TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	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

Development Phase I

Effective Date: 07-FEB-2017

Protocol Amendment Number: 02

Author(s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N242776_00	2016-MAR-02	Original
2015N242776_01	2016-JUL-22	Amendment No. 1
Amendment No.1: 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. Several administrative changes were also made.		
2015N242776_02	2017-JAN-22	Amendment No. 2
Amendment No.2: 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. Several administrative changes were also made.		

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7 FEB 2017

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number: 204856

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.
-

Investigator Name: _____

_____ _____

Investigator Signature Date

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1. INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) represents a continuum of liver disease centered on fat accumulation. NAFLD prevalence is on the rise in parallel with the rise of obesity worldwide (Satapathy 2015). Steatosis (nonalcoholic fatty liver; NAFL), nonalcoholic steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma (HCC) represent increased pathology from mild to severe disease. NAFLD etiology is multifactorial and progression is not predictable at this time, though risk factors are being identified (Satapathy 2015).

NASH starts with liver fat (triglyceride) accumulation followed by inflammation and fibrosis. Liver biopsy is the gold standard for diagnosing and staging NASH as defined by the presence of steatosis, inflammation and hepatocyte ballooning with or without fibrosis (Chalasani 2012). An intervention for the treatment or prevention of NASH would have to modulate one or more of these findings.

The two diacylglycerol acyltransferase (DGAT) enzymes, DGAT1 and DGAT2, catalyze the final step of triacylglycerol (triglyceride; TG) biosynthesis (Yen 2008). DGAT is expressed in all tissues evaluated including liver, skeletal muscle and adipose tissue with the highest expression levels in the small intestine (Cases 1998) and is upregulated in NAFLD (Kohjima 2007). Decreased DGAT1 activity can reduce circulating TG, reduce liver TG and is implicated in preventing activation of hepatic stellate cells (HSC) and the resultant production of liver fibrosis (Yamaguchi 2008; Yuen 2015). Inhibiting DGAT1 could have the potential to treat NASH.

1.1. Study Rationale

GSK3008356 is a potent and selective DGAT1 inhibitor and is primarily intended for the treatment of NASH. In nonclinical studies, GSK3008356 has efficacy in blocking postprandial hypertriglyceridemia in a mouse lipid challenge model. A significant reduction in liver TG and lipid accumulation, body weight and food intake was observed in the mouse diet-induced obesity model (DIO). Please refer to the GSK3008356 Investigator's Brochure (IB) [GlaxoSmithKline Document Number 2015N255332_00] for details.

DGAT1 inhibitors have been evaluated in healthy and obese subjects (Denison 2014; Meyers 2015). Activity was elicited via a high fat challenge meal measuring inhibition of postprandial TG excursion. Gastrointestinal (GI) intolerability with repeat daily dosing was the main issue with compound progression (Denison 2014; Meyers 2015). The symptoms were postulated to be due to DGAT1 inhibition resulting in increased free fatty acids in the intestine and resultant inflammation and diarrhea (Denison 2014). One compound continuing in development (pradigastat/LCQ908) has show efficacy in decreasing liver fat in NAFLD subjects when dosed for 6 months despite dose limiting diarrhea (Moffet 2015).

This study will be the first to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and repeat doses of GSK3008356 administered subjects. Since the main objective is understanding tolerability, the population planned is

healthy and healthy obese subjects. NAFLD and NASH patients will be evaluated in subsequent studies once tolerated and active doses are identified. Since DGAT1 activity in the liver may be of more importance than effects in the intestine, tolerability will be evaluated through evening (versus morning) repeat dosing to minimize exposure during daytime meals.

The activity of GSK3008356 on DGAT1 inhibition will be assessed through measurement of postprandial TG elevation after a standardized fat challenge meal as previously published (Denison 2014; Meyers 2015).

2. 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.
Part 3 28d Repeat Dose To characterize the safety, and tolerability of 28 daily repeat doses of GSK3008356 in obese subjects.	**Part 3 28d 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.
Secondary	
Part 1 Single Dose To determine the pharmacokinetics of GSK3008356 after a single dose in healthy subjects	**Part 1 Single Dose** PK endpoints include the AUC(0-t), AUC(0-24), Cmax, tmax, AUC(0-∞), t½, Ae, and CLr of GSK3008356 as data permit.
To assess dose proportionality of GSK3008356 after a single dose in healthy subjects	AUC(0- t), AUC(0-∞), and Cmax for the assessment of dose proportionality as data permit.
To evaluate the preliminary pharmacodynamics after a single dose of GSK3008356 in healthy subjects.	Fat challenge meal postprandial triglyceride levels.
Part 2 14d Repeat Dose To determine the pharmacokinetics of GSK3008356 after 14 daily doses in healthy subjects.	**Part 2 14d Repeat Dose** PK endpoints include the AUC(0-τ) Cmax, and tmax on Day 1 and 14, and t½, Ae, and CL_R on Day 14 of GSK3008356 as data permit.
To assess dose proportionality of GSK3008356 after 14 daily doses in healthy subjects.	AUC(0- τ) and Cmax on Day 1 and 14 for the assessment of dose proportionality as data permit.
To examine the extent of accumulation and achievement of steady-state following 14 daily doses of GSK3008356 in healthy subjects.	Observed accumulation ratio based on AUC(0- τ), (R_o), and Cmax (R_{Cmax}) on Day 14 versus Day 1 as data permit. Trough plasma concentrations (C_{trough}) to

Objectives	Endpoints
	assess steady state after repeat dosing, as data permit.
To evaluate the preliminary pharmacodynamics after 14 daily repeat doses of GSK3008356 in healthy subjects.	Fat challenge meal postprandial triglyceride levels.
Part 3 28d Repeat Dose	
To determine the pharmacokinetics of GSK3008356 after 28 daily doses in obese subjects.	**Part 3 28d Repeat Dose** PK endpoints include the AUC(0- τ) Cmax, and tmax on Day 1 and 28, and t½, Ae, and CLr on Day 28 of GSK3008356 as data permit.
To assess dose proportionality of GSK3008356 after 28 daily doses in obese subjects.	AUC(0- τ) and Cmax on Day 1 and 28 for the assessment of dose proportionality as data permit.
To examine the extent of accumulation and achievement of steady-state following 28 daily doses of GSK3008356 in obese subjects.	Observed accumulation ratio based on AUC(0-τ), (R_o), and Cmax (R_{Cmax}) on Day 28 versus Day 1 as data permit. Trough plasma concentrations (C_{trough}) to assess steady state after repeat dosing, as data permit.
To evaluate the preliminary pharmacodynamics of 28 daily doses of GSK3008356 in obese subjects.	Fat challenge meal postprandial triglyceride levels.
Exploratory	
Part 2 14d Repeat Dose **Part 3 28d Repeat Dose**	**Part 2 14d Repeat Dose** **Part 3 28d Repeat Dose**
To evaluate the change in serum lipid levels and weight after 14 daily repeat doses of GSK3008356 in healthy subjects and 28 daily repeat GSK3008356 doses in obese subjects.	Serum lipid panel, weight.
To evaluate the impact of evening dosing on tolerability.	Clinical monitoring/observation for adverse events with a focus on gastrointestinal findings and a stool scale.
To evaluate partitioning of GSK3008356 into skin in Part 2 only.	Skin biopsy for drug concentration and activity.

3. STUDY DESIGN

3.1. Overall Design

Study 204856 will be a randomized, double-blind (sponsor unblind), placebo controlled trial in three Parts.

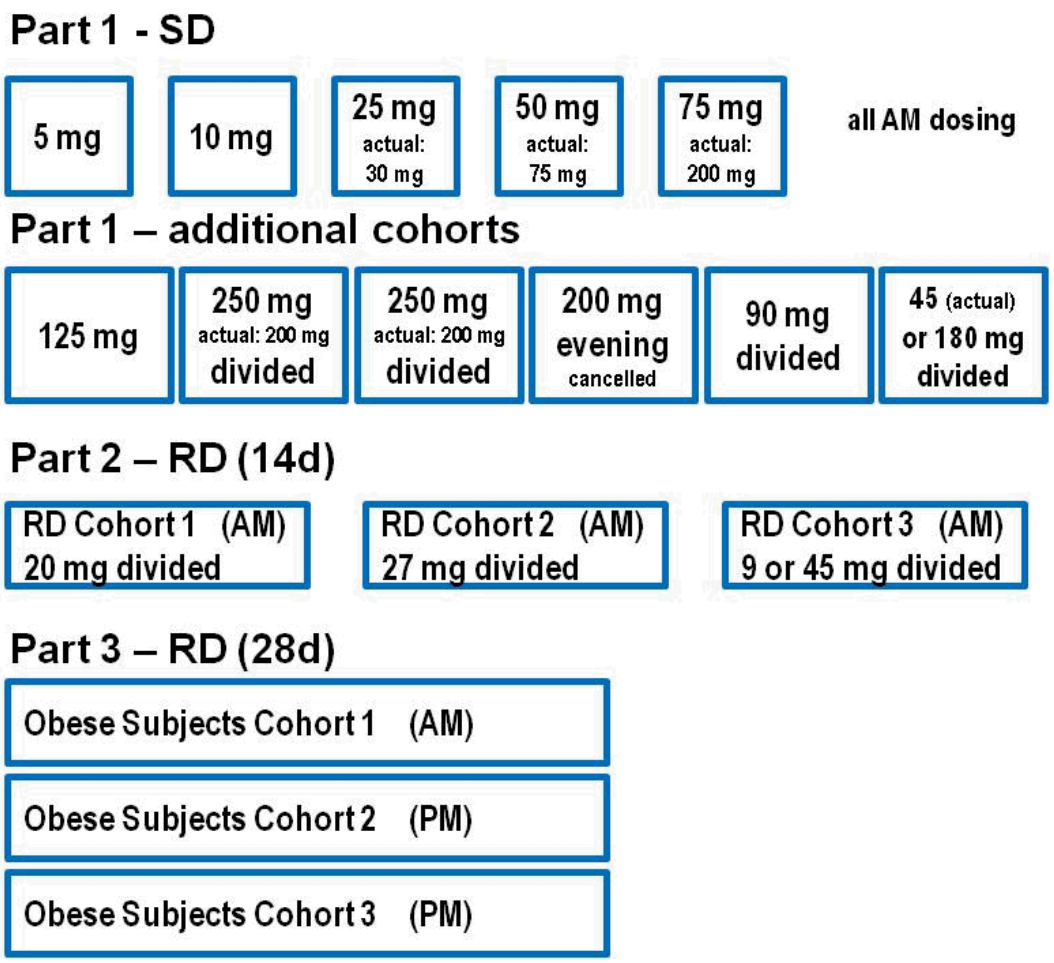
1. Part 1, will be a single-dose (SD), dose-rising study in healthy subjects. Subjects will receive GSK3008356 (or matching placebo), as a single dose in each of five sequential cohorts while receiving a standard 30% fat meal. The initial dosing for the first cohort will be staggered so that 2 subjects will be dosed as sentinel subjects. Provided there are no safety concerns, the remainder of the subjects scheduled for the cohort may be dosed.

2. Part 2, will be a 14-day, repeat-dose (RD), dose-rising study in healthy subjects. Subjects will receive GSK3008356 (or matching placebo), as 14 daily doses in each of three sequential cohorts. Day 1 and day 14 dosing for the first cohort will occur while receiving a standard 30% fat meal. The final two cohorts will receive the same morning 30% fat meals, but will explore daily dosing in the evening rather than in the morning.

3. Part 3, will be a 28-day, repeat-dose study in obese subjects. Subjects will receive GSK3008356 (or matching placebo), as 28 daily doses in each of three parallel cohorts. Cohort 1 will evaluate 1 dose strength of GSK3008356 (or matching placebo) administered as morning doses. Cohorts 2 and 3 will evaluate 2 dose strengths (1 per cohort) of GSK3008356 (or matching placebo) administered in the evening.

Please refer to Figure 1 for details.

Figure 1 Study Part Schematic



3.1.1. Additional Cohorts for Part 1

Based on emerging PK data, the original planned Part 1 doses were adjusted, per protocol, to 5, 10, 30, 75 and 200 mg (Section 5.3, Figure 1). This was due to a much shorter observed half-life compared to the predicted half-life (1.5-3h observed versus 14.1h predicted).

While the adjusted doses did allow observation of a PD response in Cohort 5, the overall single dose data were limited and could not adequately inform a PK/PD model or support informed progression into Part 2 of the study. It was determined to further explore the PK/PD through additional Part 1 cohorts. The purpose of the additional cohorts is to explore dose administration in a manner that should provide a more acceptable PK profile than that observed to date. This includes divided doses to achieve time above the target exposure with varying levels of Cmax and doses directly related to regimens that may be used in Part 2 of the study. There will be no changes to the current challenge meal or assessments.

3.1.2. Revised Dosing Regimens for Part 2

Based on preliminary PK data from Part 1, the doses and regimens are now better clarified for Part 2. Part 2 Cohorts 1, 2 and 3 will be administered in the AM as divided doses to achieve a daily time above the target exposure with varying levels of Cmax. Specifically, Cohort 1 will have a regimen of 2 doses separated by 16 hours similar to Part 1 Cohort 8. The purpose is to explore a BID PK profile. Cohorts 2 and 3 will have a regimen of nine hourly doses similar to Part 1 Cohorts 10 and 11. The purpose is to explore PK profiles that approximate a sustained release formulation to guide further dosage development. There will be no changes to the current challenge meal or assessments except for the addition of a skin biopsy outlined in Section 6.4.5.

The regimens are as follows:

Part 2, Cohort 1 would evaluate 10 mg administered twice at time 0h and 16h for a total dose of 20 mg.

Part 2, Cohort 2 would evaluate 27 mg daily administered as 9 doses of 3 mg hourly from time 0 to time 8h daily for 14 days.

Part 2, Cohort 3 would evaluate either 9 mg daily administered as 9 doses of 1 mg hourly from time 0 to time 8h or 45 mg daily as 9 doses of 5 mg hourly from time 0 to time 8h.

Neither the predicted human Cmax, nor the predicted daily human AUC of evaluated doses is expected to exceed the dog NOAEL exposure of Cmax (7.73 µg/mL) and AUC(0-t) (111 µg.h/mL).

However, data from a 13-week oral toxicity study in dogs indicate that the NOAEL for dosing duration >28 days will likely be lower than the current NOAEL. While these dog data do not impact the risk for this protocol as they do not change the NOAEL (Section 3.5.1), these data will impact the future viability of certain dose regimens.

The regimens selected for Part 2 as outlined above are regimens have future development viability based on human exposure below the oral 13-week repeat dose dog testicular observation NOAEL exposure of Cmax (0.642 µg/mL) and AUC(0-t) (5.49 µg.h/mL).

The highest dose regimen planned for Part 3 (45 mg daily as 9 doses of 5 mg hourly from time 0 to time 8h) is expected to result in the highest Part 2 Cmax (0.203 µg/mL) and AUC (1.261 µg.h/mL) exposure, based on Part 1 data.

These predicted exposures are still 3.2-fold and 4.4-fold below the oral 13-week repeat dose dog testicular observation NOAEL Cmax and AUC exposure, respectively. The predicted exposures are 38.1-fold and 88.1-fold below the current NOAEL Cmax and AUC exposure, respectively.

3.2. Type and Number of Subjects

Part 1, Single Dose, Healthy Subjects:

Approximately 40 subjects will be enrolled, 8 in each cohort, such that approximately 6-8 subjects complete dosing and critical assessments in each Part 1 Cohort. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels. The six additional cohorts will enrol approximately 48 subjects.

Part 2, 14d Repeat Dose, Healthy Subjects:

Approximately 24 subjects will be enrolled, 8 in each cohort, such that approximately 6-8 subjects complete dosing and critical assessments in each Part 2 Cohort. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels.

Part 3, 28d Repeat Dose, Obese Subjects:

Approximately 30 subjects will be enrolled, 10 in each cohort, such that approximately 6-10 subjects complete dosing and critical assessments in each Part 3 Cohort. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels.

If subjects prematurely discontinue the study, additional replacement subjects may be randomised and assigned to the same treatment sequence at the discretion of the Sponsor in consultation with the investigator.

For Parts 1 and 2, data from prior doses cohorts will be available prior to escalation decisions. Data from Parts 1 and 2 will be available prior to initiation of the three parallel cohorts in Part 3. A dose escalation meeting will be held to review these data and document the decision to proceed as planned or make any alterations in dosing, if indicated (Section 9.8.1).

Subjects in Parts 1 and 2 will be randomized such that 6 subjects receive GSK3008356 and 2 subjects receive matching placebo in each cohort of 8 subjects. Subjects in Part 3 will be randomized such that 8 subjects receive GSK3008356 and 2 subjects receive matching placebo in each cohort of 10 subjects.

3.3. Design Justification

Parts 1 and 2 designs are based on well established and published methods to evaluate the first single and repeat dose administration of experimental drugs, including the use of sentinel dosing for Part 1, Cohort 1. Part 3 design is based on established and published methods to evaluate both inpatient and outpatient dosing in subjects. The use of a fat meal challenge and postprandial TG as a PD measure for DGAT1 inhibition is based on published clinical trial design.

Part 1 is not expected to have significant gastrointestinal tolerability issues, so will only use daytime dosing and TG evaluation to identify the active dose range to progress into Part 2.

Part 2 will evaluate daytime dosing for the first cohort, but will switch to evening dosing based on prior published DGAT1 inhibitor clinical trial data where daytime dosing resulted in GI intolerability. Postprandial TG will be used to measure PD response. The Bristol Stool Form Scale (BSFS) will be used in this part to assist in evaluating GI tolerability. The purpose is to identify an active dose which is also tolerated to progress into Part 3.

Part 3 will evaluate daytime and evening dosing in obese subjects under both controlled (inpatient) and less controlled (outpatient/home dosing) conditions of drug administration and diet. The obese subject population is at the beginning of the "healthy-obese-NAFLD-NASH-cirrhotic" continuum. Postprandial TG measure and BSFS will be utilized to evaluate DGAT1 inhibition PD and GI tolerability, respectively.

As noted, GI intolerability is a liability with other DGAT1 inhibitors and may be a liability with GSK3008356. This may be due to accumulation of free fatty acids in the intestine, associated with meals, causing inflammation and diarrhea (Denison 2014). The GSK3008356 concentration at 12 hour post-dose is estimated to be ~42% of maximum observed plasma concentration (Cmax). This indicates that, if the drug is given in the evening, by the time a subject is consuming daytime meals (~12 h post-dose the next morning), the plasma concentration would be significantly lower. Based on the DGAT1 inhibition mechanism of action, a lower exposure during daytime meals may improve GI tolerability.

