TITLE PAGE

Division: Worldwide Development

Title:	A single-center, randomized, blinded, placebo-controlled two-part study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of the Selective Androgen Receptor Modulator (SARM), GSK2849466, in single and repeat doses, with and without food, in healthy male subjects

Compound Number: GSK2849466

Effective Date: 10-AUG-2012

Description: This study is the first administration of GSK2849466 in humans. This will be a single centre, randomized, placebo-controlled study, to investigate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of GSK2849466, given as single and repeat oral doses of up to 14 days to healthy male subjects 18-50 years of age. This study will be double-blind with respect to subjects, investigator and site staff (with the exception of the site pharmacist). The Sponsor, GSK, will be unblinded.

Part A will consist of two cohorts of 8 subjects to assess the safety, tolerability, and PK of ascending single oral doses of GSK2849466. Cohorts 1 and 2 will include healthy male subjects and all available safety, tolerability, and PK data will be reviewed prior to each dose escalation. The first ("bridging dose") dose provided to subjects in Cohort 2 will be the same as the last dose provided to subjects in Cohort 1.

Part B (Cohorts 3, 4 and 5) will include three cohorts of 12 healthy male subjects to examine the safety, tolerability, PK, and PD of repeated doses of GSK2849466 over 14 days. The doses chosen for Part B will be based on the safety, tolerability, and PK data from Part A. Subjects in Cohort 4 (and/or an another cohort(s) as determined based on Part A PK data) will be dosed in the fasted state on Days 1 and 14 and in the fed state on Day 7 when subjects will receive a standard meal 30 minutes prior to dosing.

Subject: FTIH, SARM, pharmacokinetics, safety

Author(s): [redacted] (CPSSO), [redacted] (Clinical Matrix Leader), [redacted] (Clinical Statistics), [redacted] (PTS DMPK), [redacted] (PTS PD), [redacted] (Safety Assessment), and [redacted] (Early Development Leader-Discovery Medicine)

SPONSOR SIGNATORY:

[redacted] 10 Aug 2012

[redacted] MD, PhD, FACP **Date**
Project Physician and Early Development Leader
Senior Director - Discovery Medicine, MM-DPU,
MPC-TU

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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.

Regulatory Agency Identifying Number(s): US IND Number 115580

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- 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 clinical 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 Address:		
Investigator Phone Number:		
Investigator Signature		Date

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
BMI	Body mass index
BP	Blood pressure
BPM	Beat Per Minute
BUN	Blood urea nitrogen
CL	Systemic clearance of parent drug
Cmax	Maximum observed concentration
Cτau	Pre-dose (trough) concentration at the end of the dosing interval
Ct	Last observed quantifiable concentration
CPK	Creatine phosphokinase
CPSR	Clinical Pharmacology Study Report
CRF	Case Report Form
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
FTIH	First time in humans
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilence
GGT	Gamma glutamyltransferase
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
HR	Heart rate
IB	Clinical Investigator's Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDSL	Integrated Data Standards Library
IND	Investigational New Drug
IRB	Institutional Review Board
kg	Kilogram

L	Liter
LFTs	Liver function tests
µg	Microgram
µL	Microliter
MABEL	Minimally active biological effect level
MAT	Mean absorption time
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligrams
mL	Milliliter
MRT	Mean residence time
MSDS	Material Safety Data Sheet
msec	Milliseconds
PBO	Placebo
PD	Pharmacodynamic
PGx	Pharmacogenetics
PK	Pharmacokinetic
QC	Quality control
QD	Once daily
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBA	Relative Bioavailability
RBC	Red blood cells
RD	Repeat dose
SAD	Single ascending dose
SAE	Serious adverse event(s)
SARM	Selective Androgen Receptor Modulator
SAS	Statistical Analysis Software
SD	Standard deviation
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard Operating Procedure
SPM	Study Procedures Manual
T	Infusion duration
t	Time of last observed quantifiable concentration
t½	Terminal phase half-life
τ	Dosing interval
tlag	Lag time before observation of drug concentrations in sampled matrix
tlast	Time of last quantifiable concentration
tmax	Time of occurrence of Cmax
ULN	Upper limit of normal
US	United States
WBC	White blood cells

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1. INTRODUCTION

GSK2849466 is a non-steroidal, Selective Androgen Receptor Modulator (SARM) under investigation by GSK for treatment of mobility, disability and functional limitation in men and post-menopausal women with muscle loss associated with chronic illness. Conditions such as chronic heart failure, chronic obstructive pulmonary disorder, and chronic kidney disease can demonstrate significant muscle wasting and associated functional impairment, especially in advanced states. Physical therapy and exercise have been shown in these conditions to increase muscle mass and improve physical function. The use of the natural steroidal androgen receptor agonist, testosterone, has also been shown in these conditions to induce similar benefits. A non-steroidal, selective androgen receptor agonist can potentially act positively on muscle and bone while not adversely affecting the prostate gland in men, or inducing hirsutism or virilization in women.

This study is the first administration of the SARM GSK2849466 to humans. The purpose of the study is to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single and repeat doses of up to 14 days with GSK2849466 in healthy male subjects. This information would provide the necessary basis for further clinical studies to determine the safety of the compound with longer periods of dosing and to assess the efficacy on functional parameters.

1.1. Background

Currently, there are no medications approved by the United States Food and Drug Administration (FDA) for the treatment of muscle wasting disorders of any etiology. The scientific opportunity for the treatment of muscle-wasting and associated disorders is presented through the development of non-steroidal molecules that act via the androgen receptor in a cofactor/cellular/tissue-selective manner. SARMs bind to the androgen receptor inducing a unique receptor conformation which allows only certain co-activator and co-repressor proteins to interact. These unique receptor-cofactor ensembles confer differential regulation of target genes and other receptor-mediated pathways. The differential activity allows SARMs to function as potent androgens in target tissues such as muscle and bone, but function as antagonists, or partial agonists, in other tissues or organs such as the prostate or skin. Further, an appropriately selective SARM would be given to post-menopausal women without inducing hirsutism or virilisation, which occurs with steroidal androgen receptor modulators.

While no SARM has been approved for clinical use, there is growing clinical experience with this class of compounds. Enobosarm has been through a series of clinical studies and is now in a Phase 3 program evaluating the efficacy for treatment of muscle loss and functional impairment in cancer cachexia (Dalton, 2011). An additional SARM has shown both safety and increased lean body mass in repeat dosing in healthy volunteers (Basaria, 2012). This compound is planned to progress to Phase 2 programs in cancer cachexia. GSK also has clinical experience with a SARM, GSK971086. This compound completed a first-time-in-human study in healthy male volunteers, showing safety and expected effects on biomarkers. However, the program was discontinued because of unexpected toxicity in subsequent preclinical safety studies.

1.2. Study and Dose Rationale

1.2.1. Study Rationale

This study is the first administration of GSK2849466 to man. The study will evaluate the safety, tolerability, PK, and PD of single and repeat oral doses of GSK2849466 in healthy subjects. The intention of this study is to provide sufficient confidence in the safety of the molecule to inform progression to further repeat dose and proof of concept studies. The dose range proposed in this study is based on a low starting dose escalating to supra-therapeutic doses; see Section 1.2.2 and Section 3.5.2).

