Please follow the sample code in the Section 8.1.3.2: Statistical Analysis of Pharmacokintic Parameters	SAC
4.11	PKP	Non-standard Mock PK_T3	Summary of Statistical Analysis of Assessment of Steady-State (Part 2)	(U) Please follow the sample code in the Section 8.1.3.2: Statistical Analysis of Pharmacokintic Parameters	SAC

11.12.5.5. Pharmacokinetic Figures

Pharmacokientic: Figures					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
Concentration-time					
4.1 4.2	PKC	PK16a	Individual Plasma Pharmacokinetic Concentration-Time Plots (Linear and Semi-log) (Part X)	IDSL (U)	SAC
4.3 4.4	PKC	PK17	Mean Plasma Pharmacokinetic Concentration-Time Plots (Linear and Semi-log) (Part X)	IDSL (U)	SAC
4.5 4.6	PKC	PK18	Median Plasma Pharmacokinetic Concentration-Time Plots (Linear and Semi-log) (Part X)	IDSL (U)	SAC

11.12.5.6. Pharmacodynamic (and / or Biomarker) Tables:

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
Postprandial Triglyceride (TG)					
5.1 5.2	PD	PD1	Summary of Absolute TG Values by Treatment, Day, and Time Point (Part X)	IDSL (U) Include baseline day time points Footnote will be as follows: Pooled placebo excludes cohort 8. Placebo in cohort 8 and active treatment in	SAC

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
				cohort 8 are presented separately.	
5.3 5.4	PD	PD1	Summary of Corrected TG Values by Treatment, Day, and Time Point (Part X)	IDSL (U) Please use the correction value which present in the Section 8.2.1.2 to adjust the TG values. It will be displayed by Day in Part 1 (Day -1 and Day 1) It can be by Day in Part 2 (Day -1, Day 1 and Day 14)	SAC
5.5 5.6	PD	PD4	Summary of TG AUC and Corrected TG AUC by Treatment and Day (Part X)	IDSL (U) Column name "Add Time Var.' should be "Day"	SAC
5.7 5.8	PD	PD4	Summary of Percent (%) Change from Baseline in TG AUC and Corrected TG AUC (Part X)	IDSL (U) Column 'Add Time Var.' should be 'Day 1 – Day -1' for Part 1; "Day 1 – Day -1" and "Day 14 – Day -1" for Part 2, respectively. Remove columns 'N' and 'n'.	SAC
Biomark: Bristol Stool Form Scale (BSFS)					
5.9 5.10	Safety	Non-standard Mock PD_T1	Summary of Number of Subjects and Number of Bristol Stool Form Scale by Type and Day and Treatment (Part X)	(U)	SAC
5.11 5.12	Safety	Non-standard Mock PD_T2	Summary of Total Number of Bristol Stool Form Scale by Day and Treatment (Part X)	(U)	SAC
Exploratory PD Labs					

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
5.13	Safety	LB1	Summary of Change from Baseline in Exploratory PD Labs Parameter (Part X)	ICH E3 (U)	SAC

11.12.5.7. Pharmacodynamic (and / or Biomarker) Figures:

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/Repeat)**	**Deliverable**
Postprandial Triglyceride (TG)					
5.1 5.2	PD	Non-standard PD_F1	Mean (±SD) of Absolute TG Values by Treatment, Day, and Time Point Plot (Part X)	Non-standard (U) For Part 1, Day -1 and Day 1 will be displayed in different pages but in the same plot. For Part 2, Day -1, Day 1 and Day 14 will be displayed in different pages but in the same plot. Name of X-axis is 'Time Point (hr)'. Name of Y-axis is 'Mean Absolute TG Values'	SAC
5.3 5.4	PD	Non-standard PD_F1	Individual Absolute TG Values by Treatment, Day and Time Point (Part X)	Non-standard (U) For Part 1, Day -1 and Day 1 will be displayed in different pages but in the same plot.	SAC