3.4. Dose Justification

GSK3008356 dose selection in this study is based on the no-observed adverse event level (NOAEL) and respective exposures in 4-week dog study, and takes into consideration the predicted human PK and the target systemic exposure predicted for efficacy, as well as the minimum anticipated biological effect level (MABEL), and US Food and Drug Administration (FDA) guidance.

3.4.1. Prediction of human Clearance (CL) and Volume of Distribution (Vss)

Human blood clearance (CL) of GSK3008356 is predicted to be low (Table 1) based on the various methods employed and assuming that the blood to plasma ratio is 1 for all species.

Table 1 Summary of Predicted Human Pharmacokinetic Parameters[1]

Prediction Method	Human CL (mL/min)	Human CL/F (mL/min)	Human Blood Vss (L)	Human Blood Vss/F (L)
Method 1: allometric scaling of apparent clearance CL/F	-	58	-	-
Method 2: allometric scaling of clearance CL	82.3	82.3[2]	92	92[2]
Method 3: IVIVC (Well Stirred model)	76	76[2]	-	-

[1]Assuming human body weight of 70 kg; [2]assuming bioavailability of 100%

The preclinical and *in vitro* data used for the above prediction are listed in Table 2 and Table 3.

Table 2 Plasma clearance in preclinical species

Plasma Clearance (*in vivo*) in preclinical species				
	CL (mL/min/kg)		Body Weight (kg)	Fup (%)
	Mean	Std Dev	Mean	Mean
Mouse	1.39	0.10	0.025	29.1
Rat	6.65	1.60	0.25	15.4
Dog	2.60	0.23	11.00	66.2

Table 3 Intrinsic clearance in vitro in human hepatocytes

Intrinsic clearance *in vitro* in human hepatocytes			
	CL (mL/min/g)	Liver Scaling Factor (g/kg)	Human Fup (%)
Human	0.120	24.5	37.1

3.4.2. Prediction of Human Efficacious Dose

Overall, the CL/F (82.3 mL/min) and Vss/F (92 L) with the assumption of 100% bioavailability based on Method 2 is considered the most appropriate for simulations to estimate the human efficacious dose. Of the three preclinical species, dog exhibited a 2-compartmental PK profile following intravenous (IV) infusion. Fitting the dog data with

a 2-compartmental model showed a Vc/Vp ratio of 1.31 and a Q/CL ratio of 2.5. In humans it is very likely the PK will also exhibit 2-compartmental behaviour. Assuming same Vc/Vp and Q/CL ratio in humans, the intra-compartmental clearance (Q/F) would be 205 mL/min, and Vc and Vp would be 52.4 L and 40 L, respectively, with a sum of 92 L as predicted by allometric scaling. These parameters will translate to a k_e of 0.094 h^{-1}, a k12 of 0.235 h^{-1}, and a k21 of 0.307 h^{-1}, which can then be used in simulations to obtain the Cmax, C4, C24 and AUC(0-∞) at a specific dose, assuming tmax of 1.5 h (k_a of 1.4 h^{-1}).

The human efficacious dose was calculated based on doses required to maintain trough levels from the (A) animal efficacy models and (B and C) a published PK/PD model.

A. The human efficacious dose was calculated based on the doses required to maintain trough levels as seen in the mouse DIO studies at 3mg/kg BID. The mean trough level from three mouse DIO studies was 169.8 ng/mL. After correcting for potency differences between mouse and human *in vitro* cell-based assay (human keratinocyte IC_{50} = 74 nM; mouse C2C12 IC_{50} = 100.8 nM) this translates to a prediced human C_{trough} of 124.7 ng/mL. The human dose required to achieve the total target concentration was simulated (C_{24}, i.e., C_{trough} >124.7 ng/mL). By this method the projected efficacious human oral dose for a 70 kg human is 43 mg once daily. Since the mouse DIO studies did not explore doses lower than 1mg/kg BID, 1 mg/kg BID and its associated mean trough level (81.66 ng/mL) were considered the MABEL in mouse. This translates to a human C_{trough} of 60 ng/mL and human MABEL of ~21 mg. The MABEL is the dose/exposure that results in 10-20% of the maximum pharmacologic effect of receptor blockade. If the human keratinocyte IC_{20} (15 nM) rather than the IC_{50} (74 nM) is used, the human MABEL dose will be ~8.7 mg.

B. Denison published a PK/PD model of the DGAT1 inhibitor AZD7687 based on a single-dose study (Denison 2014). In the study, postprandial increases in TG were measured (AUC_{incr}) under untreated conditions (baseline AUC_{incr}) versus AZD7687 treated conditions (TG AUC_{incr}). Using an inhibitory effect sigmoid Emax model ($E = E0 - [E0 - Emax] * [C^{\tau} / (C^{\tau} + EC_{50}^{\tau})]$), he described a steep concentration–effect relationship between the postprandial TG AUC_{incr} decrease compared to the baseline AUC_{incr} versus plasma concentration of AZD7687 at start of the meal (C4). The maximal reduction (Emax) in TG AUC_{incr} versus baseline AUC_{incr} that could be achieved was −84±9%. Half of the Emax was observed at a concentration of 0.44±0.07 µmol/L (EC_{50}). The percent change in TG AUC_{incr} versus baseline AUC_{incr} at an AZD7687 concentration of 0 (E0) was estimated to be 15±6% and the shape factor (τ) was estimated to be 4±2. AZD7687 had a plasma protein binding of 94.5% (fu of 5.5%) and an IC_{50} of 0.014 µM in a human duodenal cell line (HuTu80) based on TG synthesis measurement.
Assuming GSK3008356 also exert same effect on postprandial serum TG concentrations, and accounting for plasma protein binding difference (62.9% for GSK3008356) and IC_{50} difference (74 nM for GSK3008356), the total plasma concentration to exert half of the maximal reduction in TG (EC_{50}) will be 0.345 µmol/L. The projected efficacious dose is 18 mg using this approach (~75%

reduction in TG AUC_{incr} versus baseline AUC_{incr}). Similarly, the calculated MABEL dose is 9.6 mg (~20% reduction in TG AUC_{incr} versus baseline AUC_{incr}).

C. Denison did not model the exposure-effect relationship between the decrease in TG AUC_{incr} compared to baseline AUC_{incr} versus plasma AZD7687 AUC(0-∞). However, we estimated the AZD7687 AUC(0-∞) based on their published plasma concentration versus time curves, and model it using the inhibitory effect sigmoid Emax model: $E = E0 - [E0 - Emax] * [AUC^{\tau} / (AUC^{\tau} + EAUC_{50}^{\tau})]$. According to the model the maximal reduction (Emax) in TG AUC_{incr} versus baseline AUC_{incr} was −81%. Half of the maximal reduction was observed at an AUC of 6.21 µmol.h/L ($EAUC_{50}$). The percent change in TG AUC_{incr} versus baseline AUC_{incr} at an AZD7687 AUC of 0 (E0) was estimated to be 13% and the shape factor (τ) was estimated to be 6. Assuming GSK3008356 follows same PK/PD relationship, and accounting for plasma protein binding difference and IC_{50} difference, the final estimated $EAUC_{50}$ for GSK3008356 would be 4.87 µmol.h/L. The projected efficacious dose would therefore be 12 mg with ~75% reduction in TG AUC_{incr} versus baseline AUC_{incr}. The calculated MABEL dose would be 7 mg with ~20% reduction in TG AUC_{incr} versus baseline AUC_{incr}.

Overall, based on models A, B, and C, the efficacious human oral dose is projected to be 12-43 mg, and the MABEL dose is projected as 7-21 mg. Simulated PK parameters are shown in Table 4 and predicted PK parameters for the planned study doses are shown in Table 5. Note the 25 mg dose was selected as the target efficacious dose based on the models and used to set the planned dose range with a starting dose at or lower than MABEL dose of 7 mg (Table 5).

Table 4 Simulated PK parameters at a particular dose for GSK3008356

Dose (mg)	Cmax (ng/mL)	C24 (ng/mL)	AUC(0-∞) (ng.h/mL)	Tmax (h)	T1/2 (h)
7	88.55	20.37	1421	1.5	14.1
12	151.8	34.92	2436	1.5	14.1
25	316.25	72.75	5075	1.5	14.1
43	543.95	125.13	8729	1.5	14.1

3.4.3. Planned Doses and Safety Coverage

Five (5) dose levels are planned for the study: 5 mg, 10 mg, 25 mg, 50 mg, and 75 mg.

3.4.3.1. Starting Dose

The starting dose of 5 mg is justified based the maximum recommended safe starting dose (MRSD) method as outline by the FDA.

The FDA guidance suggests calculating a human equivalent dose (HED), based on the NOAEL in the most sensitive or most relevant preclinical species, using scaling factors that are based on differences in body surface area between species. The HED is converted to an MRSD in humans by dividing by a safety factor. The safety factor may be adjusted depending on the pharmacology, toxicology, and preclinical pharmacokinetics of the drug, or previous experience with compounds in the same pharmacologic/structural class. Using the 4-week dog study safety information (NOAEL at 50 mg/kg), the HED was estimated to be 28 mg/kg. Using a safety factor of 100, the estimated MRSD in humans would be 17 mg for a 60 kg human.

The planned doses and the predicted exposure compared to the 4-week dog study NOAEL (C_{max} = 7.73 µg/mL, AUC 111 µg.h/mL at 50 mg/kg) are presented in Table 5. The estimated human dose that would result in an AUC exposure equivalent to the 4-week dog study NOAEL exposure is 547 mg. Using a safety factor of 100, the starting dose would be ~5.5 mg. As stated above, the MABEL dose may be 7-21 mg. To be conservative, a dose of 5 mg was chosen as the starting dose.

The GSK3008356 starting dose of 5 mg in humans is 0.083 mg/kg based on a 60 kg body weight. This is ~600-fold lower than the dog NOAEL dose (50 mg/kg). The predicted human exposure after a single 5 mg dose is ~122-fold below the C_{max} and ~109-fold below the AUC at the dog NOAEL (Table 5).

Planned Doses and Safety Cover

Plasma GSK3008356 concentrations will be determined after each dose cohort and the AUC and Cmax will be estimated. The dose for the next cohort will be determined by estimating the predicted exposure based on the observed exposure in the preceding cohort(s). Dose escalation will not exceed the NOAEL exposure in the 4-week dog study.

Table 5 Predicted, Human Cmax, C12, C24, and AUC(0-∞)Observed and Additional Predicted Human Exposures Following Single Oral Administration of GSK3008356

Proposed dose		Predicted Cmax	Fold-cover for Cmax	Predicted C12	Predicted C24	Predicted AUC(0-∞)	Fold-cover for AUC
(mg)	(mg/kg)[1]	(ng/mL)	Dog[2]	(ng/mL)	(ng/mL)	(ng.h/mL)	Dog[2]
5	0.083	63.25	122	26.35	14.55	1015	109
10	0.167	126.5	61	52.70	29.1	2030	55
25	0.417	316.25	24	131.75	72.75	5075	22
50	0.833	632.5	12	263.50	145.5	10150	11
75	1.250	948.75	8	395.25	218.25	15225	7
Actual dose		Cmax	Fold-cover for Cmax			Observed AUC(0-∞)	Fold-cover for AUC
(mg)	(mg/kg)[1]	(ng/mL)	Dog[2]			(ng.h/mL)	Dog[2]
5	0.083	92	84			191	581
10	0.167	191	40			314	353
30	0.500	458.5	17			841	132
75	1.250	890.9	9			1963	57
200	3.333	1865.3	4			5488	20
Additional Predicted doses		Predicted Cmax	Fold-cover for Cmax			Predicted AUC(0-∞)	Fold-cover for AUC
(mg)	(mg/kg)[1]	(ng/mL)	Dog[2]			(ng.h/mL)	Dog[2]
125	2.08	1290	6.0			3620	30.7
250 125q4 x2	4.17	1500	5.2			7236	15.3
250 125q16 x2	4.17	1300	5.9			7115	15.6
200 evening	3.33	2070	3.7			5797	19.1
90 10q1h x 9	1.50	300	25.8			2601	42.7
45 5q1h x 9	0.75	150	51.5			1297	85.6
180 20q1h x 9	3.00	600	12.9			5201	21.3

1. Based on 60 kg human body weight
2. Based on the 4-week dog study, 50 mg/kg/day dose, week 4 average Cmax (7.73 µg/mL) and AUC(0-t) (111 µg.h/mL)

Observed Doses, Additional Planned Doses, and Safety Cover

The actual doses administered and observed exposures relative to the dog NOAEL are found in Table 5. The highest dose administered (200 mg) had a 4-fold and 20-fold safety coverage to the dog NOAEL Cmax and AUC, respectively.

The expected exposures for the additional Part 1 cohorts will be at or below those observed in the Part 1 cohorts dosed to date (Table 5).

The proposed doses of GSK3008356 may be adjusted, as appropriate, based on the safety, tolerability, and pharmacokinetic data obtained in preceding cohorts.

3.5. Benefit:Risk Assessment

Summaries of findings from non-clinical studies conducted with GSK3008356 can be found in the IB. The current study, 204856, represents the first administration of GSK3008356 to healthy subjects. Considerations for safety monitoring are derived primarily from non-clinical data. The following section (Section 3.5.1) outlines the risk assessment and mitigation strategy for this protocol.

3.5.1. Risk Assessment

Potential Risk of Clinical Significance and Summary of Data/Rationale for Risk	Impact on eligibility criteria	Mitigation Strategy
Investigational Product (IP) [e.g., GSK3008256]		
Hepatic Effects Oral 7d repeat dose dog study: Minimal to mild, focal hepatocellular degeneration/necrosis was observed (minimal in one female given 50 mg/kg/day; minimal to mild in the male and female given 200 mg/kg/day). Minimal mixed inflammatory cell infiltrates within liver sinusoids noted for the female given 200 mg/kg/day. Clinical pathology findings included increases in alanine aminotransferase (ALT) (up to 1.96X baseline), increases in aspartate aminotransferase (AST) (up to 1.76X baseline), increased glutamate dehydrogenase (GLDH) (to 3.8X baseline) at all dose levels. Increased total bile acid concentrations (to 3.2X baseline) and decreased plasma albumin and total protein concentrations (to 0.90X baseline) were noted at various testing intervals for dogs given 50 or 200 mg/kg/day. These changes may be related to hepatocellular injury and/or associated with reduced food consumption. Oral 28d and 13 week repeat dose dog studies: Increases ALT were noted for males and females given 2, 5 and 50 mg/kg/day at Week 1 (ranging from1.88X to 2.5X baseline). By Week 4, increases were 1.72X to 2.2X baseline values. The ALT increases were not progressive with continued dosing. There were no correlative liver histopathology findings. Similar increases in ALT (up to 2.71X baseline) and AST (up to 1.57X) were observed in the 13 week study (evaluating doses up to 60 mg/kg/day) and were reversible following a 4-week off-treatment period.	Exclusion criterion #1: ALT and bilirubin > 1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). Exclusion criterion #2: Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Exclusion criterion #6 History of regular alcohol consumption within 6 months of the study. Exclusion criterion #10: A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening.	Sentinel dosing – staggered dosing in 2 subjects in Part 1 Cohort 1 prior to enrolment of the remainder of Cohort 1. LFT evaluation planned at baseline, day 2, day 4, day 7, day 14, day 21, day 28, and also as indicated. Exclusion criteria as noted in column 2. Stopping criterion of ALT ≥3xULN with no rechallenge of drug product.

Potential Risk of Clinical Significance and Summary of Data/Rationale for Risk	Impact on eligibility criteria	Mitigation Strategy
Oral 7d and 28 repeat dose rat study: No hepatic related findings. Oral 13 week repeat dose rat study: Increased liver weights (to 1.2X mean control) were observed in female rats given 1000 mg/kg/day with no clinical pathology or microscopic correlates. HepatoTaq: No significant findings.		
Gastrointestinal Tolerability Oral 7d, 28d, and 13 week repeat dose dog studies: In the 28d study, excessive salivation was observed for males given ≥2 mg/kg/day. Dose-related effects on body weight (decreased body weight gain or body weight loss) and/or reduced food consumption were observed in all studies. Increased frequency of fecal abnormalities (unformed/ stool/mucous and/or watery) were observed in the 13 week study. Oral 7d, 28d, and 13 week repeat dose rat studies: Non-dose related decreases in mean body weight gain for rats were observed in the 7day study. No effects on body weight were noted in the 28 day and 13-week rat studies. Scientific Literature: Clinical DGAT1 inhibition may result in dose limiting nausea, vomiting and, watery (non-malabsorption) diarrhea which stopped upon discontinuation of dosing. (Denison 2014; Meyers 2015).	Exclusion criterion #4: Current or chronic history of gastrointestinal illness or conditions interfering with normal gastrointestinal anatomy or motility. Examples include gastrointestinal bypass surgery, cholecystectomy, partial or total gastrectomy, small bowel resection, vagotomy, malabsorption, Crohn's disease, ulcerative colitis, IBS, or celiac sprue.	Diarrhea scale (Bristol Stool Form Scale) and frequency of stool (Section 6.5.2). Subject may be withdrawn at any time at the discretion of the investigator for safety.

Potential Risk of Clinical Significance and Summary of Data/Rationale for Risk	Impact on eligibility criteria	Mitigation Strategy
Dermal Effects Oral 7d, 28d, and 13 week repeat dose dog studies: Dose-related, minimal to mild atrophy of the sebaceous glands was observed and was considered to be related to pharmacology. Finding was reversible in the 13 week study following a 4-week off-dose period. Oral 7d, 28d, and 13 week repeat dose rat studies: No dermal-related findings. Scientific Literature: DGAT1 inhibition may result in sebaceous gland atrophy and alopecia as observed in animal studies (Floettmann 2015), but similar effects have not been reported in clinical trials to date.	None	Subject may be withdrawn at any time at the discretion of the investigator for safety.

Potential Risk of Clinical Significance and Summary of Data/Rationale for Risk	Impact on eligibility criteria	Mitigation Strategy
Testicular Effects Oral 7d and 28d repeat dose dog study: No effects in testes or epididymides observed at doses up to 200 mg/kg/day for 7d and up to 50 mg/kg/day for 28d. Oral 7d, 28d and 13w repeat dose rat study: No effects in testes or epididymides observed at doses up to 300 mg/kg/day for 7d and 28d and up to1000 mg/kg/day for 13w. Oral 13w repeat dose dog study: Minimal to mild degeneration of the testicular seminiferous tubule epithelium with secondary changes within the epididymides (luminal germ cell debris and/or reduced sperm) was observed in terminal dogs given ≥30 mg/kg/day. Following the end of the 4-week off-dose period, testicular degeneration was still present in dogs given 60 mg/kg/day and is not unexpected given the long spermatogenic cycle in dogs (typically 90 days).	None	While there is no impact on the study NOAEL, dose regimen selection will be based regimens which will result in human exposure below the oral 13w repeat dose dog testicular observation NOAEL exposure of Cmax (0.642 µg/mL) and AUC(0-t) (5.49 µg.h/mL). Subject may be withdrawn at any time at the discretion of the investigator for safety.