1.2.2. Dose Rationale

The planned doses for the first time in human single dose study of GSK2849466 are 0.01, 0.03, 0.1, 0.3, 1, 3, and 10mg. These doses were selected on the basis of predictions and preclinical data summarized below to attain exposures across a clinically relevant range spanning sub-therapeutic to higher than the expected clinical doses.

In a 7-day orchiectomized (ORX) rat model, 0.003, 0.01, 0.03, 0.1, and 0.3 mg/kg GSK2849466 demonstrated dose-dependent anabolic stimulation of the *levator ani* muscle. A dose of 0.001 mg/kg in this study provided minimal evidence for activity and thus represents the minimal effect level for anabolic effects in the *levator ani* muscle. Based on proportional scaling from the 0.01 mg/kg dose, this 0.001 mg/kg dose corresponds to an estimated AUC of 1.9 ng.h/mL. This estimated AUC is the current best estimate for the minimally active biological effect level (MABEL). The ED_{90} for *levator ani* efficacy was 0.01 mg/kg (approximately 19 ng.h/mL), which is the target clinical exposure. In comparison, doses of 0.03, 0.1 and 0.3 mg/kg exhibited increased activity in this study.

GSK2849466 has been evaluated in 5 and 14-day rat toxicity studies at doses of 0.05 – 10 mg/kg and 7 and 14-day dog toxicity study at doses of 0.25 – 6 mg/kg. No dose limiting responses have been observed; however, animals showed changes that were generally related to SARM pharmacology. Exposure in comparison to the clinical target (19 ng.h/mL) is large with rats exhibiting 744-763-fold and dogs 80-93-fold margins in the 14-day toxicity studies. Predicted human PK has been modelled on the basis of allometric scaling using preclinical PK derived in rat, and dog studies and *in vitro* hepatocyte incubations. These PK results and *in vitro* metabolism studies predict that GSK2849466 will be a moderate to high clearance drug in humans (~60% liver blood flow) with a volume of distribution of ~350 L.

Assuming moderate to high bioavailability and incorporating uncertainty around the allometric scaling derived parameters, a simulation model was developed to compute predicted human doses required to reach exposure targets based on the preclinical pharmacology and safety studies. To reach the MABEL exposure a dose of 0.23mg (0.14 – 0.37mg, 10th-90th percentiles) is predicted to be required. Likewise, the exposure at which the rat ED_{90} was achieved (19 ng.h/mL) corresponds to a dose in humans of 2.3mg (range 1.4 – 3.7mg).

Table 1 provides the target predicted exposures and the planned doses for the single ascending dose phase of the study. Along with safety and tolerability, the PK of GSK2849466 will be observed prior to each dose escalation and doses may be adjusted to reach the proposed AUC range for each escalation. Additionally, emergent clinical findings during dose escalation that are related to either safety or SARM pharmacology may result in further modifications to the targeted exposure ranges and corresponding doses.

Table 1 Predicted Exposures and Planned GSK2849466 Doses

Planned Dose, (mg)	Planned AUC targets, ng.h/mL			Predicted margin to efficacious exposure (fold)	Exposure Reference
	Median	10th Percentile	90th Percentile		
0.01	0.08	0.05	0.13	227	
0.03	0.25	0.16	0.39	76	
0.1	0.84	0.53	1.32	23	MABEL (1.9 ng.hr/mL)
0.3	2.52	1.58	3.95	7.6	
1	8.38	5.27	13.15	2.3	ORX Rat (ED_{90} 19 ng.hr/mL)
3	25.15	15.82	39.46	0.76	
10	83.85	52.74	131.53	0.23	

The maximal recommended starting dose based on FDA guidance was not used in defining the starting dose. Because an effect level apart from expected SARM pharmacology has not been reached, there is no NOAEL to base the maximal recommended starting dose calculation.

The two very low doses (0.01mg and 0.03mg) were selected because of this uncertainty, and provide a substantial margin based on biologic effect on the *levator ani* in the ORX rat model. The highest planned exposure (84 ng.h/mL) has been selected to provide a 4 to 5-fold margin over the rat ED90 clinical target. It is anticipated that this exposure will be achieved with a dose of approximately 10mg.

1.3. Summary of Risk Management

GSK has assessed this study for any risks that may exist to subjects taking part. Only healthy subjects will participate in this study. First-time-in-human clinical monitoring and a risk mitigation strategy (see Table 2) are in place to manage any potential risks.

1.3.1. First-time-in-human Acute Clinical Monitoring

In this first-time-in-human single and repeat dose study, evidence of acute clinical toxicity will be monitored, both via subjective reporting and by objective means (i.e., serial assessments of vital signs and clinical laboratory information). Consistent with GSK guidance for early phase studies, the single ascending dose cohorts in this study will be run in an accredited Phase I clinical research unit with previous experience in first-time-in-human trials and immediate access to hospital facilities for the treatment of medical emergencies. Subjects enrolled in Part A will reside at the study center for clinical monitoring before and after treatment and will be released from the clinic approximately 24 hours after receiving study medication in each of 4 treatment periods, provided there are no safety concerns.

Subjects in Part B will remain in the clinic from Day -1 through the completion of assessments on Day 15, when they will be released provided there are no safety concerns.

Because animal reproductive studies have not been conducted with GSK2849466, subject enrolment will be limited to males who agree to adhere to mandated contraception requirements (see Section 7.1).

1.3.2. Risk Management Strategy

GSK2849466 has not been previously administered to human subjects. Based on what is known of other compounds with a similar mechanism of action and findings in non-clinical studies of GSK2849466, potential risks have been identified. The potential risks to subjects in this study, along with the Sponsor's risk mitigation strategy with methods to monitor those risks, are summarized in Table 2. These strategies are in addition to the limitations on dose escalation (see Section 3.5 - Dose Adjustment/Stopping Criteria).

Table 2 Summary of Risk Management

Potential Risk	Risk Mitigation Strategy	Monitoring Implemented
Elevation of ALT and other liver function tests (AST, bilirubin, total and direct). This has been observed in a variety of SARMs, but was not observed in the 14-day toxicity study.	The following liver chemistry stopping criteria are in place: • ALT ≥ 3xULN This study will use standard follow-up procedures for Phase I studies for subjects who have met liver stopping criteria (see Section 3.5.1.1 and Section 12).	Frequent monitoring of liver function tests during both the single-dose and repeat-dose components of the study.
Effects on reproductive organs/tissues: • Women –ovaries and uterus • Men – testes, epididymis, and prostate gland. These are recognized effects of SARM pharmacology.	Females will not be enrolled in this study. Females in later studies will only be enrolled if post-menopausal. Males with PSA levels ≥ 2.5 ng/mL will be excluded.	Subjects in the repeat dose portion of this study will be monitored for changes in the following levels: • luteinizing hormone • follicle stimulating hormone • testosterone • dihydrotestosterone • sex hormone binding globulin • prolactin • inhibin B
Perturbation of other hormonal axes, in the unlikely event that GSK2849466 is not clinically selective.	Sponsor will monitor for unexpected effects in the repeat dose phase of study for appropriate hormones.	Subjects in the repeat dose portions of the study will be monitored for the following: • Adrenal o Corticotropin o Cortisol o Dehydroepiandrosterone sulfate • Metabolic o Insulin-like growth factor-1 o Insulin-like growth-factor Binding-protein 3 o Fasting Insulin and glucose
CPK elevation, is potentially an unexpected class effect of GSK2849466	Stopping criteria for CPK elevation in the absence of muscle injury: • If CPK is ≥4xULN and ≤8xULN, perform a repeat test • If CPK is >8xULN, subject will be withdrawn.	Monitoring of CPK levels in the single and in the repeat dose portions of the study.