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/Repeat)**	**Deliverable**
				For Part 2, Day -1, Day 1 and Day 14 will be displayed in different pages but in the same plot. Name of X-axis is 'Treatment'. Name of Y-axis is 'Absolute TG Values'	
5.5 5.6	PD	Non-standard PD_F1	Mean (±SD) of Corrected TG Values by Treatment, Day, and Time Point Plot (Part X)	Non-standard (U) For Part 1, Day -1 and Day 1 will be displayed . For Part 2, Day -1, Day 1 and Day 14 will be displayed in different pages but in the same plot. Name of X-axis is 'Time Point (hr)'. Name of Y-axis is 'Mean Corrected TG Values'	SAC
5.7 5.8	PD	Non-standard PD_F1	Individual Corrected TG Values by Treatment, Day and Time Point (Part X)	Non-standard (U) For Part 1, Day -1 and Day 1 will be displayed in different pages but in the same plot. For Part 2, Day -1, Day 1 and Day 14 will be displayed in different pages but in the same plot. Name of X-axis is 'Treatment'. Name of Y-axis is 'Corrected TG Values'	SAC
5.9 5.10	PD	Non-standard PD_F1	Mean (±SD) of Percent (%) Change from Baseline of TG AUC (Corrected TG Values) by Treatment and Day Plot (Part X)	Non-standard (U) For Percent (%) Change from Baseline of Corrected TG AUC in Part 1, there is Day 1. For Part 2, Day 1, and Day 14 will be displayed in the same plot. Percent (%) Change from Baseline of Corrected TG AUC will be presented for TG AUC(1-12),TG AUC(2-5) on different pages in the	SAC

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/Repeat)**	**Deliverable**
				same plot, respectively. Name of X-axis is 'Treatment'. Name of Y-axis is 'Mean Percent Change from Baseline in Corrected TG AUC (1-12)' and 'Mean Percent Change from Baseline in Corrected TG AUC (2-5)', respectively	
Biomark: Bristol Stool Form Scale (BSFS) Figures					
5.11 5.12	Safety	Non-standard Mock PD_F2	Number of Bristol Stool Form Scale by Type and Treatment Histogram Plot (Part X)	(U)	SAC
5.13 5.14	Safety	Non-standard Mock PD_F3	Number of Bristol Stool Form Scale by Type and Treatment Line Plot (Part X)	(U)	SAC

11.12.5.8. ICH Listings

Combined both parts into one listing by part. Similar will be applied all other listings unless otherwise specified.

ICH: Listings					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
Subject Disposition					
1	Screened	ES7	Listing of Reasons for Screen Failure	(U)	SAC
		ES2	Listing of Reasons for Study	ICH E3	

ICH: Listings					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
2	Safety		Withdrawal	(U)	SAC
3	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3 (U) Only for Part 2 since it is required for all studies except single dose studies.	SAC
4	Safety	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	SAC
5	Safety	TA1	Listing of Planned and Actual Treatments	IDSL	
Protocol Deviations					
6	Safety	DV2	Listing of Important Protocol Deviations	ICH E3 (U)	SAC
7	Safety	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3 (U)	SAC
Demographic and Baseline Characteristics					
8	Safety	DM2	Listing of Demographic Characteristics	ICH E3 (U)	SAC
9	Safety	DM9	Listing of Race	ICH E3 (U)	SAC
Prior and Concomitant Medications					
10	Safety	CP_CM3	Listing of Concomitant Medications	IDSL (U)	SAC
Exposure and Treatment Compliance					
11	Safety	EX3	Listing of Exposure Data	ICH E3 (U)	SAC

ICH: Listings					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
Adverse Events					
12	Safety	AE8	Listing of All Adverse Events	ICH E3 (U)	SAC
13	Safety	AE7	Listing of subject Numbers for Individual Adverse Events	ICH E3 (U)	SAC
14	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL (U)	SAC
Serious and Other Significant Adverse Events					
15	Safety	AE8	Listing of Serious Adverse Events	ICH E3 (U)	SAC
16	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3 (U)	SAC
17	Safety	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3 (U)	SAC
18	Safety	Non-standard SAFE_L1	Listing of Pregnancy Results	Mock example shell reference is SAFE_L1 below (U)	SAC
Hepatobiliary (Liver)					
19	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting	IDSL (U)	SAC
All Laboratory					
20	Safety	LB5	Listing of Laboratory Data for Subjects with Any Values of Potential Clinical Importance	ICH E3 (U) Display ALL labs for a subject who	SAC