Potential Risk of Clinical Significance and Summary of Data/Rationale for Risk	Impact on eligibility criteria	Mitigation Strategy
Cardiovascular Effects Single dose cardiovascular rat and dog studies: In rats, transient increases in heart rate (17%) and blood pressure (18%) were observed at 100 mg/kg but not as 30 and 300 mg/kg. The increases in both heart rate and blood pressure produced a transient increase in rate-pressure-product (RPP; an index of cardiac workload; 37%), Because similar changes were not observed at the highest evaluated dose of 300 mg/kg, a clear relationship to GSK3008356 administration was not established. No acute effects on cardiovascular function were noted in dogs. Oral 28d and 13 week dog studies: No cardiovascular-related findings (ECG assessments). Rabbit left ventricular wedge assay: No effects on QT interval, transmural dispersion of repolarization, QRS duration or contractility (concentrations of up to 10 μM). hERG: IC_{25} value was estimated to be 85.7 μM (31.49 μg/mL). Insufficient inhibition of hERG occurred to allow for the reliable estimation of an IC_{50} value. The estimated IC_{25} value is >150X greater than the estimated free C_{max} in humans at the maximum predicted clinical efficacious dose of 43 mg. Based on the low magnitude and transient nature of the heart rate and blood pressure increases noted in rats and the low risk for QT prolongation (based on in vitro findings), the risk for CV effects in humans is considered low.	Exclusion criterion #3: QTcF < 450 msec.	Monitoring via telemetry (day 1), 12-lead ECG, and vital signs monitoring. Stopping Criteria (Section 4.5.2): QTcF > 500 msec QTc change from baseline > 60 msec.

Potential Risk of Clinical Significance and Summary of Data/Rationale for Risk	Impact on eligibility criteria	Mitigation Strategy
Study Procedures		
Skin Biopsy Complications of punch skin biopsy are uncommon but may include bleeding, infection, and scarring. Bleeding and infection risk are very uncommon with underlying disease conditions (hemophilia, diabetes, older age, and immunosuppression) slightly increasing the risk. Scarring risk is increased in individuals with a history of scarring.	Exclusion criterion #5: History of risk for or actual experience of complications from skin biopsy including excess bleeding, infection, or scarring/keloid formation.	Observation of the subject while in the clinical unit and at follow-up after discharge from the unit. Subject may be withdrawn at any time at the discretion of the investigator for safety.

3.5.2. Benefit Assessment

As the subjects of this study are healthy subjects they are not expected to receive any direct benefits from the investigation product. The subject may benefit from the general medical data collected through study assessments such as clinical laboratory tests and ECGs. Participation in the study may provide societal benefit through advancing development of new treatments in an area of unmet need.

3.5.3. Overall Benefit:Risk Conclusion

Conducting this clinical trial is reasonable based on the measures taken to minimize risk to subjects participating, balanced against the potential risks identified in associated with GSK3008356 and the potential general benefits outlined above.

4. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Investigator's Brochure (IB).

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

AGE
1. Between 18 and 65 years of age inclusive, at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. For Part 1 and Part 2: Healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. 3. For Part 3: Obese subjects may have chronic disease not specifically excluded and not requiring chronic medication for treatment and are otherwise healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. A subject with a clinical abnormality or laboratory parameter(s) which is/are not

specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator in consultation with the Medical Monitor agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

WEIGHT
4. Body weight ≥ 50 kg 5. For Part 1 and Part 2 body mass index (BMI) 19 – 25 kg/m^2 (inclusive) 6. For Part 3 BMI ≥30 kg/m^2

SEX
7. Males or Females of non-childbearing potential as follows: **Males**: Male subjects with female partners of child bearing potential must comply with the following contraception requirements (Section 4.3) from the time of first dose of study medication until at least five half-lives of study medication after the last dose of study medication. a. Vasectomy with documentation of azoospermia. b. Male condom plus partner use of one of the contraceptive options below: • Contraceptive subdermal implant • Intrauterine device or intrauterine system • Oral Contraceptive, either combined or progestogen alone [Hatcher 2007] Injectable progestogen [Hatcher 2007] • Contraceptive vaginal ring [Hatcher 2007] • Percutaneous contraceptive patches [Hatcher 2007] **Females**: A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test), not lactating, and the following conditions applies: a. Non-reproductive potential defined as: • Pre-menopausal females with one of the following: • Documented tubal ligation • Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion • Hysterectomy

- Documented Bilateral Oophorectomy
- Postmenopausal defined as 12 months of spontaneous amenorrhea in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) > 40 MlU/ml and estradiol < 40 pg/ml (<147 pmol/L) is confirmatory. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will not be allowed.

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

INFORMED CONSENT
8. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

4.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. ALT and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
2. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
3. QTcF> 450 msec (Section 4.3)
4. Current or chronic history of gastrointestinal illness or conditions interfering with normal gastrointestinal anatomy or motility. Examples include gastrointestinal bypass surgery, cholecystectomy, partial or total gastrectomy, small bowel resection, vagotomy, malabsorption, Crohn’s disease, ulcerative colitis, IBS, or celiac sprue.
5. History of risk for or actual experience of complications from skin biopsy including excess bleeding, infection, or scarring/keloid formation (Part 2 only).

CONCOMITANT MEDICATIONS
6. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John’s Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study drug, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety. By exception, subject may take acetaminophen (≤ 2 grams/day) up to 48 hours prior to the first dose of study drug.

RELEVANT HABITS
7. Subjects should refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days prior to the first dose of study medication until after the final dose. 8. History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >14 standard drinks. One standard drink is equivalent to 10 g of alcohol: 285 ml of beer, 100 ml of wine or 30 ml of 40% alcohol by volume distilled spirits. 9. For Part 1 and Part 2, urinary cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 3 months prior to screening.

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

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
11. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. For potent immunosuppressive agents, subjects with presence of hepatitis B core antibody (HBcAb) should also be excluded. 12. A positive pre-study drug/alcohol screen. 13. A positive test for HIV antibody. 14. Where participation in the study would result in donation of blood or blood products in excess of 750 mL within 90 day period. 15. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). 16. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

4.3. Inclusion and Exclusion Criteria Notes

For contraception requirements, the list provided is an all-inclusive list of those methods that meet the following GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and correctly and, when applicable, in accordance with the product label. For non-product methods (e.g., male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the International Conference on Harmonization (ICH) [ICH, M3 (R2) 2009]."

4.4. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (SAE) (see Section 6.3.1.4).

4.5. Withdrawal/Stopping Criteria

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

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.

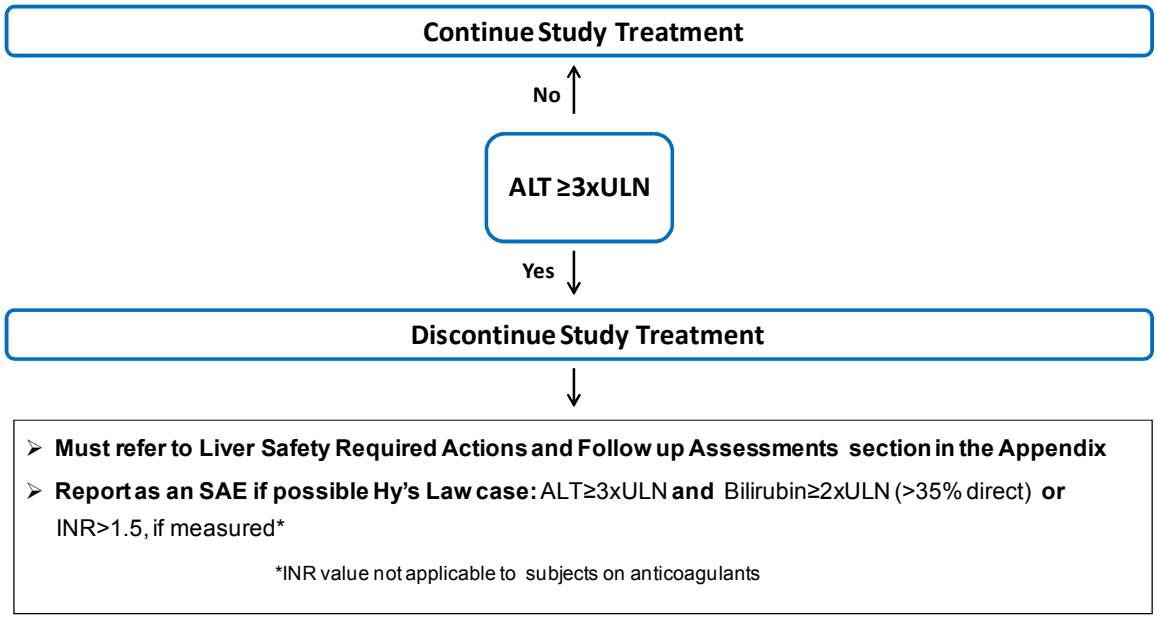
The reason(s) for not completing the study will be recorded in the case report form (CRF), and the investigator must document, if applicable, the reason (if specified by the subject) for withdrawal of consent. A withdrawn subject may be replaced with another subject who will be assigned to the same treatment randomization.

4.5.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Study treatment will be discontinued **for a subject** if liver chemistry stopping criteria are met:

Figure 2 Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2 (Section 11.2).

4.5.1.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

4.5.2. QTc Stopping Criteria

A subject that meets either bulleted criterion below will be withdrawn from the study.

- QTcF > 500 msec,
- Change from baseline: QTc >60 msec

For trial eligibility the same QT correction formula (QTcF) will be used. The same QT correction formula (QTcF) will be used for all QTc data being collected for data analysis. Discontinuation decisions would ideally use the same QT correction formula will be used. The exception would be safety ECGs or other non-protocol specified ECGs outside the control of the clinical unit.

Withdrawal of subjects is to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, then obtain 2 more ECGs over a brief (e.g.,

5-10 minute) recording period and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

4.6. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up visit.

The end of the study is defined as the last subject's last visit.

5. STUDY TREATMENT

5.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments (Table 6).

Table 6 Study Treatment

	Study Treatment	
Product name:	GSK3008356	Placebo
Formulation description / Dosage form:	Tablet	Tablet
Unit dose strengths/Dosage levels:	0.5, 1, 5, and 25 mg	
Route of Administration	Administered orally	Administered orally
Dosing instructions:	Daily for up to 28 days	Daily for up to 28 days
Physical description:	White Tablet	White Tablet
Manufacturer	GlaxoSmithKline	GlaxoSmithKline

5.2. Treatment Assignment

Subjects will be assigned to treatments in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated software.

A description of each regimen is provided in the table below (Table 7):

Table 7 Regimen Description

Regimen Code	Study Medication	Regimen Code	Study Medication
AA	5 mg GSK3008356, morning dosing	AP	5 mg GSK3008356, evening dosing
BA	10 mg GSK3008356, morning dosing	BP	10 mg GSK3008356, evening dosing
CA	25 mg GSK3008356, morning dosing	CP	25 mg GSK3008356, evening dosing
DA	50 mg GSK3008356, morning dosing	DP	50 mg GSK3008356, evening dosing
EA	75 mg GSK3008356, morning dosing	EP	75 mg GSK3008356, evening dosing
FA	Matched placebo, morning dosing	FP	Matched placebo, evening dosing
GA	125 mg GSK3008356, morning dosing	LA	5 mg GSK3008356 q1h x 9 doses, morning dosing
HA	125 mg GSK3008356 q4h x 2 doses, morning dosing	MA	20 mg GSK3008356 q1h x 9 doses, morning dosing
IA	125 mg GSK3008356 q16h x 2 doses, morning dosing	NA	10 mg GSK3008356 q16h x 2 doses, morning dosing
JA	200 mg GSK3008356, evening dosing	OA	3 mg GSK3008356 q1h x 9 doses, morning dosing
KA	10 mg GSK3008356 q1h x 9 doses, morning dosing	PA	1 mg GSK3008356 q1h x 9 doses, morning dosing

5.3. Planned Dose Adjustments

- This protocol allows some alteration from the currently outlined dosing schedule, but the maximum predicted daily exposure will not exceed Cmax = 7.73 µg/mL or AUC 111 µg.h/mL.
- The decision to proceed to the next dose level will be made by the GSK Study Team, in conjunction with the investigator based on safety, tolerability and preliminary pharmacokinetic and/or pharmacodynamic data obtained in at least 4 subjects at the prior dose level in Parts 1 and 2 (dose escalation Parts). The actual doses to be administered may be adjusted based on safety, tolerability and preliminary pharmacokinetic and/or pharmacodynamic data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose.
- The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety, pharmacokinetic and/or pharmacodynamic findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects. Any cohort expansion or addition will be

contingent on approval of an amended protocol by the Human Research Ethics Committee (HREC).

- If the same Serious Adverse Event occurs in more than one subject, the dose escalation will be temporarily halted and no further subject will be dosed until a full safety review of the data has taken place. Relevant reporting and discussion with the Medical Monitor, relevant GSK personnel, and with the Ethics Committee will then take place prior to any resumption of dosing.
- The above criteria will apply even if measured pharmacokinetic parameters are below the above mentioned PK stopping criteria, and every effort will be made to take a blood sample at the time of the event for pharmacokinetic analysis in the presence of any of the above events.

5.4. Blinding

This will be a double blind (sponsor unblind) study and the following will apply.

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF

A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

5.5. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

5.6. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the Study reference Manual (SRM).
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

5.7. Compliance with Study Treatment Administration

When the individual dose for a subject is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.

When subjects are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each subject's mouth to ensure that the study treatment was ingested.

When subjects self-administer study treatment(s) at home, compliance with study drug will be assessed through querying the subject during the site visits and documented in the source documents and CRF. A record of the number of study drug tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose reductions will also be recorded in the CRF.

5.8. Treatment of Study Treatment Overdose

GSK does not recommend specific treatment for an overdose. The investigator or physician in charge of the subject at the time will use clinical judgment to treat any overdose.

5.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because only healthy subjects or healthy obese subjects are eligible for study participation.

5.10. Lifestyle and/or Dietary Restrictions

5.10.1. Meals and Dietary Restrictions

Subjects should refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice and/or pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days prior to the first dose of study medication until after the final dose.

Subjects in Part 3, evening dosing, should refrain from any meals after the evening dose until breakfast the next morning.

5.10.2. Caffeine, Alcohol, and Tobacco

- For Part 1 and Part 2, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and or pharmacodynamic sample during each cohort.
- For Part 3, during each inpatient visit, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and or pharmacodynamic sample during the inpatient stay.
- During each dosing session, subjects will abstain from alcohol for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and or pharmacodynamic sample during each session.
- For Part 1 and Part 2, use of tobacco products is not allowed from inpatient check-in and the start of dosing until after the final follow-up visit.
- For Part 3 inpatient sessions, use of tobacco products is not allowed from inpatient check-in until after discharge from the unit.
- For Part 3, outpatient Subjects who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the Clinical Unit.

5.10.3. Activity

Subjects will abstain from strenuous exercise for 1 hour prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

5.11. Concomitant Medications and Non-Drug Therapies

Based on the *in vitro* data generated to date, it is unlikely for GSK3008356 to affect the pharmacokinetics of co-administered CYP, OATP1B1/1B3, P-gp or BCRP substrates. Please refer to the IB [GlaxoSmithKline Document Number 2015N255332_00] for details.

5.11.1. Permitted Medications and Non-Drug Therapies

Paracetamol, at doses of ≤ 1 grams/day is permitted for use any time during the study. Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the Medical Monitor if required.

5.11.2. Prohibited Medications and Non-Drug Therapies

Subjects must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements), within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until completion of the follow-up visit, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study.

6. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 6.1

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
    1. 12-lead ECG
    2. vital signs
    3. blood draws
    4. skin biopsy.

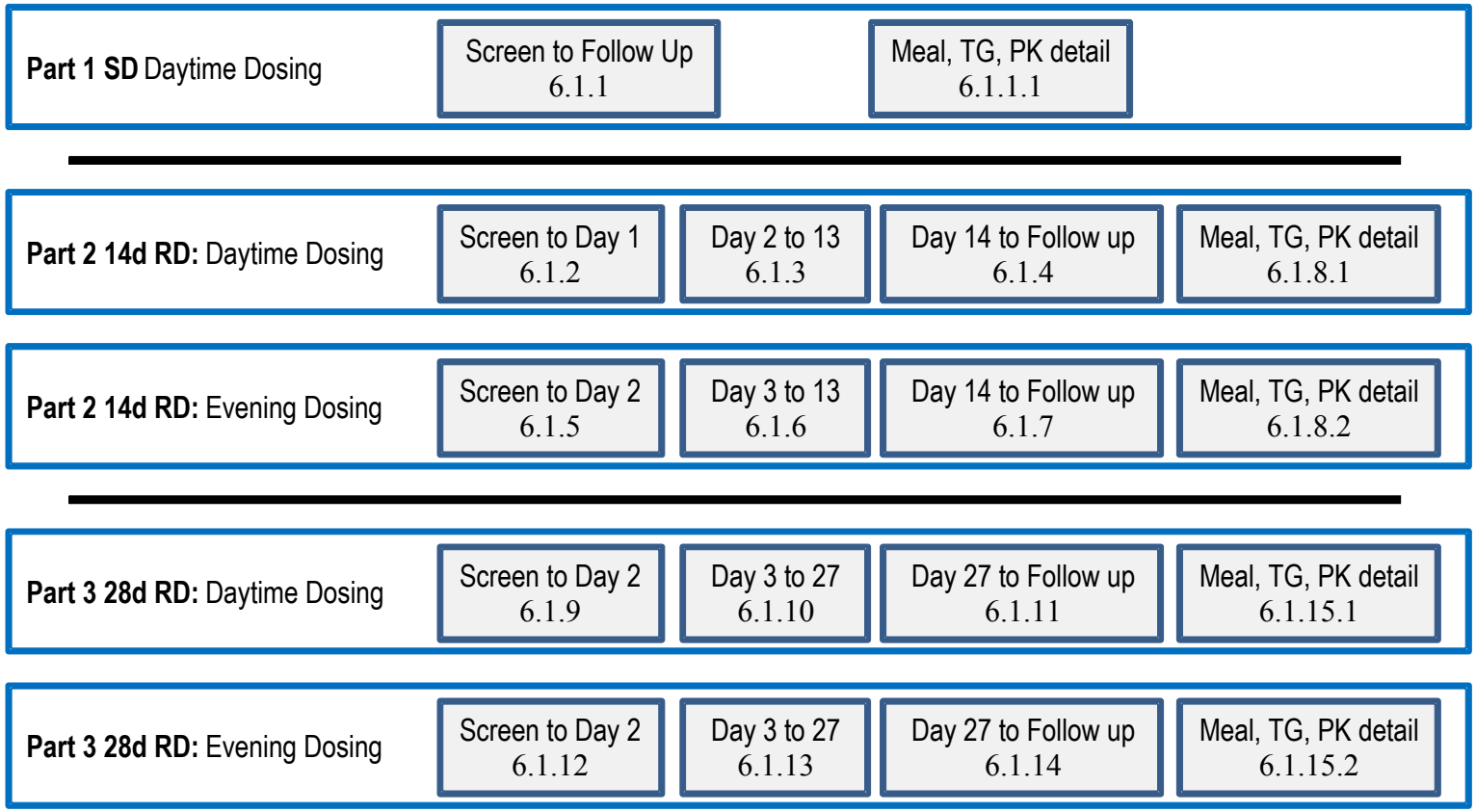
  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or others assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- The nominal dosing time for evening dose cohorts (20:00 local) in the respective Time and Events Tables is for illustrative purposes only. The nominal evening dose time selected for use will be documented for each evening dose cohort. The actual dose time will be recorded as well.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The HREC and investigators will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 650 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

6.1. Time and Events Tables

Please refer to Figure 3 below to understand the how the multiple Time and Events Tables relate to the study Parts.