Potential Risk	Risk Mitigation Strategy	Monitoring Implemented
Lowering of HDL levels - a class effect of SARMs.	Monitoring lipid profiles during the 14-day repeat dose exposure and, if decreased at Day 15, will be repeated at follow-up to confirm return to baseline levels following completion of study treatment.	Lipid panels will be monitored in the repeat dose portion of this study.
Coagulation parameters - aPPT was observed to be increased in rats and decreased in dogs in 14-day toxicity study.	Monitoring of coagulation parameters during the 14-day repeat dose exposure for clinically significant changes	PT with and without INR correction and aPTT will be monitored in the repeat dose portion of this study.
Monitoring of heart function - increase in absolute (not relative) heart weight was observed in female rats in 14-day toxicity study.	Monitoring of heart size and ejection fraction will be under taken in longer term studies of 12 weeks or more. Such monitoring would not provide useful information in a 14 day first-time-in-human study. ECGs will be performed, per FTIH standards, and biomarkers (including troponin and brain natriuretic protein) will be monitored in this study	Monitor ECGs (per first-time-in human standards) and biomarkers (troponin and brain natriuretic protein) in the repeat dose portion of the study.

2. OBJECTIVES AND ENDPOINTS

The objectives and endpoints for this study are provided in Table 3.

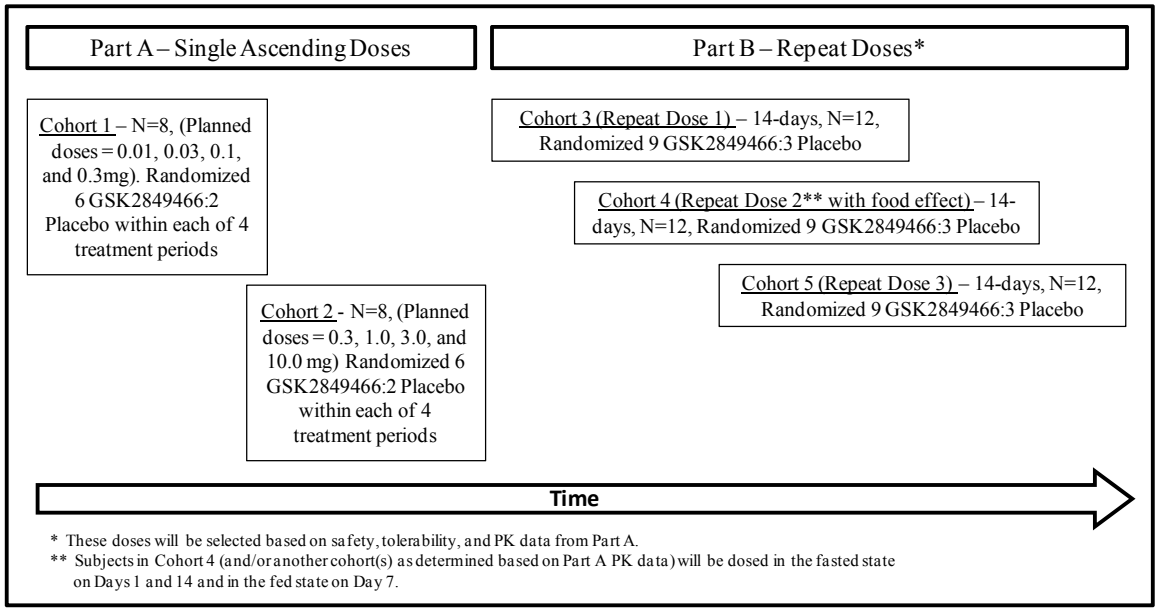
Table 3 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety and tolerability of single and repeat doses of GSK2849466 in healthy male subjects	Safety and tolerability of GSK2849466 as assessed by clinical monitoring of blood pressure, heart rate, cardiac telemetry, ECG and laboratory safety data, as well as reporting of AEs.
Secondary	
To characterise the PK profile of single doses of GSK2849466 in healthy male subjects	Derived PK parameters for GSK2849466, including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-\infty)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (T_{max}), and terminal half-life ($t_{1/2}$) following single doses, where data allow.
To characterise the PK profile of repeat doses of GSK2849466 in healthy male subjects 18-50 years of age, with and without food (Cohort 4 and/or another cohort(s) as determined based on Part A PK data).	In Part B - Derived PK parameters for GSK2849466, including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-\infty)}$, $AUC_{(0-\tau)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (T_{max}), and terminal half-life ($t_{1/2}$) following single and repeat doses, and estimation of an accumulation ratio where data allow.

Objectives	Endpoints
Exploratory	
To assess the effect, if any, of GSK2849466 on reproductive hormones, adrenal and metabolic hormones, and cardiovascular biomarkers during repeat dosing	In Part B – at pre-dose, Day 7, and Day 15 assess levels of: • reproductive hormones (i.e, leuteinizing hormone, follicle stimulating hormone, testosterone, dihydrotestosterone, sex hormone binding globulin, prolactin, and Inhibin B) • adrenal (i.e., corticotropin, cortisol, dehydroepiandrosterone sulfate) and metabolic hormones (i.e., Insulin-like growth factor-1, Insulin-like growth-factor Binding-protein 3, fasting insulin, and fasting glucose) and • cardiovascular biomarkers (brain natriuretic peptide and troponin).

3. INVESTIGATIONAL PLAN

3.1. Study Design/Schematic



This study will include approximately 52 subjects and consist of 2 parts:

1. Part A - randomized, placebo-controlled, 4-way crossover, and
2. Part B - randomized, placebo-controlled, parallel-group.

This study will be double-blind with respect to subjects, investigator and site staff (with the exception of the site pharmacist). The Sponsor, GSK, will be unblinded.

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 (see Section 3.6 Time and Events Tables), are essential and required for study conduct.

3.1.1. Study Duration

The study duration, including screening and follow-up, is not expected to exceed 70 days for subjects in the study (Table 4 and Table 5).

Table 4 Study Duration – Part A (Cohorts 1 and 2)

Screening	Approximately 28 days.
Number of Subjects	2 cohorts of 8 subjects each (N=16)
Treatment Period	Each cohort will be comprised of four study periods each approximately one week (7 days) in duration with subjects in-house for 2 nights (through 24 hours post-dose). During each treatment period, subjects will be admitted to the unit the day before dosing and will be discharged after completion of the 24-hour post-dose assessments.
Washout Period	Will be at least 6 days between treatment period doses for an individual subject
Follow-up	At least 7 days or 5 half lives (as determined from Part A PK data), whichever is longer, and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.

Table 5 Study Duration – Part B (Cohort 3, 4 and 5)

Screening	Approximately 28 days.
Number of Subjects	3 cohorts of 12 subjects each (N=36)
Treatment Period	Will be 14 days. Subjects will be admitted to the unit the day before dosing, will remain in the unit overnight, and will be released following completion of the assessments on Day 15, provided there are no safety concerns.
Follow-up	At least 7 days or 5 half lives (as determined from Part A PK data); whichever is longer, and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.