ICH: Listings					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
				experienced a value of potential clinical concern/importance.	
21	Safety	LB5	Listing of Laboratory Values of Potential Clinical Importance	ICH E3 (U) Only list the subject who has PCI value	SAC
ECG					
22	Safety	CP_EG3	Listing of All ECG Data for Subjects with Any Value of Potential Clinical Importance	IDSL Note: IDSL shell in development. Required for ClinPharm studies only. Display ALL ECGs for a subject who experienced a value of potential clinical importance.	SAC
23	Safety	CP_EG3	Listing of All ECG Value of Potential Clinical Importance	IDSL	SAC
24	Safety	EG5	Listing of Abnormal ECG Findings	IDSL (U)	SAC
Vital Signs					
25	Safety	CP_VS4	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance	IDSL (U) Display ALL Vital Signs for a subject who experienced a value of potential clinical importance.	SAC
26	Safety	CP_VS4	Listing of Vital Signs of Potential Clinical Importance	IDSL (U)	SAC
Other Exams					
27	Safety	Non-standard SAFE_L2	Listing of Physical Exams	Mock example shell reference is SAFE_L2 below (U)	SAC

ICH: Listings					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**

11.12.5.9. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
Pharmacokinetic Concentrations					
28	PKC	PK07	Listing of Plasma Pharmacokinetic Concentration-Time Data by Treatment	IDSL (U) Combined both parts into one listing by part. Similar will be applied all other listings unless otherwise specified.	SAC
29	PKC	PK07	Listing of Plasma Trough Concentration-Day/Time Data by Treatment	IDSL (U) Only for Part 2 since it is required for all studies except single dose studies. Only include the following scheduled time points: pre-dose at days 2, 4, 5, 6, 12, 13, 14, and 15 (or day 14 24 hours post-dose).	SAC
Pharmacokinetic Parameters					
30	PKP	PK13	Listing of Derived Pharmacokinetic Parameters by Treatment	IDSL (U) Include all derived PK parameters	SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
31	PKP	Non-standard	Listing of SAS Output of Statistical Analysis of Dose Proportionality (Part 1)	(U) Dump the SAS output from the PROC MIXED outputs and the details of modelling checking into the output.	SAC
32	PKP	Non-standard	Listing of SAS Output of Statistical Analysis of Dose Proportionality (Part 2)	(U) Only for Part 2 on Day 1 and Day 14. Dump the SAS output from the PROC MIXED outputs and the details of modelling checking into the output.	SAC
33	PKP	Non-standard	Listing of SAS Output of Statistical Analysis of Accumulation Ratio (Part 2)	(U) Only for Part 2 on parameters Ro and Rcmax Dump the SAS output from the PROC MIXED outputs and the details of modelling checking into the output.	SAC
34	PKP	Non-standard	Listing of SAS Output of Statistical Analysis of Assessment of Steady-State (Part 2)	(U) Only for Part 2 Ctrough values at pre-dose on days 2, 4, 5, 6, 12, 13, 14, and 15 (or day 14 24 post-dose). Dump the SAS output from the PROC MIXED outputs and the details of modelling checking into the output.	SAC
Pharmacodynamic: Postprandial Triglyceride					
35	PD	PD10	Listing of Postprandial TG Value Over Time by Treatment and Day	IDSL (U) Include baseline values on day -1. Include corrected TG values as well	SAC
36	PD	PD16	Listing of Individual TG AUC	IDSL (U)	SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID/ Example Shell**	**Title**	**Programming Notes ((U)nique/(R)epeat)**	**Deliverable**
				To Modify PD16 to add a column Time variable (Day). Replace the column from Baseline [analyte] (unit) to Weighted Mean (0-24h) with all derived TG AUC variable.	
Biomarker: Bristol Stool Form Scale					
37	Safety	Non-standard PD_L1	Listing of Individual Bristol Stool Form Scale	(U)	SAC
Exploratory Pharmacodynamic Lab Parameters					
38	Safety	LB5	Listing of Exploratory Pharmacodynamic Lab Parameters	ICH E3 (U) Remove Normal Range and PCI Flag columns	SAC