Figure 3 Study Part and Related Time and Events Tables



6.1.1. 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		←==========																	→
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.
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).
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.

6.1.1.1. 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
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

6.1.2. 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
Adverse Event Review		←==========													→
BSFS[8]			←==========												→
Concomitant Medication Review		←==========													→
Outpatient Visits	X														
Inpatient Check-in		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 6.1.8.1.
6. Temperature Screening and Day -1 only.
7. Plasma analysis for circulating metabolite profile; Plasma 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).
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 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.

6.1.3. 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	
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 (Section 11.5).
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.

6.1.4. 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
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).
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

6.1.5. Part 2 – Repeat Dose, Evening Dose Administration, Screening, Day -1, Day 1 and Day 2

	Screening (within 28d)	Day -1	Day 1 (6)									Day 2 (6)				
		PM	12h Pre-dose	Pre-dose	0h	0.25h	0.5h	1h	1.5h	2h	4h	6h	12h	14h	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]			←→										←=======→			
Study Drug Dose[6]					X											
Vital Signs (BP, HR, pulse, Temp)[7]	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, 8]				X		X	X	X	X	X	X	X	X	X	X	X
Adverse Event Review		←==========→														
BSFS[9]			←==========→													
Concomitant Medication Review		←==========→														
Outpatient Visits	X															
Inpatient Check-in		X														

1. Brief physical exam, weight.
2. Serum hCG at screening, urine hCG pre-dose on Day -1 – all females.
3. If indicated
4. An alcohol breath test is acceptable.
5. Detailed Fat Meal, Triglyceride Assessment, Plasma PK Sampling and Plasma Metabolite Sampling can be found in Section 6.1.8.2

6. 0hr is relative to Study Dose administered and will be approximately at 18:00 hrs, making 12h Pre-dose approximately 06:00, 6h post-dose approximately 00:00 Day 2 and 12h post-dose approximately 06:00 Day 2. The actual nominal dose time will be the same for each subject within Part 2.
7. Temperature at Screening and Day -1 only.
8. The 24h time point is Day 2 pre-dose. Plasma analysis for circulating metabolite profile; Plasma samples for metabolites will be analyzed from only the highest dose cohort.
9. The number of BSFS stool types will be collected in real time for each 24h period (Section 11.5)

6.1.6. Part 2 – Repeat Dose, Evening Dose Administration, Days 3-13

	Days 3-13 (1)		
	12h Pre-dose	Pre-dose	0h
Study Drug Dose[1]			X
Vital Signs (BP, HR, pulse)		X[2]	
12-Lead ECG		X[2]	
Hematology, Chemistry		X[3]	
UA		X[4]	
Exploratory PD Labs	X[5]		
Plasma PK and Metabolite Sampling		X[6]	
Adverse Event Review	←==========		==========→
BSFS[8]	←==========		==========→
Concomitant Medication Review	←==========		==========→

1. 0hr is relative to Study Dose administered and will be approximately at 18:00 hrs, making 12h Pre-dose approximately 06:00. The actual nominal dose time will be the same for each subject within Part 2.
2. Day 7, 12, and 13.
3. Day 4, and 7 only
4. Day 7 only
5. Day 7 12h Pre-dose only
6. Day 4, 5, 6, 12, and 13
7. The number of BSFS stool types will be collected each 24h period (Section 11.5)

6.1.7. Part 2 – Repeat Dose, Evening Dose Administration, Day 14-17, Follow-up

	Day 14								Day 15					Day 16		Day 17	Follow Up (Day 20-22)
	12h Pre-dose	0h	0.25h	0.5h	1h	1.5h	2h	4h	6h	12h	14h	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]	←→																
Study Drug Dose[4]		X															
Vital Signs (BP, HR, pulse)	X				X			X		X			X	X			X
12-Lead ECG	X				X			X		X			X				
Hematology, Chemistry	X								X				X	X			X
UA	X													X			X
Exploratory PD Labs	X													X			X
Plasma PK and Metabolite Sampling[3,5]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review	←==========→																
BSFS[6]	←==========→																
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 6.1.8.2
4. 0hr is relative to Study Dose administered and will be approximately at 18:00 hrs, making 12h Pre-dose approximately 06:00 and 6h post-dose approximately 00:00 Day 15. The actual nominal dose time will be the same for each subject within Part 2.
5. Plasma analysis for circulating metabolite profile; Plasma samples for metabolites will be analyzed from only the highest dose cohort.
6. The number of BSFS stool types will be collected in real time for each 24h period (Section 11.5)

6.1.8. Part 2 – Repeat Dose, Fat Meal Challenge and Triglyceride Assessment Relative to Dose and PK Sampling

6.1.8.1. 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 6.1.2, Section 6.1.3, and Section 6.1.4.

6.1.8.2. Evening Dose Administration, Day 1, Day 2, and Day 14

	Day 1, Day 2 and Day 14												
	Pre-dose (h)										0h	Post-dose (h)	
	11h	10h	9h	8h	7h	6h	5h	4h	3h	< 0.5h pre-dose		0.25h	0.5h
Study Drug Dose[1]											X[1,3]		
Fat Meal		X											
Triglyceride Assessment	X	X	X	X	X	X	X	X	X	X			
Plasma Pharmacokinetic Sampling[2]										X		X	X

1. Day 1 and 14 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 6.1.5, Section 6.1.6, and Section 6.1.7.
3. 0hr is relative to Study Dose administered and will be approximately at 18:00 hrs, making 12h Pre-dose approximately 06:00 and Making Day 2 Fat Meal 14h **Post**-Day 1 Dose (10h **Pre-**Day 2 Dose). The actual nominal dose time will be the same for each subject within Part 2.

6.1.9. Part 3 – Repeat Dose, Morning Dose Administration, Screening, Day -1, Day 1, Day 2

	Screening (within 28d)	Day -2, Day -1 [8]	Day 1													Day 2	
			Pre-dose	0h	0.25h	0.5h	1h	1.5h	2h	4h	6h	8h	12h	18h	24h	0h	1h
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				X												X	
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 Sampling[5,]			X		X	X	X	X	X	X	X	X	X	X	X		
Adverse Event Review		←==========→															
BSFS[7]			←==========→														
Concomitant Medication Review		←==========→															
Outpatient Visits	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 6.1.15.1.
6. Temperature Screening and Day -1 only.
7. The number of BSFS stool types will be collected in real time for each 24h period (Section 11.5).
8. 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.

6.1.10. Part 3 – Repeat Dose, Morning Dose Administration, Days 7, 14, and 21*

	Days 7, 14, and 21	
	Pre-dose	0h
Medical/medication/drug/alcohol history	X	
Brief Physical Exam, Weight	X	
Study Drug Dose		X
Vital Signs (BP, HR, pulse)	X	
12-Lead ECG	X	
Hematology, Chemistry	X	
UA	X	
Exploratory PD Labs	X	
Plasma PK Sampling	X	
Adverse Event Review	←==========→	
BSFS[1]	←==========→	
Concomitant Medication Review	←==========→	
Outpatient Visits	X	

1. The number of BSFS stool types will be collected in real time for each 24h period while at home (Section 11.5). BSFS Diary Cards to be bought to the unit and reviewed/data entered during the visit.

*NOTE for Days 3-6, 8-13, 15-20, and 22-27: Subjects will dose at home and maintain BSFS Diary cards as directed.

6.1.11. Part 3 – – Repeat Dose, Morning Dose Administration, Day 27-31 and Follow-up

	Day 27	Day 28												Day 29	Day 30	Day 31	Follow Up (Day 34-36)
	PM	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																	X
Complete Physical Exam, Weight	X[1]																X[1]	X
Pregnancy Test[2]																		X
Fat Meal[3]								X										
Triglyceride Assessment[3]						X		←==========						→				
Study Drug Dose			X															
Vital Signs (BP, HR, pulse)	X	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 Sampling[3]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review	←==========																	→
BSFS[4]	←==========																	→
Concomitant Medication Review	←==========																	→
Outpatient Visits																		X
Inpatient Check-in	X																	
Inpatient Check-out																	X	

1. Brief physical exam and weight Day 27 and 31
2. Serum hCG at follow up, all females.
3. Detailed Fat Meal, Triglyceride Assessment and Plasma PK Sampling can be found in Section 6.1.15.1
4. The number of BSFS stool types will be collected in real time for each 24h period (Section 11.5). BSFS Diary Cards to be bought to the unit and reviewed/data entered during the visit.

6.1.12. Part 3 – Repeat Dose, Evening Dose Administration, Screening, Day 1 and Day 2

	Screening (within 28d)	Day -1	Day 1 (6)									Day 2 (6)						
		PM	12h Pre-dose	Pre-dose	0h	0.25h	0.5h	1h	1.5h	2h	4h	6h	12h	14h	18h	24h	0h	1h
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]			←→										←=========→					
Study Drug Dose[6]					X												X	
Vital Signs (BP, HR, pulse, Temp)[7]	X	X	X	X				X			X							
12-Lead ECG	X		X	X				X			X							
Telemetry				←==========→														
Hematology, Chemistry	X		X									X				X		
UA	X		X													X		
Exploratory PD Labs	X		X										X					
Plasma PK Sampling[5, 8]				X		X	X	X	X	X	X	X	X	X	X	X		
Adverse Event Review		←==========→																
BSFS[9]			←==========→															
Concomitant Medication Review		←==========→																
Outpatient Visits	X																	
Inpatient Check-in		X																
Inpatient Check-out																		X

1. Brief physical exam, weight.
2. Serum hCG at screening, urine hCG pre-dose on Day -1 – all females.
3. If indicated
4. An alcohol breath test is acceptable.

5. Detailed Fat Meal, Triglyceride Assessment, Plasma PK Sampling and Plasma Sampling can be found in Section 6.1.15.2
6. 0hr is relative to Study Dose administered and will be approximately at 18:00 hrs, making 12h Pre-dose approximately 06:00, 6h post-dose approximately 00:00 Day 2 and 12h post-dose approximately 06:00 Day 2. The actual nominal dose time will be the same for each subject within Part 3.
7. Temperature at Screening and Day -1 only.
8. The 24h time point is Day 2 pre-dose.
9. The number of BSFS stool types will be collected in real time for each 24h period (Section 11.5)

6.1.13. Part 3 – Repeat Dose, Evening Dose Administration, Days 7, 14, and 21*

	Days 7, 14, and 21 (2)	
	Pre-dose	0h
Medical/medication/drug/alcohol history	X	
Brief Physical Exam, Weight	X	
Study Drug Dose		X
Vital Signs (BP, HR, pulse)	X	
12-Lead ECG	X	
Hematology, Chemistry	X	
UA	X	
Exploratory PD Labs	X	
Plasma PK Sampling	X	
Adverse Event Review	←==========→	
BSFS[1]	←==========→	
Concomitant Medication Review	←==========→	
Outpatient Visits	X	

1. The number of BSFS stool types will be collected in real time for each 24h period while at home (Section 11.5). BSFS Diary Cards to be bought to the unit and reviewed/data entered during the visit.
2. 0hr is relative to Study Dose administered and will be approximately at 18:00 hrs. The actual nominal dose time will be the same for each subject within Part 3.

*NOTE for Days 3-6, 8-13, 15-20, and 22-27: Subjects will dose at home and maintain BSFS Diary cards as directed. If subjects are checking into the unit prior to dosing on Day 27, the dose may be administered in the unit rather than at home

6.1.14. Part 3 – Repeat Dose, Evening Dose Administration, Day 27-31 and Follow-up

	Day 27	Day 28								Day 29					Day 30		Day 31	**Follow Up (Day 34-36)**
	PM	12h Pre-dose	0h	0.25h	0.5h	1h	1.5h	2h	4h	6h	12h	14h	18h	24h	36h	48h	72h	
Medical/medication/drug/alcohol history	X																	X
Complete Physical Exam, Weight	X[1]																X[1]	X
Pregnancy Test[2]																		X
Fat Meal[3]	X	X																
Triglyceride Assessment[3]		←→																
Study Drug Dose[4]	X		X															
Vital Signs (BP, HR, pulse)	X	X				X			X		X			X	X			X
12-Lead ECG		X				X			X		X			X				
Hematology, Chemistry		X								X				X	X			X
UA		X													X			X
Exploratory PD Labs		X													X			X
Plasma PK Sampling[3]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Review	←==========→																	
BSFS[5]	←==========→																	
Concomitant Medication Review	←==========→																	
Outpatient Visits																		X
Inpatient Check-out	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 and Plasma PK Sampling can be found in Section 6.1.15.2
4. 0hr is relative to Study Dose administered and will be approximately at 18:00 hrs, making 12h Pre-dose approximately 06:00 and 6h post-dose approximately 00:00 Day 29. Day 27 dose may be administered in the unit rather than at home if the subject has checked in prior to Day 27 dose. The actual nominal dose time will be the same for each subject within Part 3.
5. The number of BSFS stool types will be collected in real time for each 24h period (Section 11.5). BSFS Diary Cards to be bought to the unit and reviewed/data entered during the visit.

6.1.15. Part 3 – Repeat Dose, Fat Meal Challenge and Triglyceride Assessment Relative to Dose and PK Sampling

6.1.15.1. Morning Dose Administration, Day -1, Day 1, and Day 28

	Day -1, Day 1, Day 28															
	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 28 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 6.1.9, Section 6.1.10, and Section 6.1.11.

6.1.15.2. Evening Dose Administration, Day 1, Day 2, and Day 28

	Day 1, Day 2 and Day 28												
	Pre-dose (h)										0h	Post-dose (h)	
	11h	10h	9h	8h	7h	6h	5h	4h	3h	< 0.5h pre-dose		0.25h	0.5h
Study Drug Dose[1]											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

1. Day 1, Day 2, and 28 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 6.1.12, Section 6.1.13, and Section 6.1.14.
3. 0hr is relative to Study Dose administered and will be approximately at 18:00 hrs, making 12h Pre-dose approximately 06:00 and Making Day 2 Fat Meal 14h **Post**-Day 1 Dose (10h **Pre-**Day 2 Dose). The actual nominal dose time will be the same for each subject within Part 3.

6.2. Screening and Critical Baseline Assessments

Cardiovascular medical history/risk factors (as detailed in the CRF) will be assessed at screening.

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed at screening as related to the inclusion/exclusion criteria listed in Section 4. All subsequent assessments will be updates.

6.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Table (Section 6.1). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

6.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Appendix 3 (Section 11.3)

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

6.3.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 6.3.1.3), at the time points specified in the Time and Events Table (Section 6.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 11.3.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Section 11.3.

6.3.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- "How are you feeling?"
- "Have you had any (other) medical problems since your last visit/contact?"
- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

6.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 3.5.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 4.5). Further information on follow-up procedures is given in Section 11.3.

6.3.1.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, HREC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the HREC, if appropriate according to local requirements.

6.3.2. Pregnancy

- Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until after the follow-up visit.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Section 11.4 (Appendix 4).

6.3.3. Physical Exams

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal, Dermatologic and Neurological systems, height, and weight. Height will be measured and recorded only at screening.
- A brief physical examination will include, at a minimum assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen). Weight will be recorded with the brief physical exam as per the Time and Events Tables, but is not part of the brief physical exam.
- Investigators should pay special attention to clinical signs related to previous serious illnesses

6.3.4. Vital Signs

- Vital signs include systolic and diastolic blood pressure and pulse and will be measured in semi-supine position after 5 minutes rest.
- Temperature will also be measured as a vital sign but will not require positioning or rest prior to measuring.

6.3.5. Electrocardiogram (ECG)

- Triplicate 12-lead ECGs will be obtained for trial eligibility
- Single 12-lead ECGs will be obtained at each timepoint during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 4.5.2 for QTc withdrawal criteria.
- Withdrawal of subjects is to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, then obtain 2 more ECGs over a brief period of time and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study
- Continuous cardiac telemetry will be performed. Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents

6.3.6. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments, as defined in Table 8, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Schedule. Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the SRM or the laboratory manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the SRM for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 8.

Table 8 Protocol Required Safety Laboratory Assessments

Hematology			
Platelet Count	*RBC Indices*:	*Automated WBC Differential:*	
RBC Count	MCV	Neutrophils	
WBC Count (absolute)	MCH	Lymphocytes	
Reticulocyte Count	MCHC	Monocytes	
Hemoglobin		Eosinophils	
Hematocrit		Basophils	
Clinical Chemistry (Chemsitry)			
BUN	Potassium	AST (SGOT)	Total and direct bilirubin
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Glucose, fasting/non-fasting*	bicarbonate	GGT	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
Bile Acids			
*Glucose will be fasting for all screening, day 1 pre-dose, and follow-up assessments. Glucose will be non-fasting for all other time points.			
NOTE: Details of Liver Chemistry Stopping Criteria and Follow-Up Procedures are given in Section 4.5.1 and Section 11.2 (Appendix 3)			
Routine Urinalysis (UA)			
Specific gravity			
pH, glucose, protein, blood and ketones by dipstick			
Microscopic examination (within 120 minutes of collection)			
Triglyceride Assessment (Postprandial response)			
Triglycerides			
Exploratory Pharmacodynamics (Exploratory PD Labs)			
Cholesterol			
Triglycerides			
HDL			
LDL			
VLDL-Triglycerides (if feasible)			
Other screening tests			
HIV			
Hepatitis B (HBsAg)			
Hepatitis C (Hep C antibody -- if second generation Hepatitis C antibody positive, a hepatitis C antibody Chiron RIBA immunoblot assay (or other third generation immunoassay) or Hepatitis C Virus RNA test (either quantitative or qualitative) should be reflexively performed **on the same sample** to confirm the result)			
FSH and estradiol (as needed in women of non-child bearing potential only)			
Serum and urine hCG Pregnancy test (as needed for women of child bearing potential)			
Urine cotinine levels			
Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).			