3.1.2. Part A (Cohorts 1 and 2)

Up to approximately 8 healthy subjects will be enrolled in each cohort of Part A. Each subject will participate in 4 dosing periods and receive one dose of study drug (GSK2849466 or matched-placebo) during each treatment period. Each subject will receive a total of 3 active doses and 1 placebo dose during the course of their participation in the study.

During each treatment period in Part A, subjects will report to the unit on Day -1 for assessments and a meal. Subjects will fast overnight (at least 8 hours) and be dosed the following morning on Day 1 followed by post-dose assessments. Subjects will be discharged following completion of the 24-hour post-dose assessments the next day.

3.1.2.1. Subject Dosing and Planned Doses

The single doses of GSK2849466 planned in Part A of this study are: 0.01, 0.03, 0.1, and 0.3 mg in Cohort 1 and 0.3, 1, 3, and 10 mg in Cohort 2. These planned doses may be adjusted based on findings in previous treatment sessions, but will not exceed 30 mg in a 24-hour period. The planned 0.3mg dose ("bridging dose") provided to subjects in the first treatment period of Cohort 2 will be the same as the last dose provided to subjects in Cohort 1.

first treatment period of Cohort 2 will be the same as the last dose provided to subjects in Cohort 1.

Doses in Part A will escalate from a low starting dose to a maximum safe and well-tolerated dose (provided that dose does not exceed 30 mg over a 24-hour period). The planned doses for both Cohorts 1 and 2 may be modified based on emerging data, such as the review of safety, tolerability and PK data. Progression from one dose level to the next dose level in Part A will be based on acceptable safety, tolerability and PK data.

Based on the very low starting doses (see Section 1.2.2) and experience with SARMs, which in general have been found to be clinically safe and well tolerated; sentinel dosing is not proposed for this study. The doses in the first two treatment periods of Cohort 1 (0.01mg and 0.03mg) are predicted to provide very low exposures, and could be regarded as "sentinel treatment periods" for any unexpected adverse findings. These findings are considered to be unlikely given the experience with SARMs as a class, and with internal SARM experience at GSK. Enobosarm has the most published data, and others have provided data in the literature or at presentations at meetings (Basaria, 2012; Dalton, 2011). The key safety findings for the SARM-class have been ALT elevation and HDL lowering, both occurring at low frequency within the efficacious dose range, and showing clear dose response. There have been no reports of idiosyncratic effects, especially on the immune system.

The dosing schedule in Part A may be adjusted to expand a cohort or to add an additional cohort(s) in order to further evaluate additional doses or repeat evaluation of a dose level already studied. Any dose that is greater than or equal to a dose that caused clinically significant adverse events will not be re-tested. The maximum daily systemic exposures will not intentionally exceed those described in Section 3.5.2. The study procedures and stopping criteria for these additional cohorts will be the same as those described for other study subjects in Part A of the study.

3.1.2.2. Dose Escalation/Selection/Frequency Decisions

Dose escalation decisions in Part A, including the determination of the next dose, will be made by the GSK Study Team with agreement of the Principal Investigator or delegate, based upon review of safety and available PK data from the previous dose(s) (see Section 3.5). The Principal Investigator, or delegate, and other relevant clinical staff will attend the review meeting to update the GSK Study Team on clinical observations from the previous dose level. The review data will, at minimum, consist of: any adverse events, liver function test results, vital signs, ECG and laboratory findings, and PK results derived from 24-hour plasma concentration time profiles.

3.1.3. Part B (Cohorts 3, 4, and 5)

Part B (Cohorts 3, 4, and 5) will be 3 cohorts of 12 healthy male subjects to examine the safety, tolerability and PK of a repeated dose of GSK2849466 over 14 days.

A progression to Part B from Part A will be based on an acceptable safety, tolerability and PK profile. The selection of appropriate doses for Part B will be performed upon consideration of available safety and tolerability and PK data from Part A and/or any

preceding repeat dose cohorts. The review data set will, at minimum, consist of: any adverse events, liver function test results, flagged vital signs, ECG and laboratory findings, and PK results derived from 24-hour plasma concentration time profiles. The dose in any cohort may be titrated down based on emerging safety, tolerability, and PK data from at least 4 subjects on active treatment.

On Day -1 subjects will report to the unit for assessments and a meal. The subjects will then fast overnight (at least 8 hours) and be dosed the following morning (Day 1). Post-dose, subjects will undergo safety and PK assessments. On Day 14, subjects will repeat these safety and PK assessments, also in a fasted state. Subjects in Cohort 4 (or another cohort(s) as determined based on Part A PK data) will be dosed in the fasted state on Days 1 and 14 and in the fed state on Day 7 when subjects will receive a standard meal 30 minutes prior to dosing. Each subject will remain in the unit overnight and be released following completion of the assessments on Day 15, provided there are no safety concerns.

Subjects will also report to the clinic for a follow-up visit approximately 7 days or 5 half lives (as determined from Part A PK data), whichever is longer, and no greater than 14 days after last study drug administration.

3.2. Discussion of Design

The study design has addressed regulatory recommendations for FTIH studies and pre-clinical findings for GSK2849466, contributing to the frequency, type and duration of safety assessment and monitoring during treatment periods during each cohort.

The sequential design of the single dose components (Part A) will allow for dose escalation to occur weekly, including at least 6-days of washout. This will allow any adjustment needed based on emerging safety, tolerability, and PK information.

In Part B, the 14-day dosing was chosen as it is thought to provide sufficient safety and tolerability data to bridge to longer duration studies.

3.3. Treatment Assignment

Subjects will be assigned to GSK2849466 or placebo in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

In both cohorts of Part A (Cohorts 1 and 2), subjects will be randomized to one of 4 treatment sequences. Within each period, allocation of active to placebo treatment will be 3:1. The treatment sequences are outlined in Table 6 and planned dose levels (DLs) are defined in Section 1.2.2.

Table 6 Treatment Sequences for Cohorts 1 and 2

Number of subjects (N=8)	Cohort 1			
	Period 1	**Period 2**	**Period 3**	**Period 4**
n=2	Placebo	DL 2	DL 3	DL 4
n=2	DL 1	Placebo	DL 3	DL 4
n=2	DL 1	DL 2	Placebo	DL4
n=2	DL 1	DL 2	DL 3	Placebo
Number of subjects (N=8)	**Cohort 2**			
	Period 1	**Period 2**	**Period 3**	**Period 4**
n=2	Placebo	DL 5	DL 6	DL 7
n=2	DL 4	Placebo	DL 6	DL 7
n=2	DL 4	DL 5	Placebo	DL 7
n=2	DL 4	DL 5	DL 6	Placebo

In each cohort of Part B (Cohorts 3, 4, and 5), approximately 12 subjects will be randomized to receive either GSK2849466 or placebo in a 3:1 randomization ratio resulting in 9 subjects receiving GSK2849466 and 3 subjects receiving placebo.

3.4. Investigational Product and Other Study Treatment Dosage/Administration

	Study Treatment	
Product name:	GSK2849466	Placebo
Dosage form:	Hot melt solution within capsule	Hot melt solution within capsule
Unit dose strength(s)/Dosage level(s):	Dose Strengths of 0.01, 0.1, 1.0, and 2.5 mg Planned Dose Levels of 0.01, 0.03, 0.1, 0.3, 1.0, 3.0, and 10.0 mg	NA
Route/ Administration/ Duration:	Oral Single ascending doses (Part A) or Repeat doses (Part B)	Oral Single ascending doses (Part A) or Repeat doses (Part B)
Dosing instructions:	Take as directed	Take as directed
Manufacturer/ source of procurement:	GlaxoSmithKline	GlaxoSmithKline
Method for individualizing dosage:	Pharmacist at the clinical site.	Pharmacist at the clinical site.

Hot melt solutions will be prepared by clinical staff pharmacists using detailed instructions contained within the Study Procedures Manual. GSK2849466 Hot Melt Solutions, ranging in concentration from 0.05 mg/g to 12.5 mg/g, will be prepared by the clinical staff pharmacists by weighing drug substance directly into specific quantities of the Hot Melt Vehicle Solution as defined within the Study Procedures Manual.

Clinical staff pharmacists will dispense 0.200 g aliquots of either Hot Melt Vehicle as placebo or GSK2849466 Hot Melt Solutions into HPMC capsules for administration to subjects. Subjects will take required number of capsules with water.

3.5. Dose Adjustment/Stopping Criteria

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum total daily dose will not exceed 30 mg of GSK2849466 and the exposure will not intentionally exceed 200 ng.h/mL for $AUC_{(0\text{-}inf)}$ allowing for an 8-fold margin of cover with respect to the 14 day dog NOAEL.

The decision to proceed to the next dose level of GSK2849466 in each part of this study will be made by the GSK Study Team, including the Medical Monitor and the investigator and relevant clinical site staff (see Section 10.1), based on safety, tolerability, and preliminary PK data obtained in at least 6 subjects (through at least 24 hours post-dose) with at least 4 subjects having received active treatment (GSK2849466) at the prior dose level. The actual doses to be administered may be adjusted based on safety, tolerability and preliminary PK data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose, but will not exceed pharmacokinetic criteria defined in Section 3.5.2.

Dosing will be suspended/may not continue if at least one SAE occurs that is reasonably attributable (in the opinion of the investigator) to study drug, or if AEs or unacceptable pharmacological effects occur in more than one subject that are:

- moderate or severe intensity,
- consistent across subjects in a group,
- reasonably attributable (in the opinion of the investigator) to dosing with the study drugs.

However, if any of the above defined conditions are met, dose escalations will not proceed as originally planned and a lower dose may be repeated.

3.5.1. Dose Adjustment/Stopping Safety Criteria

3.5.1.1. Liver Chemistry Stopping Criteria

Liver chemistry threshold 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).

Study treatment will be stopped for a subject if any of the following liver chemistry stopping criteria is met:

- ALT ≥ 3xULN

Refer to Section 12, Liver Chemistry Follow-up Procedures, for details of the required assessments if a subject meets the above criteria.

3.5.1.2. QTc Withdrawal Criteria

A subject that meets any criterion below will be withdrawn from the study. The QT correction formula used to determine discontinuation should be the same one used throughout the study.

- QTcF > 500 msec, OR
- Change from baseline: QTcF>60 msec
- For subjects with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTcF with bundle branch block	Discontinuation QTcF with bundle branch block
<450 msec	>500 msec
450-480 msec	≥530 msec

Withdrawal decisions are to be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period, and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

3.5.1.3. Other Dose Adjustment/Stopping Safety Criteria

Creatine phosphokinase (CPK) – A subject that meets the criterion below will be withdrawn from the study (provided the CPK elevation occurs in the absence of muscle injury):

- If CPK is ≥4xULN and ≤8xULN, perform a repeat test and
- If CPK is > 8xULN at any time, withdraw subject.
- If CPK on retest is <8xULN, the subject may continue with repeat labs every 24 hours until CPK is <4xULN.

Troponin, 3rd generation (cTnI) – dose administration should be withheld for any subject who has a clinically significant cTnI level during dosing. A repeat sample should be drawn for verification. Subjects with cTnI levels that have been confirmed to exceed 10ng/mL (or the given laboratory's level for clinical significance) should be withdrawn from investigational product dosing. Dose escalation will be paused until any such findings are evaluated.

Brain natriuretic peptide (BNP) –dose administration should be withheld for any subject whose BNP level meets either of the following criteria:

- BNP level has been confirmed to exceed 100pg/mL (or the given laboratory's level for clinical significance), **OR**
- BNP level has doubled over the subject's baseline value (even if the increased value remains within the normal range).

A repeat sample should be drawn for verification. Subjects should be withdrawn from investigational product administration if any of these findings is confirmed. Dose escalation will be paused until any such findings are evaluated.

3.5.2. Dose Adjustment/Stopping Pharmacokinetic Criteria

The intent of this study is to examine a range of exposures in plasma spanning what is anticipated to be sub-therapeutic to supra-therapeutic concentrations as described in Table 1. As such, doses may be adjusted to account for differences between predicted and actual observed PK. The targeted range of plasma concentrations is significantly below the AUC at the NOAEL in the 14-day dog study (end of study, gender mean AUC = 1650 ng.h/mL) the species with lower exposure. An absolute maximum plasma exposure of 200 ng.h/mL will not be intentionally exceeded (~5.6 x below the dog NOAEL Cmax of 1125 ng/mL). Dose escalation will be stopped if 2 or more subjects exceed 200 ng.h/mL at any given dose level, or if the mean predicted AUC for a subsequent is expected to exceed 200 ng.h/mL.

3.6. Time and Events Tables

3.6.1. Part A – Single Ascending Doses

Procedure	**Screening** (up to 28 days prior to Day 1)	**Study Day (each dosing session)**																**Follow-up Visit***
			Day 1 (time in hours relative to dosage)[1]														**Day 2**	
		Day -1	**Pre-dose**	**0 h**	**0.25h**	**0.5**	**0.75**	**1**	**1.5**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**24**	
Outpatient Visit	X																	X
Informed Consent	X																	
Medical/medication/drug/alcohol history	X																	
Demographics	X																	
Full Physical Examination[2]	X																	
Brief Physical Examination[2]		X																X
Drug / alcohol screen [3]	X	X																
HIV, Hep B and Hep C screen	X																	
Hema/Chem/Urinalysis tests	X	X															X	X
Cotinine testing	X	X																
Height and weight	X																	
4-hour Holter monitor	X																	
Prostate Specific Antigen	X																	
Telemetry				←=continuous at least 12 hrs post-dose=→														
12-lead ECG and vital signs[4]	T	T	T			T		T		T		T		T		T	T	T
Meals [5]		D								S		L			D		B	
Study treatment dosing				**X**														
PK Blood Sample			X		X	X	X	X	X	X	X	X	X	X		X	X	
PGx Sample		X																
Adverse Event Review		X		←==========												==========→		X
Concomitant Medication Review		X		←==========												==========→		X

For ECG and vital signs T=Triplicate; For Meals B=Breakfast, S=Snack, L=Lunch, D=Dinner (continued on next page)

Part A – Single Ascending Doses

***Note: Visit to occur approximately 7 days or 5 half lives (as determined from Part A PK data), whichever is longer, and no greater than 14 days after last study drug administration.**

1. Subjects to be admitted to the unit the day before dosing (Day -1), and remain in house until discharge after 24-hour post-dose assessments (Day 2) are completed.
2. Additional examinations may be performed, or brief examinations made full examinations, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate).
3. Drugs of abuse and alcohol assessments to be performed at screening and on Day -1 of each dosing period. Additional assessments may be performed at the discretion of the Investigator.
4. Timings will be reviewed as cohorts' progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts. Vital signs to include HR and BPs.
5. Prior to dosing on Day 1, subjects will fast for 8 hours overnight; no food will be allowed for at least 2 hours post-dose. Water will be allowed as desired. Subjects will receive standardised meals scheduled at the same time in each period of the study.