6.4. Pharmacokinetics

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation Department, GlaxoSmithKline. Plasma GSK3008356 concentration-time data will be analyzed by non-compartmental methods with WinNonlin [Version 5.2 or higher]. Calculations will be based on the actual sampling times recorded during the study. Full details will be provided in the reporting and

analysis plan (RAP). The following plasma pharmacokinetic parameters will be determined for each treatment, as data permit:

Table 9 GSK3008356 Pharmacokinetic Parameters to be Estimated

Part/Day	Plasma GSK3008356 PK Parameters Calculated (as data permit)
Part 1 Single Dose	AUC(0-∞), AUC(0-t), AUC(0-24), Cmax, tmax, t1/2
Part 2 Day 1	AUC(0-τ), Cmax, tmax
Part 2 Day 14	AUC(0-τ), Cmax, tmax, t1/2
Part 3 Day 1	AUC(0-τ), Cmax, tmax
Part 3 Day 28	AUC(0-τ), Cmax, tmax, t1/2

Additional GSK3008356 PK Parameters to be Calculated:

Dose proportionality of GSK3008356 PK parameters will be assessed following single dose administration (AUC0-t), AUC(0-∞), Cmax) and repeat dose administration (AUC(0-τ), Cmax).

Accumulation ratio will be determined by comparing AUC(0-τ) on Days 14 (Part 2) and 28 (Part 3) to AUC(0-τ) obtained on Day 1:

Part 2: Ro= [AUC(0-τ),day 14]/ [AUC(0-τ), Day 1]

Part 3: Ro= [AUC(0-τ),day 28]/ [AUC(0-τ), Day 1]

Achievement of steady-state will be determined by evaluating trough plasma concentrations (C_{trough}) following repeat oral doses, as data permit

Part 2: Plasma GSK3008356 pre-dose concentration will be determined on Days 2, 4, 5, 6, 12, 13, 14 and the 24 h post dose on Day 14 of Part 2,

Part 3: Plasma GSK3008356 pre-dose concentration will be determined on Days 2, 7, 14, 21, 28 and the 24 h post dose on Day 28 of Part 3

From the GSK3008356 urine data, the total amount excreted (Ae) will be determined following single dose in Part 1 and on Day 14 (Part 2) and Day 28 (Part 3).

Additional PK parameters may be calculated and details will be provided in the RAP. Actual elapsed times from dosing will be used in the PK analysis. Individual PK parameter values will be listed and a descriptive summary by treatment will be provided. Additional comparative plots of the PK parameters for other comparisons of interest may also be generated.

6.4.1. Blood Sample Collection

Blood samples for PK analysis of GSK3008356 and for circulating metabolite analysis will be collected at the time points indicated in the Time and Events Tables (Section 6.1). The actual date and time of each sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of the blood sample collection, including volume to be collected, processing, storage and shipping procedures are provided in the Study Reference Manual.

6.4.2. Urine Sample Collection

Urine samples for PK analysis of GSK3008356 and for metabolite analysis will be collected at the time points indicated in the Time and Events Tables (Section 6.1). The timing of urine samples may be altered and/or samples may be obtained at additional time points to ensure thorough monitoring.

Details of urine sample collection, including volume to be collected, processing, storage and shipping procedures are provided in the SRM.

6.4.3. Sample Analysis

Plasma and urine (if feasible) analysis will be performed under the management of Platform Technology and Sciences, Drug Metabolism and Pharmacokinetics (PTS-DMPK), GlaxoSmithKline. Concentrations of GSK3008356 will be determined in plasma and urine (if feasible) samples using the currently approved analytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma has been analyzed for GSK3008356 any remaining plasma may be analyzed qualitatively for other compound-related metabolites and the results reported under a separate PTS-DMPK protocol. The urine samples will also be analyzed for compound-related metabolites and the results reported under a separate PTS-DMPK protocol.

6.4.4. Statistical Analysis of Pharmacokinetic Data

Details of the statistical analyses of PK data, including dose proportionality, accumulation ratio, steady-state assessment, and pharmacokinetic/pharmacodynamic analysis will be provided in the RAP.

6.4.5. Skin Biopsy Sample Collection and Analysis

Skin biopsy for PK analysis and activity of GSK3008356 will be collected at the time points indicated in the Time and Events Tables (Section 6.1). The actual date and time of each sample collection will be recorded.

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 samples 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 (detailed in the SRM). All skin biopsy analysis results will be reported under a separate PTS-DMPK protocol.

6.5. Biomarker(s)/Pharmacodynamic Markers

6.5.1. Postprandial Triglyceride Assessment

DGAT1 inhibition has been observed to cause a decrease in postprandial TG levels after subjects are dosed with a high-fat meal (Meyers 2015; Denison 2014).

Fat content of 40% to 60% by calories in a 1000kcal meal were used in the clinical trials (Meyers 2015; Denison 2014). In one study, the fat content was decreased to 20% and 30% due to intolerability at higher percentages (Denison 2014).

The meals were administered either without prior DGAT1 inhibitor dosing or 1-2h after DGAT inhibitor dosing and were consumed within 15 minutes. They were prepared as a standardized mixed fat meal (Karpe 1997).

TG levels were obtained across 7-11h post meal (9-12h post-dose). The TG AUC increase at baseline was compared to the post-dose TG AUC increase and evaluated for evidence of DGAT1 inhibition PD activity.

For the present study, the fat meal will be set at 30% fat by calories and will be consumed within 15 minutes (15 minutes ± 10 minutes). The 30% fat meal provided adequate postprandial excursion allowing TG AUC measurement at baseline (Meyers 2015).

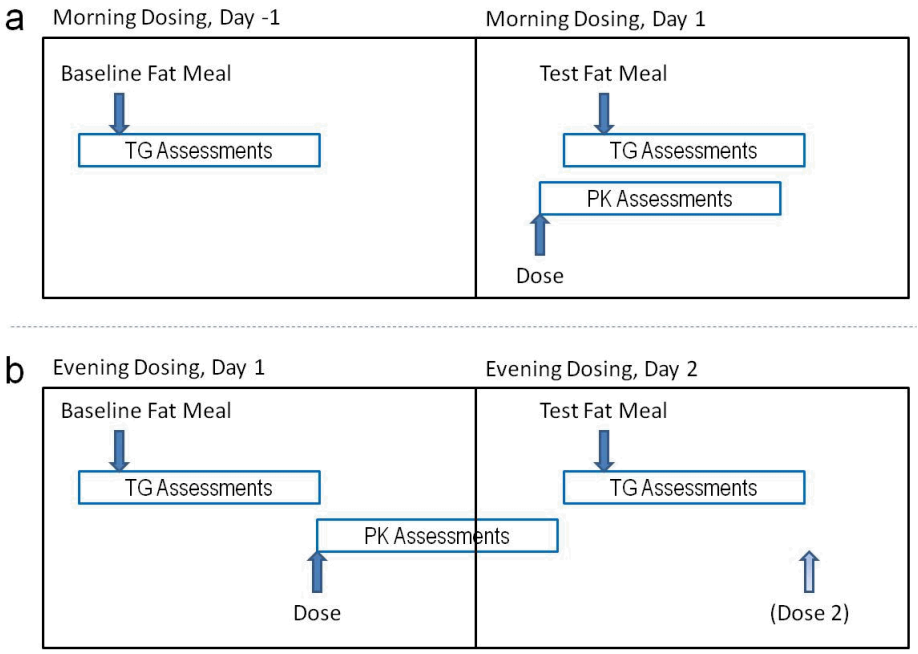
The baseline meal for morning dose subjects will be administered on Day -1, 2h after the nominal "dose" time (Figure 4a). The test meals will be administered 2h post-GSK3008356 dose for subjects receiving morning doses (Figure 4b). This will be days 1 and 14 or 28, depending on the study Part.

The baseline meal for evening dose subjects will be administered 10h pre-GSK3008356 dose on Day 1 (Figure 4b). This is 10h prior to the very first dose. The evening dose test meals will be administered 10h prior to the evening dose on Day 2 (14h after the first dose on Day 1; Figure 4b). The evening dose test meals will also be administered 10h prior to the evening dose on Day 14 or 28 (14h after the first dose on Day 13 or 27), depending on the study Part.

The TG measurement will be collected from 1h prior to meal through 10h after meal. This is from 1h post GSK3008356 dose through 12h post-GSK3008356 dose for subjects receiving morning doses. It is from 11h pre-GSK3008356 dose (13h post-dose) to just prior to next dose (12h post-previous dose) for subjects receiving evening dose. Please refer to the Time and Events Tables for details (Section 6.1.8.1 and Section 6.1.8.2 for examples).

The TG collection time will result in a pre-meal "baseline" and continue to where the levels return to pre-meal baseline after postprandial excursion (Meyers 2015; Denison 2014).

Figure 4 Postprandial Triglyceride Assessment Schematic



6.5.2. Bristol Stool Form Scale

The Bristol Stool Form Scale (Lewis 1997) 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. Please refer to Section 11.5 for scale details. The number of each type of stool will be collected across the 24h calendar day.

6.5.3. Exploratory PD Markers

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.

7. DATA MANAGEMENT

- For this study subject data will be entered into CRO eCRFs (approved by GSK), transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.

- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and a validated medication dictionary, (internal GSKDrug or external WHODrug).
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

8. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

8.1. Hypotheses

There are no formal hypotheses being tested. An estimation approach will be taken to provide a plausible range of values. For the pharmacokinetic endpoints, where appropriate, point estimates and 90% confidence intervals will be provided.

8.2. Sample Size Considerations

Sample sizes are based on feasibility. No formal power calculations were performed.

8.2.1. Sample Size Sensitivity

No statistical sample size sensitivity calculations were performed.

8.2.2. Sample Size Re-estimation or Adjustment

Sample size re-estimation will not be conducted.

8.3. Data Analysis Considerations

8.3.1. Analysis Populations

PK Concentration Population: Subjects for whom a pharmacokinetic sample was obtained and analyzed.

PK Parameter Population: All subjects in the PK Concentration Population who receive at least one active dose of GSK3008356 and provide pharmacokinetic parameters.

Safety Population: All subjects who received at least one dose of study medication.

8.3.2. Interim Analysis

No interim analysis is planned.

8.4. Key Elements of Analysis Plan

8.4.1. Primary Analyses

All data listings and summaries will be presented. Listings will be sorted by subject and time. Summaries will be presented by regimen, and nominal time. Unless stated otherwise, descriptive summaries will include n (number of subjects), mean, standard deviation (SD), coefficient of variation (CV), median, minimum, and maximum for continuous variables, n and percent for categorical variables. In addition, the geometric mean, with associated 95 % confidence interval and between-subject CVs (CVb), based on the geometric mean, will be included for the log-transformed PK parameters.

8.4.2. Secondary Analyses

Please refer to Section 6.4.4.

8.4.3. Other Analyses

Please refer to Section 6.4.4 and Section 6.4.5.

9. STUDY GOVERNANCE CONSIDERATIONS

9.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

9.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of the site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- HREC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to the HREC)

- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study

9.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

9.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

9.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.

- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the HREC promptly and provide the reason for the suspension or premature discontinuation.

9.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

9.7. Provision of Study Results to Investigators, Posting of Information on Publically Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

9.8. Review Committees

9.8.1. Dose Escalation Committee

For Part 1 and Part 2, the decision to proceed to the next dose level within the study part will be made by a Dose Escalation Committee (DEC) consisting of the Principal Investigator (or appropriate designee), Medical Monitor, GSK Study Team Leader, GSK Pharmacokineticist, a GSK GCSP representative and GSK Statistician**.** The GSK Medical Monitor and the GSK Pharmacokineticist will remain unblinded throughout the course of the study. The decision to progress from Part 1 to Part 2 and from Part 2 to Part 3 will also be made by the DEC.

Dose escalation decisions will be based on data obtained from 4 or more subjects receiving GSK3008356 at the prior dose level. The review data set will at minimum consist of AE listings, liver function test results, PK results derived from 24 hour plasma profiles, and PD (TG) data. Flagged vital signs, cardiac monitoring (telemetry), ECG and laboratory findings will also be reviewed.

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11. APPENDICES

11.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

Ae	cumulative amount of unchanged drug excreted into the urine
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC(0-τ)	area under the concentration-time curve from time zero (pre-dose) to the end of dosing interval
AUC(0-t)	area under the plasma concentration-time curve from time zero to time t
AUC(0-∞)	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
BID	twice a day
BMI	body mass index
BP	blood pressure
BSFS	Bristol Stool Form Scale
BUN	blood urea nitrogen
C12	concentration at 12 hours
C24	concentration at 24 hours
CL	apparent total body clearance of drug from plasma
CL_R	renal clearance of drug from plasma
Cmax	maximum observed plasma concentration
CONSORT	consolidated standards of reporting trials
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
C_{trough}	trough plasma concentrations
CV	cardiovascular
CV	coefficient of variation
CVb	between-subject coefficient of variation
CYP	cytochrome P450
DEC	Dose Escalation Committee
DGAT	diacylglycerol acyltransferase
DGAT1	diacylglycerol acyltransferase 1
DGAT2	diacylglycerol acyltransferase 2
DIO	diet-induced obesity
DMPK	Drug Metabolism and Pharmacokinetics
eCRF	electronic case report form
e.g.	exempli gratia (for example)
E	effect

E(0)	effect at baseline
$EAUC_{50}$	AUC in which 50% of E_{max} is achieved
EC_{50}	concentration in which 50% of Emax is achieved
ECG	electrocardiogram
Emax	maximum drug-induced effect
FDA	(US) Food and Drug Administration
FRP	females of reproductive potential
FSH	follicle stimulating hormone
g	grams
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLDH	glutamate dehydrogenase
GSK	GlaxoSmithKline
HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HDL	high-density lipoprotein
HED	human equivalent dose
hERG	human Ether-à-go-go-Related Gene
HIV	human immunodeficiency virus
HR	heart rate
HREC	Human Research Ethics Committee
HRT	hormone replacement therapy
HSC	hepatic stellate cells
IB	investigator's brochure
IBS	irritable bowel syndrome
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
INR	international normalized ratio
IV	intravenous
k_a	absorption rate constant
k_e	elimination rate constant from the central compartment
kg	kilogram
L	liter
LC MS/MS	liquid chromatography tandem mass spectrometry
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LFT	liver function test
m^2	square meter
MABEL	minimum anticipated biological effect level
MALDI	matrix assisted laser desorption/ionization
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration

MCV	mean corpuscular volume
MedDRA	medical dictionary for regulatory activities
mg	milligram
mIU/ml	milli-international units per milliliter
mL	milliliter
MRSD	maximum recommended safe starting dose
MSDS	material safety data sheet
msec	millisecond
NAFL	nonalcoholic fatty liver
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
ng	nanogram
ng/mL	nanogram per millilitre
nM	nanometer
NOAEL	no observed adverse effect level
NSAIDS	nonsteroidal anti-inflammatory drugs
OATP	organic anion-transporting polypeptide
PD	pharmacodynamics
P-gp	P-Glycoprotein
PK	pharmacokinetics
PTS-DMPK	Platform Technology and Sciences, Drug Metabolism and Pharmacokinetics
QTc	corrected QT interval
QTcF	corrected QT interval to Fridericia's formula
RAP	report and analysis plan
RBC	red blood cell
R_{Cmax}	accumulation ratio calculated from $C_{max,ss}$ and C_{max}
RD	repeat-dose
RNA	ribonucleic acid
R_o	observed accumulation based on AUC(0-τ)
RPP	rate-pressure-product
SAE	serious adverse event
SD	single-dose
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SLiP	skin lipogenesis (assay)
SRM	study reference manual
τ	shape factor
$t_{1/2}$	elimination half-life
TG	triglyceride
Tmax	time to maximum observed plasma concentration
UA	urinalysis
ULN	upper limit of normal
µg/mL	microgram per milliliter
µg.h/mL	Microgram per hour per milliliter

µM	micrometer
µmol.h/L	micromole-hour per liter
Vc	volume of central compartment
Vp	volume of peripheral compartment
Vss	volume of distribution at steady state
Vss/F	volume of distribution at steady state after non-IV administration
VLDL	very-low density lipoprotein
VLDL-TG	very-low density lipoprotein triglycerides
WBC	white blood cell

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

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Chiron RIBA
HepatoTaq
WinNonlin

11.2. Appendix 2: Liver Safety Required Actions and Follow up Assessments

Phase I Liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥ 2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is</td><td>• Viral hepatitis serology[3]
• Blood sample for pharmacokinetic (PK) analysis, obtained within 7 days of the last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form
If ALT≥3xULN AND bilirubin ≥ 2xULN or</td></tr>
</table>

Liver Chemistry Stopping Criteria – Liver Stopping Event	
recommended **If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	**INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James 2009]. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants\
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

11.3. Appendix 3: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

11.3.1. Definition of Adverse Events

Adverse Event Definition:
• 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. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae).

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE. • Situations where an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.3.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE:

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

11.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

11.3.4. Recording of AEs and SAEs

AEs and SAE Recording:
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the CRF • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

11.3.5. Evaluating AEs and SAEs

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign 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. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. • A "reasonable possibility" is meant to convey that there are facts/evidence or

arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

11.3.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool
• Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool • If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor and the SAE coordinator. • Site will enter the serious adverse event data into the electronic system as soon as it becomes available. • The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE. • After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor and the SAE coordinator by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

11.4. Appendix 4: Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP and Collection of Pregnancy Information

11.4.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Oral Contraceptive, either combined or progestogen alone [Hatcher 2007]
- Injectable progestogen [Hatcher 2007]
- Contraceptive vaginal ring [Hatcher 2007]
- Percutaneous contraceptive patches [Hatcher 2007]
- Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007].
- Male condom plus partner use of one of the contraceptive options below:
    - Contraceptive subdermal implant
    - Intrauterine device or intrauterine system
    - Oral Contraceptive, either combined or progestogen alone [Hatcher 2007] Injectable progestogen [Hatcher 2007]
    - Contraceptive vaginal ring [Hatcher 2007]
    - Percutaneous contraceptive patches [Hatcher 2007]

This is an all inclusive list of those methods that meet the GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and, correctly and, when applicable, in accordance with the product label. For non-product methods (e.g. male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the ICH [ICH, M3 (R2) 2009].

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study medication.

- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

11.5. Appendix 5: Bristol Stool Form Scale

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

11.6. Appendix 6: Protocol Amendment Changes

AMENDMENT 1

Where the Amendment Applies

This Protocol Amendment 1 applies to all sites participating in the study.

Summary of Amendment Changes with Rationale

This Protocol Amendment 1 is to add additional Part 1 cohorts which dose the compound in a way that provides a more appropriate exposure profile. This is 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. The additional cohorts include divided doses to achieve time above the target exposure with varying levels of Cmax and doses directly related to regimens that may be used in Part 2 of the study. There will be no changes to the current challenge meal or assessments. Several administrative changes were also made.

Detailed Rationale and Planned Additional Cohorts

Part 1, Cohort 6 would evaluate 125 mg as a single dose. This would provide exposure and time above the target threshold between 75 mg and 200 mg. The objective would be to determine if activity is present with potentially lower incidence of GI tolerability signals. This would support potential daily repeat dose cohorts in Part 2.

Part 1, Cohort 7 would evaluate 125 mg administered twice at time 0h and 4h for a total dose of 250 mg. The objective of this cohort is to explore maintenance of time above target efficacy threshold with Cmax exposure less than that observed at 200 mg SD and enable up to 250 mg/day (given as dived doses) as potential regimens for Part 2 of the study.

Part 1, Cohort 8 would evaluate 125 mg administered twice at time 0h and 16h for a total dose of 250 mg. Like Cohort 7, this cohort would provide further information on tolerability and enable the potential regimen of 125 mg BID (daily in the morning and at night) for Part 2 of the study.

Part 1, Cohort 9 would evaluate 200 mg administered once at night. The objective would be to determine if the active dose has less GI AEs if administered so that peak exposure is not associated with meals. This cohort would also enable a potential regimen of 200 mg once daily at night for Part 2 of the study.

Part 1, Cohort 10 would evaluate 90 mg administered as 9 doses of 10 mg hourly from time 0 to time 8h. The objective would be to administer the compound in a way that results in exposures more closely resembling an extended release formulation.

Part 1, Cohort 11 would evaluate either 45 mg administered as 9 doses of 5 mg hourly from time 0 to time 8h or 180 mg as 9 doses of 20 mg hourly from time 0 to time 8h. The choice of the hourly 5 mg versus 20 mg would depend on whether PD was observed in Cohort 7. The objective would be to administer the compound in a way that results in exposures more closely resembling an extended release formulation and to more narrowly confirm the target threshold for PD activity.

The predicted exposures relative to the dog NOAEL for the proposed additional Part 1 cohorts is found in Table 5. Neither the predicted human Cmax, nor the predicted human AUC is expected to exceed the dog NOAEL.

List of Specific Changes

NOTE: for PREVIOUS TEXT, the content is exactly as in the original; for REVISED TEXT, text deleted from the original has a dotted underline and text added has a solid underline.

Change 1: Title Page

PREVIOUS TEXT

Author(s):

PPD

REVISED TEXT

Author(s):

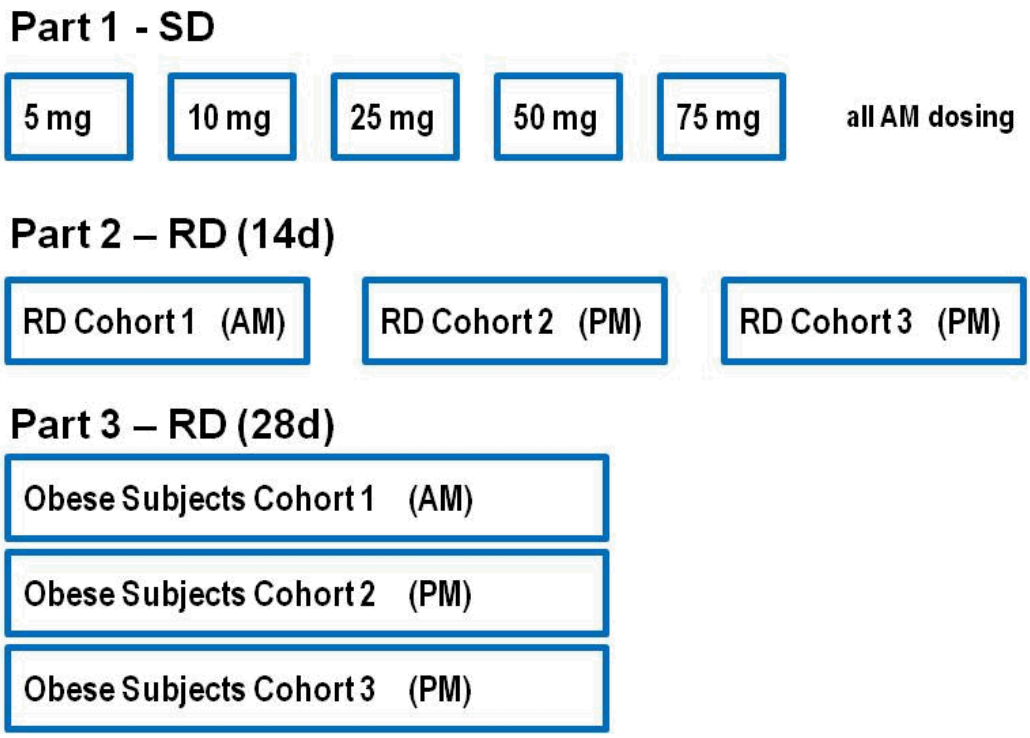
PPD

RATIONALE

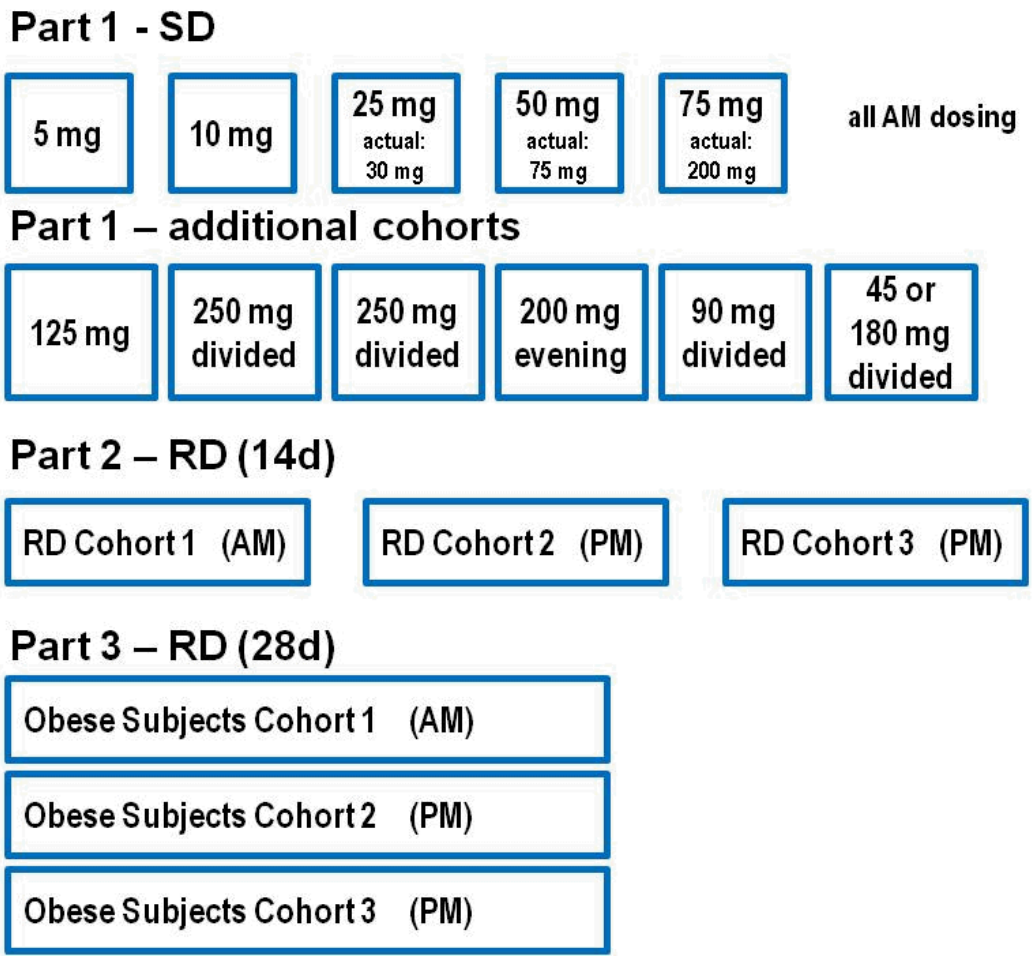
Administrative: Two authors were removed as they have left the project. Two authors were added who are new to the project and contributed to the amendment. The names were re-formatted.

Change 2: Figure 1 Study Part Schematic

PREVIOUS TEXT



REVISED TEXT



RATIONALE

The Figure was modified to reflect the actual doses administered in Part 1, Cohorts 1-5 and to provide information regarding the additional Part 1, Cohorts 6-11.

Change 3: New Section 3.1.1 Additional Cohorts for Part 1

Based on emerging PK data, the original planned Part 1 doses were adjusted, per protocol, to 5, 10, 30, 75 and 200 mg (Section 5.3, Figure 1). This was due to a much shorter observed half-life compared to the predicted half-life (1.5-3h observed versus 14.1h predicted).

While the adjusted doses did allow observation of a PD response in Cohort 5, the overall single dose data were limited and could not adequately inform a PK/PD model or support informed progression into Part 2 of the study. It was determined to further explore the PK/PD further through additional Part 1 cohorts. The purpose of the additional cohorts is to explore dose administration in a manner that should provide a more acceptable PK profile than that observed to date. This includes divided doses to achieve time above the target exposure with varying levels of Cmax and doses directly related to regimens that

may be used in Part 2 of the study. There will be no changes to the current challenge meal or assessments.

RATIONALE

The section was added to provide background and information regarding the additional Part 1, Cohorts 6-11.

Change 4: Section 3.2 Type and Number of Subjects

PREVIOUS TEXT

Part 1, Single Dose, Healthy Subjects:

Approximately 40 subjects will be enrolled, 8 in each cohort, such that approximately 6-8 subjects complete dosing and critical assessments in each Part 1 Cohort. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels

REVISED TEXT

Part 1, Single Dose, Healthy Subjects:

Approximately 40 subjects will be enrolled, 8 in each cohort, such that approximately 6-8 subjects complete dosing and critical assessments in each Part 1 Cohort. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels. The six additional cohorts will enrol approximately 48 subjects.

RATIONALE

The sentence was added to provide the anticipated subject numbers for the additional cohorts.

Change 5: Table 5 in Section 3.4.3.1 Starting Dose

PREVIOUS TEXT

Table 5 Predicted Human Cmax, C12, C24, and AUC(0-∞) Following Single Oral Administration of GSK3008356

Proposed dose		Predicted Cmax	Fold-cover for Cmax	Predicted C12	Predicted C24	Predicted AUC(0-∞)	Fold-cover for AUC
(mg)	(mg/kg)[1]	(ng/mL)	Dog[2]	(ng/mL)	(ng/mL)	(ng.h/mL)	Dog[2]
5	0.083	63.25	122	26.35	14.55	1015	109
10	0.167	126.5	61	52.70	29.1	2030	55
25	0.417	316.25	24	131.75	72.75	5075	22
50	0.833	632.5	12	263.50	145.5	10150	11
75	1.250	948.75	8	395.25	218.25	15225	7

1. Based on 60 kg human body weight
2. Based on the 4-week dog study, 50 mg/kg/day dose, week 4 average Cmax (7.73 µg/mL) and AUC(0-t) (111 µg.h/mL)

REVISED TEXT

Table 5 Predicted, Human Cmax, C12, C24, and AUC(0-∞) Observed and Additional Predicted Human Exposures Following Single Oral Administration of GSK3008356

Proposed dose		Predicted Cmax	Fold-cover for Cmax	Predicted C12	Predicted C24	Predicted AUC(0-∞)	Fold-cover for AUC
(mg)	(mg/kg)[1]	(ng/mL)	Dog[2]	(ng/mL)	(ng/mL)	(ng.h/mL)	Dog[2]
5	0.083	63.25	122	26.35	14.55	1015	109
10	0.167	126.5	61	52.70	29.1	2030	55
25	0.417	316.25	24	131.75	72.75	5075	22
50	0.833	632.5	12	263.50	145.5	10150	11
75	1.250	948.75	8	395.25	218.25	15225	7
Actual dose		Cmax	Fold-cover for Cmax			Observed AUC(0-∞)	Fold-cover for AUC
(mg)	(mg/kg)[1]	(ng/mL)	Dog[2]			(ng.h/mL)	Dog[2]
5	0.083	92	84			191	581
10	0.167	191	40			314	353
30	0.500	458.5	17			841	132
75	1.250	890.9	9			1963	57
200	3.333	1865.3	4			5488	20
Additional Predicted doses		Predicted Cmax	Fold-cover for Cmax			Predicted AUC(0-∞)	Fold-cover for AUC
(mg)	(mg/kg)[1]	(ng/mL)	Dog[2]			(ng.h/mL)	Dog[2]
125	2.08	1290	6.0			3620	30.7
250 125q4 x2	4.17	1500	5.2			7236	15.3
250 125q16 x2	4.17	1300	5.9			7115	15.6
200 evening	3.33	2070	3.7			5797	19.1
90 10q1h x 9	1.50	300	25.8			2601	42.7
45 5q1h x 9	0.75	150	51.5			1297	85.6
180 20q1h x 9	3.00	600	12.9			5201	21.3

1. Based on 60 kg human body weight
2. Based on the 4-week dog study, 50 mg/kg/day dose, week 4 average Cmax (7.73 µg/mL) and AUC(0-t) (111 µg.h/mL)

RATIONALE

Actual doses and observed exposures for Part 1, Cohorts 1-5 were added to provide context to the pharmacokinetic profile to date and understand the safety coverage related to the dog NOAEL exposures. Predicted exposures for the additional Part 1 cohorts and the related safety coverage to the dog NOAEL were also added.

Change 6: New Text in Section 3.4.3.1 Starting Dose

Observed Doses, Additional Planned Doses, and Safety Cover

The actual doses administered and observed exposures relative to the dog NOAEL are found in Table 5. The highest dose administered (200 mg) had a 4-fold and 20-fold safety coverage to the dog NOAEL Cmax and AUC, respectively.

The expected exposures for the additional Part 1 cohorts will be at or below those observed in the Part 1 cohorts dosed to date (Table 5).

The proposed doses of GSK3008356 may be adjusted, as appropriate, based on the safety, tolerability, and pharmacokinetic data obtained in preceding cohorts.

RATIONALE

The new text provides a description of the new data added to Table 5.

Change 7: Table 6 in Section 5.1 Investigational Product and Other Study Treatment

PREVIOUS TEXT

Table 6 Study Treatment

	Study Treatment	
Product name:	GSK3008356	Placebo
Formulation description / Dosage form:	Tablet	Tablet
Unit dose strengths/Dosage levels:	0.1, 0.5, 1, 5, and 25 mg	
Route of Administration	Administered orally	Administered orally
Dosing instructions:	Daily for up to 28 days	Daily for up to 28 days
Physical description:	White Tablet	White Tablet
Manufacturer	GlaxoSmithKline	GlaxoSmithKline

REVISED TEXT

Table 6 Study Treatment

	Study Treatment	
Product name:	GSK3008356	Placebo
Formulation description / Dosage form:	Tablet	Tablet
Unit dose strengths/Dosage levels:	0.1, 0.5, 1, 5, and 25 mg	
Route of Administration	Administered orally	Administered orally
Dosing instructions:	Daily for up to 28 days	Daily for up to 28 days
Physical description:	White Tablet	White Tablet
Manufacturer	GlaxoSmithKline	GlaxoSmithKline

RATIONALE

Administrative: Dose strength 0.1 mg was not utilized for this study and therefore that unit dose strength is removed from the table.

Change 8: Table 7 in Section 5.2. Treatment Assignment

PREVIOUS TEXT

Regimen Code	Study Medication	Regimen Code	Study Medication
AA	5 mg GSK3008356, morning dosing	AP	5 mg GSK3008356, evening dosing
BA	10 mg GSK3008356, morning dosing	BP	10 mg GSK3008356, evening dosing
CA	25 mg GSK3008356, morning dosing	CP	25 mg GSK3008356, evening dosing
DA	50 mg GSK3008356, morning dosing	DP	50 mg GSK3008356, evening dosing
EA	75 mg GSK3008356, morning dosing	EP	75 mg GSK3008356, evening dosing
FA	Matched placebo, morning dosing	FP	Matched placebo, evening dosing

REVISED TEXT

Regimen Code	Study Medication	Regimen Code	Study Medication
AA	5 mg GSK3008356, morning dosing	AP	5 mg GSK3008356, evening dosing
BA	10 mg GSK3008356, morning dosing	BP	10 mg GSK3008356, evening dosing
CA	25 mg GSK3008356, morning dosing	CP	25 mg GSK3008356, evening dosing
DA	50 mg GSK3008356, morning dosing	DP	50 mg GSK3008356, evening dosing
EA	75 mg GSK3008356, morning dosing	EP	75 mg GSK3008356, evening dosing
FA	Matched placebo, morning dosing	FP	Matched placebo, evening dosing
GA	125 mg GSK3008356, morning dosing	JA	200 mg GSK3008356, evening dosing
HA	125 mg GSK3008356 q4h x 2 doses, morning dosing	KA	10 mg GSK3008356 q1h x 9 doses, morning dosing
IA	125 mg GSK3008356 q16h x 2 doses, morning dosing	LA	5 mg GSK3008356 q1h x 9 doses, morning dosing
		MA	20 mg GSK3008356 q1h x 9 doses, morning dosing

RATIONALE

The new text provides detail for the additional Part 1 Cohorts.

Change 9: Time and Events Table: Section 6.1.1 Part 1 – Single Dose

PREVIOUS TEXT

	Screening (within 28d)	Day -2, Day -1 [9]	Day 1	
			Pre-dose	0h
Study Drug Dose				X

REVISED TEXT

	Screening (within 28d)	Day -2, Day -1 [9]	Day 1	
			Pre-dose	0h
Study Drug Dose[10]				X[10]

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.