3.6.2. Part B – 14-day Repeat Dose

3.6.3. Time and Events by Study Day (Part B)

Procedure		Screening - (up to 28 days prior to Day -1)	Study Day(s)[1]															Follow-up Visit*
			-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	
Informed Consent		X																	
Medical/medication/drug/alcohol history		X																	
Demographics		X																	
Full Physical Examination[2]		X																X	
Brief Physical Examination[2]			X																X
Drug/alcohol screen[2]		X	X																
HIV, Hep B and Hep C screen		X																	
Cotinine testing		X	X																
Height and weight[3]		X	X							X								X	
4-hour Holter monitor		X																	
Prostate Specific Antigen		X																	
Telemetry (continuous at least 8 hrs post-dose)				X			X			X			X				X		
12-lead ECG[4]	Cohort 4 (or another cohort(s))	T	T	T	T		S			T	T		S				T	T	S
	Cohorts 3 and 5	T	T	T	T		S			S			S				T	T	S
Vital signs[4]	Cohort 4 (or another cohort(s))	T	T	T	T	S	S	S	S	T	T		S				T	T	S
	Cohorts 3 and 5	T	T	T	T	S	S	S	S	S			S				T	T	S
Hema/Chem/Urinalysis tests[5]		X	X		X		X			X			X					X	X
Meals served[6]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Treatment Dosing				**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
PK blood sample[7]				X	X		X	X	X	X	X						X	X	
PK Urine[8]			←X→														X	X	
Lipid Blood Sample[9]				X														X	X
CV Biomarker Sample[10]				X						X								X	
Exploratory Biomarker Sample[10]				X														X	
Adrenal / Metabolic / Reproductive Hormones[10]				X														X	
PGx Sample[8]			←X→																
AE assessment				←==========														==========→	
Concomitant Medication Review		X	←==========															==========→	X

For ECGs and vital signs T=Triplicate, S=Single (Continued on next page)

Part B – 14-day Repeat Dose

***Note: Visit to occur approximately 7 days or 5 half lives (as determined from Part A PK data), whichever is longer, and no greater than 14 days after last study drug administration.**

1. Subjects to be discharged after the 24-hour post-dose assessments are completed on Day 15.
2. Additional examinations may be performed, or brief examinations made full examinations, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate).
3. Only weight will be recorded on Days -1, 7, and 15.
4. Vital signs to include HR and BP. Single vital signs will be taken at pre-dose and at 2 hours (or at Tmax determined from Part A) post-dose on Days 3 through 7 for all cohorts. Detailed tables for Days 1 and 14, and Day 7 are provided in Section 3.6.3.1 and Section 3.6.3.2, respectively.
5. To be drawn at pre-dose in the morning on Days 2, 4, 7, and 10. Pre-dose for Day 1 may be drawn on either Day 1 or Day -1.
6. Subjects will receive meals scheduled at the same time each day.
7. Serial (24 hour) PK sampling will occur on Days 1-2 and 14-15 and pre-dose PK samples collected on Days 4 through 7 for all cohorts. For **Cohort 4 (**and/or another cohort(s) only**)** only, serial (24 hour) PK samples will be collected on Days 7-8. No PK samples will be drawn on Day 8 for cohorts that are fasted on Day 7. Detailed tables for Days 1 and 14, and Day 7 are provided in Section 3.6.3.1 and Section 3.6.3.2, respectively.
8. For Days -1 and 1 - Samples may be drawn at any time between Day -1 and Day 1 prior to dosing.
9. Follow-up draw is only required for subjects with abnormal values on Day 15, at the discretion of the investigator.
10. Samples will be drawn with subjects in the fasted state (pre-dose for CV biomarkers on Day 7).

3.6.3.1. Detailed Time and Events Table for Days 1 and 14 (Part B; All Cohorts)

Procedure		Time of Procedure - Post-dosing (hours)														Days 2 and 15
		Pre-dose	0	0.25	0.5	0.75	1.0	1.5	2	3	4	6	8	10	12	24
Hema/Chem/Urinalysis tests																X
12-lead ECG and vital signs[1]		T			T		T		T		T		T		T	T
PK blood sample[2]		X		X	X	X	X	X	X	X	X	X	X		X	X
PK Urine[2]	Day 1	X														
	Day 14 - 15		←==========0 to 4 hours==========→									←===5 to 24 hours===→				
Study Treatment Dosing[2]			X													
Meals Served[2]									S		L			D		

For ECG and vital signs T=Triplicate, For Meals S=Snack, L=Lunch, D=Dinner

1 Vital signs to include HR and BP. Additional time points may be considered after review of Part A data.

2 For PK sampling on Days 1 and 14 subjects will fast 8 hours overnight prior to dosing; no food will be allowed for at least 2h post-dose. Water will be allowed as desired.

3.6.3.2. Detailed Time and Events Table for Day 7 of Cohort 4 (Part B; Cohort 4 and/or another food effect cohort(s))

Procedure	Time of Procedure - Post-dosing (hours)															Days 8
	-0.5	Pre-dose	0	0.25	0.5	0.75	1.0	1.5	2	3	4	6	8	10	12	24
Weight	X															
Hema/Chem/Urinalysis tests		X														
12-lead ECG and Vital Signs[1]		T			T		T		T		T		T		T	T
PK blood sample		X		X	X	X	X	X	X	X	X	X	X		X	X
Study Treatment Dosing			**X**													
Meals[2,3]	B										L			D		

For ECG and vital signs T=Triplicate, For Meals B=Breakfast, L=Lunch, D=Dinner

1 Vital signs to include HR and BP. Additional time points may be considered after review of Part A data.

2 Subjects will be provided with a standard breakfast approximately 30 minutes prior to dosing.

3 Lunch will be provided following the completion of other 4 hour assessments.

4. STUDY POPULATION

4.1. Number of Subjects

Cohorts 1 and 2 (Part A): Sufficient subjects will be enrolled such that up to approximately 8 subjects per cohort complete dosing and critical assessments.

Cohorts 3, 4, and 5 (Part B): Sufficient subjects will be enrolled such that up to approximately 12 subjects per cohort complete dosing and critical assessments.

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

It is anticipated that 52 subjects (excluding replacements) will be enrolled in this study. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels or repeated evaluation of a dose level already studied. However, Part A of the study includes flexibility in adding an additional cohort, as described in Section 3.1.2.1. If an additional cohort is required in Part A, then the maximum number of subjects would be 60 (excluding replacement subjects).

4.2. Eligibility Criteria

4.2.1. Inclusion 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 GlaxoSmithKline Document Number 2012N138676_00.

Deviations from inclusion 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.