RATIONALE

The addition of citation 10 and the corresponding footnote text clarifies time 0 for cohorts where regimens consisting of multiple doses or evening doses are to be administered.

Change 10: Time and Events Table: Section 6.1.1.1 Part 1 – Single Dose Fat Meal Challenge and Triglyceride Assessment Relative to Dose and PK Sampling

PREVIOUS TEXT

	Day -1, Day 1	
	Pre-dose	0h
Study Drug Dose[1]		X

REVISED TEXT

	Day -1, Day 1	
	Pre-dose	0h
Study Drug Dose[1,3]		X[3]
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.		

RATIONALE

The addition of citation 3 and the corresponding footnote text clarifies time 0 for cohorts where regimens consisting of multiple doses or evening doses are to be administered.

Change 11: Section 11.5 Appendix 5: Bristol Stool Form Scale

PREVIOUS TEXT

The Bristol Stool Form Scale was assessed as a method to evaluate change in intestinal function, including diarrhea (Lewis 1997). For this study, the subjects will have the number of types of stool tabulated for each 24h period from Day -1 through Follow-up. The number of each type and total across types will be recorded. Stool Type will be based on the chart below.

AND

Example Collection Table:

	Day -1	Day 1	Day 2	Day 3	...	Day 28	...	.Day 36

REVISED TEXT

The Bristol Stool Form Scale was assessed as a method to evaluate change in intestinal function, including diarrhea (Lewis 1997). For this study, the subjects will have the number of types of stool tabulated for each 24h period from Day 1 through Follow-up. The number of each type and total across types will be recorded. Stool Type will be based on the chart below.

AND

Example Collection Table:

	Day 1	Day 2	Day 3	...	Day 28	...	.Day 36

RATIONALE

It was incorrectly noted that BSFS data collection was to start on Day -1. Collection of data is actually to start on Day 1.

Change 12: Section 3.5.1 Risk Assessment

PREVIOUS TEXT

HepatoTaq®: No significant findings.

REVISED TEXT

HepatoTaq: No significant findings.

RATIONALE

The symbol ® for the trademark "HepatoTaq" was removed as this trademark is not owned by GSK. The change was a required compliance review change. It was not identified by the compliance group with the original protocol compliance review.

AMENDMENT 2

Where the Amendment Applies

This Protocol Amendment 2 applies to all sites participating in the study.

Summary of Amendment Changes with Rationale

This Protocol Amendment 2 is to clarify dosing regimens for Part 2, to add skin biopsy assessment for drug level and activity, and add 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.

The regimen clarification and addition of skin biopsy is based on preliminary pharmacokinetic data indicating a much shorter observed half-life compared to the predicted half-life and the results (1.5-3h observed versus 14.1h predicted). Data from Part 1 of the study have identified the appropriate dosing regimens for Part 2 and that evening dosing was no longer indicated. Addition of skin biopsy will help 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. There will be no changes to the current challenge meal or assessments beyond the addition of the skin biopsy. Several administrative changes were also made.

Detailed Rationale and Planned Additional Cohorts

Part 2, Cohort 1 would evaluate 10 mg administered twice at time 0h and 16h for a total dose of 20 mg. The objective is to explore a non-extended release BID regimen for 14d.

Part 2, Cohort 2 would evaluate 27 mg daily administered as 9 doses of 3 mg hourly from time 0 to time 8h daily for 14 days. The objective would be to administer the compound in a way that results in exposures more closely resembling an extended release formulation.

Part 2, Cohort 3 would evaluate either 9 mg daily administered as 9 doses of 1 mg hourly from time 0 to time 8h or 45 mg daily as 9 doses of 5 mg hourly from time 0 to time 8h. The choice of the hourly 1 mg versus 5 mg would depend on whether PD was observed in Part 2, Cohort 2. The objective would be to administer the compound in a way that results in exposures more closely resembling an extended release formulation and to more narrowly confirm the target threshold for PD activity.

The predicted exposures relative to the dog NOAEL for the proposed additional Part 1 cohorts is found in Table 5. Neither the predicted human Cmax, nor the predicted human AUC is expected to exceed the dog NOAEL.

List of Specific Changes

NOTE: for PREVIOUS TEXT, the content is exactly as in the original; for REVISED TEXT, text deleted from the original has a dotted underline and text added has a solid underline.

Change 1: Title Page

PREVIOUS TEXT

Author(s):

PPD

REVISED TEXT

Author(s):

PPD

RATIONALE

Administrative: One author was removed as he has left the project. One author was added who is new to the project and contributed to the amendment.

Change 2: Title Page

PREVIOUS TEXT

Copyright 2016 the GlaxoSmithKline group of companies. All rights reserved. Unauthorised copying or use of this information is prohibited.

REVISED TEXT

Copyright 2017 the GlaxoSmithKline group of companies. All rights reserved. Unauthorised copying or use of this information is prohibited.

RATIONALE

Copyright date was updated.

Change 3: Section 2 Objective(s) and Endpoint(s)

PREVIOUS TEXT

Objectives	Endpoints
Exploratory	
Part 2 14d Repeat Dose **Part 3 28d Repeat Dose**	**Part 2 14d Repeat Dose** **Part 3 28d Repeat Dose**
To evaluate the change in serum lipid levels and weight after 14 daily repeat doses of GSK3008356 in healthy subjects and 28 daily repeat GSK3008356 doses in obese subjects.	Serum lipid panel, weight.
To evaluate the impact of evening dosing on tolerability.	Clinical monitoring/observation for adverse events with a focus on gastrointestinal findings and a stool scale.

REVISED TEXT

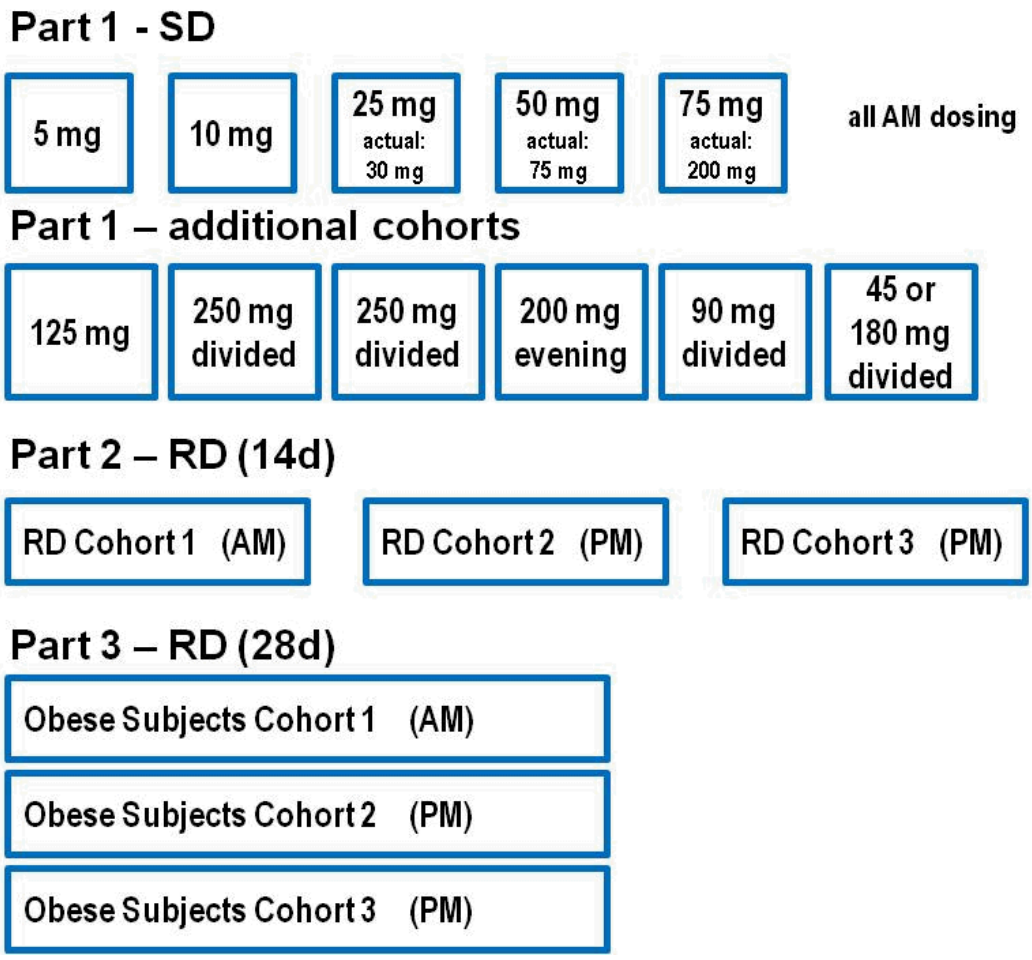
Objectives	Endpoints
Exploratory	
Part 2 14d Repeat Dose **Part 3 28d Repeat Dose**	**Part 2 14d Repeat Dose** **Part 3 28d Repeat Dose**
To evaluate the change in serum lipid levels and weight after 14 daily repeat doses of GSK3008356 in healthy subjects and 28 daily repeat GSK3008356 doses in obese subjects.	Serum lipid panel, weight.
To evaluate the impact of evening dosing on tolerability<u>.</u>	Clinical monitoring/observation for adverse events with a focus on gastrointestinal findings and a stool scale.
<u>To evaluate partitioning of GSK3008356 into skin in Part 2 only.</u>	<u>Skin biopsy for drug concentration and activity.</u>

RATIONALE

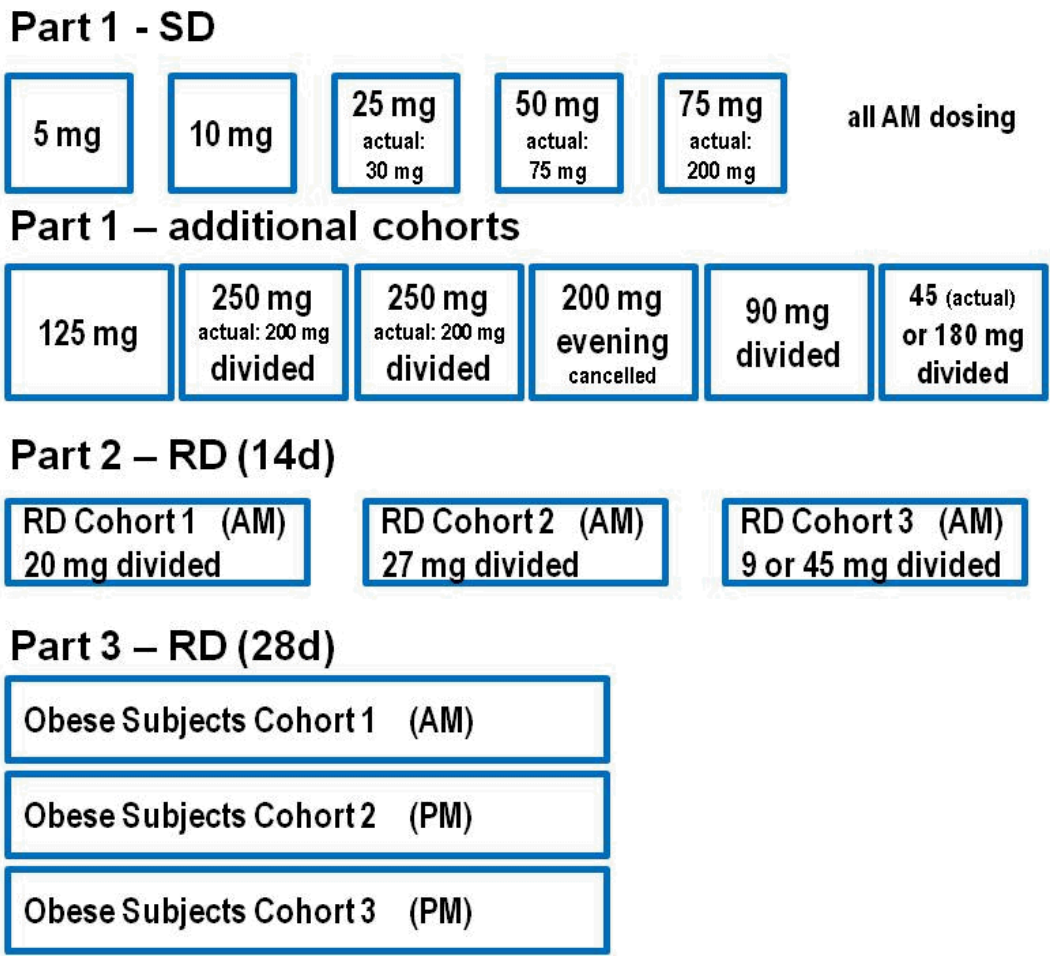
New text added to reflect the addition of skin biopsy to Part 2 of the study. A punctuation correction was also made.

Change 4: Figure 1 Study Part Schematic

PREVIOUS TEXT



REVISED TEXT



RATIONALE

The Figure was modified to reflect the actual doses administered and AM regimens in Part 2, Cohorts 1-3.

Change 5: New Section 3.1.2 Revised Dosing Regimens for Part 2

Based on preliminary PK data from Part 1, the doses and regimens are now better clarified for Part 2. Part 2 Cohorts 1, 2 and 3 will be administered in the AM as divided doses to achieve a daily time above the target exposure with varying levels of Cmax. Specifically, Cohort 1 will have a regimen of 2 doses separated by 16 hours similar to Part 1 Cohort 8. The purpose is to explore a BID PK profile. Cohorts 2 and 3 will have a regimen of nine hourly doses similar to Part 1 Cohorts 10 and 11. The purpose is to explore PK profiles that approximate a sustained release formulation to guide further dosage development. There will be no changes to the current challenge meal or assessments except for the addition of a skin biopsy outlined in Section 6.4.5.

The regimens are as follows:

Part 2, Cohort 1 would evaluate 10 mg administered twice at time 0h and 16h for a total dose of 20 mg.

Part 2, Cohort 2 would evaluate 27 mg daily administered as 9 doses of 3 mg hourly from time 0 to time 8h daily for 14 days.

Part 2, Cohort 3 would evaluate either 9 mg daily administered as 9 doses of 1 mg hourly from time 0 to time 8h or 45 mg daily as 9 doses of 5 mg hourly from time 0 to time 8h.

Neither the predicted human Cmax, nor the predicted daily human AUC of evaluated doses is expected to exceed the dog NOAEL exposure of Cmax (7.73 µg/mL) and AUC(0-t) (111 µg.h/mL).

However, data from a 13-week oral toxicity study in dogs indicate that the NOAEL for dosing duration >28 days will likely be lower than the current NOAEL. While these dog data do not impact the risk for this protocol as they do not change the NOAEL (Section 3.5.1), these data will impact the future viability of certain dose regimens.

The regimens selected for Part 2 as outlined above are regimens have future development viability based on human exposure below the oral 13-week repeat dose dog testicular observation NOAEL exposure of Cmax (0.642 µg/mL) and AUC(0-t) (5.49 µg.h/mL).

The highest dose regimen planned for Part 3 (45 mg daily as 9 doses of 5 mg hourly from time 0 to time 8h) is expected to result in the highest Part 2 Cmax (0.203 µg/mL) and AUC (1.261 µg.h/mL) exposure, based on Part 1 data.

These predicted exposures are still 3.2-fold and 4.4-fold below the oral 13-week repeat dose dog testicular observation NOAEL Cmax and AUC exposure, respectively. The predicted exposures are 38.1-fold and 88.1-fold below the current NOAEL Cmax and AUC exposure, respectively.

RATIONALE

The section was added to provide clarification, background and information regarding the selected regimens for Part 2, Cohorts 1-3. The section also creates context for the expected Part 2 maximal exposure compared to the 13-week dog oral toxicity study testicular observation NOAEL. The context defines dose regimens with future development viability.

Change 6: Section 3.2 Type and Number of Subjects

NEW TEXT

Subjects in Parts 1 and 2 will be randomized such that 6 subjects receive GSK3008356 and 2 subjects receive matching placebo in each cohort of 8 subjects. Subjects in Part 3

will be randomized such that 8 subjects receive GSK3008356 and 2 subjects receive matching placebo in each cohort of 10 subjects.

RATIONALE

The new wording was added at the end of Section 3.2 to clarify the allocation of active versus placebo in the completed Part 1 cohorts and the upcoming Parts 2 and 3 cohorts.

Change 7: Section 3.5.1 Risk Assessment

PREVIOUS TEXT

Potential Risk of Clinical Significance and Summary of Data/Rational for Risk	Impact on eligibility criteria	Mitigation Strategy
Investigational Product (IP) [e.g., GSK3008256]		
Hepatic Effects Oral 7d repeat dose dog study: Minimal to mild, focal hepatocellular degeneration/necrosis was observed (minimal in one female given 50 mg/kg/day; minimal to mild in the male and female given 200 mg/kg/day). Minimal mixed inflammatory cell infiltrates within liver sinusoids noted for the female given 200 mg/kg/day. Clinical pathology findings included increases in alanine aminotransferase (ALT) (up to 1.96X baseline), increases in aspartate aminotransferase (AST) (up to 1.76X baseline), increased glutamate dehydrogenase (GLDH) (to 3.8X baseline) at all dose levels. Increased total bile acid concentrations (to 3.2X baseline) and decreased plasma albumin and total protein concentrations (to 0.90X baseline) were noted at various testing intervals for dogs given 50 or 200 mg/kg/day. These changes may be related to hepatocellular injury and/or associated with reduced food consumption. Oral 28d repeat dose dog study: Increases ALT were noted for males and females given 2, 5 and 50 mg/kg/day at Week 1 (ranging from1.88X to 2.5X baseline). By Week 4, increases were 1.72X to 2.2X baseline values. The ALT increases were not progressive with continued dosing. There were no correlative liver histopathology findings. Oral 7d and 28 repeat dose rat study: No hepatic related findings. HepatoTaq: No significant findings.	Exclusion criterion #1: ALT and bilirubin > 1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). Exclusion criterion #2: Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Exclusion criterion #6 History of regular alcohol consumption within 6 months of the study. Exclusion criterion #10: A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening.	Sentinel dosing – staggered dosing in 2 subjects in Part 1 Cohort 1 prior to enrolment of the remainder of Cohort 1. LFT evaluation planned at baseline, day 2, day 4, day 7, day 14, day 21, day 28, and also as indicated. Exclusion criteria as noted in column 2. Stopping criterion of ALT ≥3xULN with no rechallenge of drug product.

Potential Risk of Clinical Significance and Summary of Data/Rational for Risk	Impact on eligibility criteria	Mitigation Strategy
Gastrointestinal Tolerability Oral 7d and 28d repeat dose dog study: In the 28d study, excessive salivation was observed for males given ≥2 mg/kg/day. Dose-related effects on body weight (decreased body weight gain or body weight loss) and/or reduced food consumption were observed in both studies. Oral 7d and 28d repeat dose rat study: Non-dose related decreases in mean body weight gain for rats were observed in the 7day study. No effects on body weight were noted in the 28 day rat study. Scientific Literature: Clinical DGAT1 inhibition may result in dose limiting nausea, vomiting and, watery (non-malabsorption) diarrhea which stopped upon discontinuation of dosing. (Denison 2014; Meyers 2015).	Exclusion criterion #4: Current or chronic history of gastrointestinal illness or conditions interfering with normal gastrointestinal anatomy or motility. Examples include gastrointestinal bypass surgery, cholecystectomy, partial or total gastrectomy, small bowel resection, vagotomy, malabsorption, Crohn's disease, ulcerative colitis, IBS, or celiac sprue.	Diarrhea scale (Bristol Stool Form Scale) and frequency of stool (Section 6.5.2). Subject may be withdrawn at any time at the discretion of the investigator for safety.
Dermal Effects Oral 7d and 28d repeat dose dog study: In the 28 day study, dose-related, minimal to mild atrophy of the sebaceous glands was observed and was considered to be related to pharmacology. Oral 7d and 28 repeat dose rat study: No dermal-related findings. Scientific Literature: DGAT1 inhibition may result in sebaceous gland atrophy and alopecia as observed in animal studies (Floettmann 2015), but similar effects have not been reported in clinical trials to date.	None	Subject may be withdrawn at any time at the discretion of the investigator for safety.

Potential Risk of Clinical Significance and Summary of Data/Rational for Risk	Impact on eligibility criteria	Mitigation Strategy
Cardiovascular Effects Single dose cardiovascular rat and dog studies: In rats, transient increases in heart rate (17%) and blood pressure (18%) were observed at 100 mg/kg but not as 30 and 300 mg/kg. The increases in both heart rate and blood pressure produced a transient increase in rate-pressure-product (RPP; an index of cardiac workload; 37%), Because similar changes were not observed at the highest evaluated dose of 300 mg/kg, a clear relationship to GSK3008356 administration was not established. No acute effects on cardiovascular function were noted in dogs. Oral 28d dog study : No cardiovascular-related findings (ECG assessments performed in the 28 day study). Rabbit left ventricular wedge assay: No effects on QT interval, transmural dispersion of repolarization, QRS duration or contractility (concentrations of up to 10 μM). hERG: IC_{25} value was estimated to be 85.7 μM (31.49 μg/mL). Insufficient inhibition of hERG occurred to allow for the reliable estimation of an IC_{50} value. The estimated IC_{25} value is >150X greater than the estimated free C_{max} in humans at the maximum predicted clinical efficacious dose of 43 mg. Based on the low magnitude and transient nature of the heart rate and blood pressure increases noted in rats and the low risk for QT prolongation (based on in vitro findings), the risk for CV effects in humans is considered low.	Exclusion criterion #3: QTcF < 450 msec.	Monitoring via telemetry (day 1), 12-lead ECG, and vital signs monitoring. Stopping Criteria (Section 4.5.2): QTcF > 500 msec QTc change from baseline > 60 msec.

REVISED TEXT

Potential Risk of Clinical Significance and Summary of Data/Rationale for Risk	Impact on eligibility criteria	Mitigation Strategy
Investigational Product (IP) [e.g., GSK3008256]		
Hepatic Effects Oral 7d repeat dose dog study: Minimal to mild, focal hepatocellular degeneration/necrosis was observed (minimal in one female given 50 mg/kg/day; minimal to mild in the male and female given 200 mg/kg/day). Minimal mixed inflammatory cell infiltrates within liver sinusoids noted for the female given 200 mg/kg/day. Clinical pathology findings included increases in alanine aminotransferase (ALT) (up to 1.96X baseline), increases in aspartate aminotransferase (AST) (up to 1.76X baseline), increased glutamate dehydrogenase (GLDH) (to 3.8X baseline) at all dose levels. Increased total bile acid concentrations (to 3.2X baseline) and decreased plasma albumin and total protein concentrations (to 0.90X baseline) were noted at various testing intervals for dogs given 50 or 200 mg/kg/day. These changes may be related to hepatocellular injury and/or associated with reduced food consumption. Oral 28d and 13 week repeat dose dog studies: Increases ALT were noted for males and females given 2, 5 and 50 mg/kg/day at Week 1 (ranging from1.88X to 2.5X baseline). By Week 4, increases were 1.72X to 2.2X baseline values. The ALT increases were not progressive with continued dosing. There were no correlative liver histopathology findings. Similar increases in ALT (up to 2.71X baseline) and AST (up to 1.57X) were observed in the 13 week study (evaluating doses up to 60 mg/kg/day) and were reversible following a 4-week off-treatment period. Oral 7d and 28 repeat dose rat study: No hepatic related findings.	Exclusion criterion #1: ALT and bilirubin > 1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). Exclusion criterion #2: Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). Exclusion criterion #6 History of regular alcohol consumption within 6 months of the study. Exclusion criterion #10: A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening.	Sentinel dosing – staggered dosing in 2 subjects in Part 1 Cohort 1 prior to enrolment of the remainder of Cohort 1. LFT evaluation planned at baseline, day 2, day 4, day 7, day 14, day 21, day 28, and also as indicated. Exclusion criteria as noted in column 2. Stopping criterion of ALT ≥3xULN with no rechallenge of drug product.

Potential Risk of Clinical Significance and Summary of Data/Rationale for Risk	Impact on eligibility criteria	Mitigation Strategy
Oral 13 week repeat dose rat study: Increased liver weights (to 1.2X mean control) were observed in female rats given 1000 mg/kg/day with no clinical pathology or microscopic correlates. HepatoTaq: No significant findings.		
Gastrointestinal Tolerability Oral 7d, 28d, and 13 week repeat dose dog studies: In the 28d study, excessive salivation was observed for males given ≥2 mg/kg/day. Dose-related effects on body weight (decreased body weight gain or body weight loss) and/or reduced food consumption were observed in all studies. Increased frequency of fecal abnormalities (unformed/ stool/mucous and/or watery) were observed in the 13 week study. Oral 7d, 28d, and 13 week repeat dose rat studies: Non-dose related decreases in mean body weight gain for rats were observed in the 7day study. No effects on body weight were noted in the 28 day and 13-week rat studies. Scientific Literature: Clinical DGAT1 inhibition may result in dose limiting nausea, vomiting and, watery (non-malabsorption) diarrhea which stopped upon discontinuation of dosing. (Denison 2014; Meyers 2015).	Exclusion criterion #4: Current or chronic history of gastrointestinal illness or conditions interfering with normal gastrointestinal anatomy or motility. Examples include gastrointestinal bypass surgery, cholecystectomy, partial or total gastrectomy, small bowel resection, vagotomy, malabsorption, Crohn's disease, ulcerative colitis, IBS, or celiac sprue.	Diarrhea scale (Bristol Stool Form Scale) and frequency of stool (Section 6.5.2). Subject may be withdrawn at any time at the discretion of the investigator for safety.

Potential Risk of Clinical Significance and Summary of Data/Rationale for Risk	Impact on eligibility criteria	Mitigation Strategy
Dermal Effects Oral 7d, 28d, and 13 week repeat dose dog studies: Dose-related, minimal to moderate atrophy of the sebaceous glands was observed and was considered to be related to pharmacology. Finding was reversible in the 13 week study following a 4-week off-dose period. Oral 7d, 28d, and 13 week repeat dose rat studies: No dermal-related findings. Scientific Literature: DGAT1 inhibition may result in sebaceous gland atrophy and alopecia as observed in animal studies (Floettmann 2015), but similar effects have not been reported in clinical trials to date.	None	Subject may be withdrawn at any time at the discretion of the investigator for safety.
Testicular Effects Oral 7d and 28d repeat dose dog study: No effects in testes or epididymides observed at doses up to 200 mg/kg/day for 7d and up to 50 mg/kg/day for 28d. Oral 7d, 28d and 13w repeat dose rat study: No effects in testes or epididymides observed at doses up to 300 mg/kg/day for 7d and 28d and up to1000 mg/kg/day for 13w. Oral 13w repeat dose dog study: Minimal to mild degeneration of the testicular seminiferous tubule epithelium with secondary changes within the epididymides (luminal germ cell debris and/or reduced sperm) was observed in terminal dogs given ≥ 30 mg/kg/day. Following the end of the 4-week off-dose period, testicular degeneration was still present in dogs given 60 mg/kg/day and is not unexpected given the long spermatogenic cycle in dogs (typically 90 days).	None	While there is no impact on the study NOAEL, dose regimen selection will be based regimens which will result in human exposure below the oral 13w repeat dose dog testicular observation NOAEL exposure of Cmax (0.642 µg/mL) and AUC(0-t) (5.49 µg.h/mL). Subject may be withdrawn at any time at the discretion of the investigator for safety.

Potential Risk of Clinical Significance and Summary of Data/Rationale for Risk	Impact on eligibility criteria	Mitigation Strategy
Cardiovascular Effects Single dose cardiovascular rat and dog studies: In rats, transient increases in heart rate (17%) and blood pressure (18%) were observed at 100 mg/kg but not as 30 and 300 mg/kg. The increases in both heart rate and blood pressure produced a transient increase in rate-pressure-product (RPP; an index of cardiac workload; 37%), Because similar changes were not observed at the highest evaluated dose of 300 mg/kg, a clear relationship to GSK3008356 administration was not established. No acute effects on cardiovascular function were noted in dogs. Oral 28d and 13 week dog studies: No cardiovascular-related findings (ECG assessments). Rabbit left ventricular wedge assay: No effects on QT interval, transmural dispersion of repolarization, QRS duration or contractility (concentrations of up to 10 μM). hERG: IC_{25} value was estimated to be 85.7 μM (31.49 μg/mL). Insufficient inhibition of hERG occurred to allow for the reliable estimation of an IC_{50} value. The estimated IC_{25} value is >150X greater than the estimated free C_{max} in humans at the maximum predicted clinical efficacious dose of 43 mg. Based on the low magnitude and transient nature of the heart rate and blood pressure increases noted in rats and the low risk for QT prolongation (based on in vitro findings), the risk for CV effects in humans is considered low.	Exclusion criterion #3: QTcF < 450 msec.	Monitoring via telemetry (day 1), 12-lead ECG, and vital signs monitoring. Stopping Criteria (Section 4.5.2): QTcF > 500 msec QTc change from baseline > 60 msec.

Potential Risk of Clinical Significance and Summary of Data/Rationale for Risk	Impact on eligibility criteria	Mitigation Strategy
Study Procedures		
Skin Biopsy Complications of punch skin biopsy are uncommon but may include bleeding, infection, and scarring. Bleeding and infection risk are very uncommon with underlying disease conditions (hemophilia, diabetes, older age, and immunosuppression) slightly increasing the risk. Scarring risk is increased in individuals with a history of scarring.	Exclusion criterion #5: History of risk for or actual experience of complications from skin biopsy including excess bleeding, infection, or scarring/keloid formation.	Observation of the subject while in the clinical unit and at follow-up after discharge from the unit. Subject may be withdrawn at any time at the discretion of the investigator for safety.

RATIONALE

New section added to the Risk Assessment section to provide detail regarding the 13-week dog oral toxicity study testicular observation NOAEL. Details from the 13 week dog and 13 week rat oral toxicity studies regarding risk in other organ systems were also added. Detail regarding the risk for Skin biopsy was also added. A spelling error in the column heading was also corrected.

Change 8: Section 4.2 Exclusion Criteria

NEW TEXT

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
5. History of risk for or actual experience of complications from skin biopsy including excess bleeding, infection, or scarring/keloid formation (Part 2 only).

RATIONALE

The new exclusion criterion added to mitigate the risk of complications from the skin biopsy procedure.

Note that the exclusion criteria previously numbered 5 through 15 were re-numbered 6 through 16 to accommodate the new criterion number 5 inserted into the Concurrent Conditions/Medical History section.

Change 9: Table 7 Regimen Description in Section 5.2 Treatment Assignment

PREVIOUS TEXT

Regimen Code	Study Medication	Regimen Code	Study Medication
AA	5 mg GSK3008356, morning dosing	AP	5 mg GSK3008356, evening dosing
BA	10 mg GSK3008356, morning dosing	BP	10 mg GSK3008356, evening dosing
CA	25 mg GSK3008356, morning dosing	CP	25 mg GSK3008356, evening dosing
DA	50 mg GSK3008356, morning dosing	DP	50 mg GSK3008356, evening dosing
EA	75 mg GSK3008356, morning dosing	EP	75 mg GSK3008356, evening dosing
FA	Matched placebo, morning dosing	FP	Matched placebo, evening dosing
GA	125 mg GSK3008356, morning dosing	JA	200 mg GSK3008356, evening dosing
HA	125 mg GSK3008356 q4h x 2 doses, morning dosing	KA	10 mg GSK3008356 q1h x 9 doses, morning dosing
IA	125 mg GSK3008356 q16h x 2 doses, morning dosing	LA	5 mg GSK3008356 q1h x 9 doses, morning dosing
		MA	20 mg GSK3008356 q1h x 9 doses, morning dosing

REVISED TEXT

Regimen Code	Study Medication	Regimen Code	Study Medication
AA	5 mg GSK3008356, morning dosing	AP	5 mg GSK3008356, evening dosing
BA	10 mg GSK3008356, morning dosing	BP	10 mg GSK3008356, evening dosing
CA	25 mg GSK3008356, morning dosing	CP	25 mg GSK3008356, evening dosing
DA	50 mg GSK3008356, morning dosing	DP	50 mg GSK3008356, evening dosing
EA	75 mg GSK3008356, morning dosing	EP	75 mg GSK3008356, evening dosing
FA	Matched placebo, morning dosing	FP	Matched placebo, evening dosing
GA	125 mg GSK3008356, morning dosing	LA	5 mg GSK3008356 q1h x 9 doses, morning dosing
HA	125 mg GSK3008356 q4h x 2 doses, morning dosing	MA	20 mg GSK3008356 q1h x 9 doses, morning dosing
IA	125 mg GSK3008356 q16h x 2 doses, morning dosing	NA	10 mg GSK3008356 q16h x 2 doses, morning dosing
JA	200 mg GSK3008356, evening dosing	OA	3 mg GSK3008356 q1h x 9 doses, morning dosing
KA	10 mg GSK3008356 q1h x 9 doses, morning dosing	PA	1 mg GSK3008356 q1h x 9 doses, morning dosing

RATIONALE

The new text (Regimens NA, OA, and PA) provides detail for the doses planned for the Part 2 Cohorts. Note the previously included Regimen LA is also a planned dose option for Part 2. The table position of previously included Regimens JA, KA, LA, and MA were moved for formatting purposes.

Change 10: Section 6 Study Assessments and Procedures

PREVIOUS TEXT

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
    1. 12-lead ECG
    2. vital signs
    3. blood draws.

REVISED TEXT

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
    1. 12-lead ECG
    2. vital signs
    3. blood draws
    4. skin biopsy.

RATIONALE

The skin biopsy procedure was added to the procedure order list.

Change 11: Time and Events Table: Section 6.1.2 Part 2 – Repeat Dose, Morning Dose Administration, Screening, Day -1, Day 1

NEW TEXT

Citation 10 and Footnote 10 added for Study Drug Dose

10. 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.

RATIONALE

The addition of citation 10 and the corresponding footnote text clarifies time 0 for cohorts where regimens consisting of multiple doses are to be administered.

Change 12: Time and Events Table: Section 6.1.3 Part 2 – Repeat Dose, Morning Dose Administration, Days 2-13

NEW TEXT

Citation 6 and Footnote 6 added for Study Drug Dose

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.

RATIONALE

The addition of citation 6 and the corresponding footnote text clarifies time 0 for cohorts where regimens consisting of multiple doses are to be administered.

Change 13: Time and Events Table: Section 6.1.4 Part 2 – Repeat Dose, Morning Dose Administration, Days 14-17, Follow-up

NEW TEXT

Citation 6 and Footnote 6 added for Study Drug Dose

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.

Skin biopsy row added

	Day 14													Day 15	Day 16	Day 17	**Follow Up**
	Pre-dose	0h	0.25h	0.5h	1h	1.5h	2h	4h	6h	8h	12h	18h	24h	36h	48h	72h	**(Day 20-22)**
Skin Biopsy[7]					X[7]				X[7]				X[7]				

Citation 7 and Footnote 7 added for Skin biopsy

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

RATIONALE

The addition of citation 6 and the corresponding footnote text clarifies time 0 for cohorts where regimens consisting of multiple doses are to be administered. The skin biopsy procedure was added as an assessment. Citation 7 and the corresponding footnote clarify that only two biopsies are to be collected on Day 14 for each cohort. Footnote 7 also clarifies the collection times in each cohort.

Change 14: Time and Events Table: Section 6.1.8 Part 2 – Repeat Dose, Fat Meal Challenge and Triglyceride Assessment Relative to Dose and PK Sampling, 6.1.8.1. Morning Dose Administration, Day -1, Day 1, and Day 14

PREVIOUS TEXT

Footnote 1:

1. Day 1 and 14 only.

NEW TEXT

Footnote 1:

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.

RATIONALE

The addition to footnote 1 clarifies time 0 for cohorts where regimens consisting of multiple doses are to be administered.

Change 15: New Section 6.4.5 Skin Biopsy Sample Collection and Analysis

Skin biopsy for PK analysis and activity of GSK3008356 will be collected at the time points indicated in the Time and Events Tables (Section 6.1). The actual date and time of each sample collection will be recorded.

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 samples 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 (detailed in the SRM). All skin biopsy analysis results will be reported under a separate PTS-DMPK protocol.

RATIONALE

The new section details skin biopsy collection, analysis and reporting.

Change 16: Section 8.4.3 Other Analyses

PREVIOUS TEXT

Please refer to Section 6.4.4.

NEW TEXT

Please refer to Section 6.4.4 and Section 6.4.5.

RATIONALE

The addition is to clarify that other analysis will take place for the skin biopsy as described in the skin biopsy section (Section 6.4.5).

Change 17: Section 11.1 Appendix 1 – Abbreviations and Trademarks

NEW TEXT

Abbreviations added:

LC MS/MS	liquid chromatography tandem mass spectrometry
MALDI	matrix assisted laser desorption/ionization
SLiP	skin lipogenesis (assay)

RATIONALE

Abbreviations in the amendment text were added to the table.