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

1. Males between 18 and 50 years of age (inclusive), at the time of signing the informed consent form.
2. Body weight ≥ 50 kg and Body Mass Index (BMI) within the range 19 - 32 $kg/^{m2}$ (inclusive), where

$$BMI = \frac{(\text{weight in kg})}{(\text{height in meters})^2}$$

3. Healthy as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. A subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied **may be** included only if the Investigator and the GSK Medical Monitor agree that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
4. Male subjects with female partners of child-bearing potential must agree to use one of the contraception methods listed in the Lifestyle Section of the protocol. This criterion must be followed through the completion of the follow-up visit.
5. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
6. Average QTcF < 450 msec; or QTcF < 480 msec in subjects with Bundle Branch Block.

4.2.2. Exclusion Criteria

Deviations from 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.

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

4.2.2.1. Criteria Based Upon Medical Histories

1. Subjects with a history of clinically significant endocrine, gastrointestinal, hepatic, cardiovascular, neurological, haematological, immunological, renal, respiratory, or genitourinary abnormalities or diseases.
2. Subjects with a history at any time in the past of coronary artery disease, congestive heart failure, angina, myocardial infarction, any cardiac surgery, valvular heart disease, clinically significant arrhythmia, dyspnea, pulmonary edema, stroke, or transient ischemic attack.

   ECG exclusion criteria:

Heart rate	<40 and >100 beats per minute
PR Interval	<120 and >200msec
QRS duration	<70 and >110msec

3. Subjects with a history of malignancy that is not in complete remission for at least 5 years or 1 year for non-melanoma skin carcinoma.
4. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
5. History of drug or alcohol abuse within 5 years prior to the Screening Period.

6. History of regular alcohol consumption within 6 months of the study defined as an average weekly intake of >14 drinks for males or >7 drinks for females. One drink is equivalent to 12 g of alcohol: 12 ounces (360 ml) of beer, 5 ounces (150 ml) of wine or 1.5 ounces (45 ml) of 80 proof distilled spirits.
7. 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 GSK Medical Monitor, contraindicates their participation.
8. Subjects with a family history of early onset prostate cancer or multiple members with prostate cancer.

4.2.2.2. Criteria Based Upon Diagnostic Assessments

9. A positive pre-study drug or alcohol screen.
10. Cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening.
11. Subjects with values outside the specified ranges for the following Key Clinical Laboratory Tests must be excluded from the study:

    - Liver function tests - ALT, Direct Bilirubin, or Albumin more than 10% outside the normal reference range (<0.9 x LLN or >1.1 x ULN)
    - Renal function – Creatinine <1.6mg/dl with an age appropriate GFR ≥60 (mL/min/1.73 m^2) using formulae provided in the SPM
    - Electrolytes - Sodium more than ± 5mEq/L outside the normal reference range, Potassium or Calcium more than 10% outside the normal reference range (<0.9 x LLN or >1.1 x ULN)
    - Metabolic - Glucose more than 10% outside the normal reference range (<0.9 x LLN or >1.1 x ULN) and Total Cholesterol > 240mg/dl
    - Muscle – creatine phosphokinase >2.0 x ULN
    - Hematology - Hemoglobin, WBC, Neutrophils, or Platelets more than 10% outside the normal reference range (<0.9 x LLN or >1.1 x ULN)
    - Prostate Specific Antigen (PSA) ≥2.5ng/mL.

12. A positive test for HIV antibody.
13. A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening.

4.2.2.3. Other Criteria

14. Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

15. Unable to refrain from prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication and throughout the study, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.
16. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 3 months (12 weeks), 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
17. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56-day period.
18. Unable to refrain from consumption of red wine, seville oranges, grapefruit or grapefruit juice from 7 days prior to the first dose of study medication.
19. Unwillingness or inability to follow the procedures outlined in the protocol.

4.3. Screen and Baseline Failures

Data for screen and baseline failures will be collected in source documentation at the site but will not be transmitted to GSK.

5. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

5.1. Hypotheses and Treatment Comparisons

The focus of this FTIH study, both single and repeat dose phases, is to evaluate safety and tolerability of GSK2849466, and to estimate GSK2849466 PK parameters and biomarker effects (repeat dose). No formal statistical hypotheses will be tested. Descriptive statistics will be used to assess safety and tolerability objectives. An estimation approach will be used to address the PK and biomarker study objectives, where point estimates and corresponding confidence intervals will be constructed.

5.2. Sample Size Considerations

5.2.1. Sample Size Assumptions

No formal power/sample size calculations were performed. The sample size for each cohort is based on feasibility.

5.2.2. Sample Size Sensitivity

Sample size sensitivity analysis was not performed.

5.2.3. Sample Size Re-estimation

No sample size re-estimation will be performed.

5.3. Data Analysis Considerations

5.3.1. Interim Analysis

There will be no formal statistical interim analysis. However, available safety and PK data will be reviewed by the GSK Medical Monitor and/or designee and other study team members prior to each dose escalation. GSK staff will be unblinded for these reviews.

Preliminary results from available safety data may be reported prior to database freeze for the purposes of safety review by GSK, the study investigators, and where required by regulatory bodies.

Other selected preliminary data from the repeat dose phase of the study may be unblinded and reported prior to database freeze for internal decision making.

5.3.2. Final Analyses

Final analyses will be performed after all subjects have completed the study and after database freeze/unblinding. Version 9.1 or higher of the SAS system will be used to analyze the data as well as to generate tables, figures, and listings. Complete details will be documented in the Reporting and Analysis Plan (RAP).

5.3.2.1. Safety Analyses

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

5.3.2.2. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacokinetics Modeling & Simulation department within GlaxoSmithKline. Plasma GSK2849466 concentration-time data will be analyzed by non-compartmental methods with WinNonlin version 5.2 (or later). Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following PK parameters will be determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t) and AUC(0-∞)], and apparent terminal phase half-life (t1/2). AUC(0-∞) or AUC(0-τ) and Cmax following single and repeat doses may be used for assessment of dose proportionality. Trough concentration (Cτ) samples collected on the specified days may be used to assess attainment of steady state. To estimate the extent of accumulation after repeat dosing, the observed accumulation ratio (Ro) may be determined.

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively. All PK data will be stored in the archives, GlaxoSmithKline Pharmaceuticals, R&D.

Statistical analyses of the PK parameter data will be the responsibility of Clinical Statistics, GlaxoSmithKline. Dose proportionality of both single and repeat dose PK parameters will be analyzed by using appropriate power and/or ANOVA models. For

repeat dose PK, Ro and accumulation ratio at steady state (Rs) will be estimated for each dose separately using an appropriate mixed effects ANOVA model. Achievement of steady-state will be assessed visually and if appropriate, from the estimate of the slope from the linear regression of log Ctau versus time. The coefficient for the slope of the time effect will be used to evaluate steady-state. The effect of food on GSK2849466 PK parameters will be assessed by comparing Day 7 to Day 14 PK parameters (Cmax and AUC(0-τ)) using ANOVA. Pharamcokinetic parameters will be natural log-transformed prior to statistical analysis. Point estimates for the parameters and comparisons of interest will be presented along with 90% confidence intervals. Detailed descriptions of the planned analyses will be provided in the RAP.

5.3.2.3. Pharmacokinetic/Pharmacodynamic Analyses

Relationships between changes in PD parameters, biomarkers, lipids or measures of safety and GSK2849466 exposure may be explored graphically and where appropriate using modeling approaches. Variables of interest may be examined as a function of individual exposure to GSK2849466 as measured by PK parameters such as AUC and Cmax.

5.3.2.4. Pharmacodynamic/Biomarker Analyses

Biomarker, lipid and hormone values will be listed and summarized along with change from baseline. Graphical techniques will be employed to evaluate treatment related changes. For both single and repeat dose cohorts, appropriate ANCOVA models may be used to analyze change from baseline for selected lipid, biomarker and hormone parameters. The models will include the baseline value as a covariate and treatment as a fixed effect. Pairwise differences in least squares means between each active treatment and placebo will be determined along with a 95% confidence interval. Detailed descriptions of the planned analyses will be provided in the RAP.

6. STUDY ASSESSMENTS AND PROCEDURES

This section lists the parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table (Section 3.6). Other details of the procedures for assessments are provided in the Study Procedures Manual (SPM). Whenever vital signs, 12-lead ECGs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, blood draws. 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 vital signs, ECGs, blood draws for safety laboratory collection and, PK 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 change in timing or addition of time points for any planned study assessments must be approved and documented by GSK, but this will not constitute a protocol amendment. The IRB will be informed of any safety issues that require alteration of the safety monitoring scheme. No more than 500 mL of blood will be collected from any subject over the duration of the study, including any extra assessments that may be required.

6.1. Screening Assessments

6.1.1. Informed Consent/Assent

Provide the subject with verbal and written information about the study and:

- Ensure that subjects understand all aspects of the study and their participation in it.
- If a subject is willing to participate, ask them to sign and date the consent form.
- Ensure to comply fully with ICH GCP guidelines.

6.1.2. Entry Criteria

Eligibility to participate in the study is determined by the entry criteria. Each subject must satisfy all of the inclusion criteria and none of the exclusion criteria to be eligible to participate. Adherence to the eligibility criteria is essential as deviations could potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Waivers for Inclusion/Exclusion criteria will not be granted by GSK. A screening log should be completed for all subjects who are screened for a study whether they are enrolled or not.

6.1.3. Demographic/Medical History Assessments

The following demographic parameters will be captured: date of birth, gender, race and ethnicity.

6.1.4. Medical and Medication Histories

Medical/medication/alcohol history will be assessed as related to the eligibility criteria listed in Section 4.2.

6.1.5. Holter Monitoring

Four hours of Holter monitoring will be conducted at screening under the standard procedures of the site to eliminate subjects with non-clinically overt cardiac arrhythmias, who potentially may be sensitive to cardiovascular side effects.

Holter tapes will be analyzed by an analyst at the clinical unit. Those with an abnormality that does not meet the entry criteria should be considered a screen failure.

6.1.6. Alcohol Screening

An alcohol breath test will be performed as indicated in the time and events tables. A blood or urine alcohol test may be performed if preferred.

Please refer to the operating instructions for equipment use at the study site.

Regardless of test applied, alcohol levels must be within the normal limits of the study site's assay.

6.1.7. Cotinine Testing

Urine cotinine or plasma cotinine tests will be performed. Urine or plasma cotinine levels must be within the normal limits of the study site's assay.

6.1.8. Drugs of Abuse Test

A urine sample will be tested for drugs of abuse. The following will be tested: cannabis, cocaine, barbituates, benzodiazepines, methadone, amphetamines and opiates.

6.2. Safety

Planned timepoints for all safety assessments are listed in the Time and Events Table (Section 3.6). 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.

6.2.1. Physical Examinations

- A complete physical examination will include assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular, abdomen (liver and spleen), lymph nodes and extremities.
- Height and weight will be measured and recorded at screening. Weight will be recorded on Days -1, 7, and 15.
- A brief physical examination will include assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Other brief physical examinations in this study may be conducted at the discretion of the Investigator for safety reasons (other than at screening or early withdrawal/follow-up). A full physical examination may be performed in lieu of a brief examination, at the discretion of the Investigator.

6.2.2. Vital Signs

Vital sign measurements will include systolic and diastolic blood pressure, and heart rate.

Vital signs will be recorded whilst the subject is in a supine position, having rested in this position for at least 15 minutes. Subjects are permitted to make intermittent movement, if necessary, in preparation for procedures (e.g., to sit up to take study medication). When vital signs are to be taken in triplicate, an interval of 2 minutes should be used between measures. Vital sign measurements that fall outside of expected normal ranges at the site should be assessed for clinical significance and repeated when appropriate.

Vital Signs in Part A will be taken in triplicate. Single or triplicate vital signs will be recorded in Part B at the times specified in the Time and Events Tables in Section 3.6. At screening, the average of the triplicate vital sign measurements will be entered into the eCRF. On other occasions when triplicate vital sign measurements are recorded; each of the three recordings will be entered into the eCRF.

6.2.3. Electrocardiogram (ECG)

12-lead ECGs will be obtained during the study using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals at each timepoint. Refer to Section 3.5.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

ECGs will be recorded whilst the subject is in a supine position, having rested in this position for at least 15 minutes. Subjects are permitted to make intermittent movement, if necessary, in preparation for procedures (e.g., to sit up to take study medication). When ECGs are to be taken in triplicate, an interval of 5 minutes will be used between measures taken at screening or pre-dose. An interval of 1 to 2 minutes is acceptable for any post-dose triplicate ECGs, when needed.

Various values from the ECG read-out will be entered into the eCRF (the average for some will be used for measures made in triplicate).

Any result falling outside the expected normal ranges as defined by the site will be repeated at the discretion of the investigator. If any results falling outside of these expected normal ranges at the site are deemed not clinically significant by the investigator or an appropriately qualified designee, then this should be clearly stated on the hard copies of the ECG and signed and dated by the investigator.

If the ECG trace indicates an abnormality that is measured by the equipment but is deemed normal by the investigator then this should be clearly stated on the ECG tracing as normal and signed and dated by the investigator or appropriately qualified designee. If the ECG tracing indicates an abnormality that is present but deemed as not clinically significant by the investigator or appropriately qualified designee then this should be clearly stated on the ECG tracing as "NCS" and signed and dated by the investigator or appropriately qualified designee and stored with the source records for that subject. If any results falling outside of the normal ranges are deemed clinically significant by the investigator or appropriately qualified designee then these should be recorded in the eCRF as an AE.

ECGs will be stored electronically for manual measurement of intervals, if necessary.

Whenever a 12-lead ECG is scheduled at the same nominal time as other study procedures (including vital signs, blood draws, or meals), the ECG should be obtained first followed by other procedures with timing planned so that the blood draw occurs at the exact nominal time.

ECGs in Part A will be taken in triplicate. Single and triplicate ECGs will be recorded in Part B at the times specified in the Time and Events Tables in Section 3.6.

6.2.4. Cardiac Telemetry/Continuous ECG

Monitoring times will occur as directed in the Time and Events Schedule (Section 3.6). Continuous cardiac telemetry will be performed for at least 12 hours post dose in each treatment period in Part A and at least 8 hours post dose on Days 1, 3, 7, 10, and 14 in Part B. Telemetry will be performed under the standard procedures at the study site.

Any abnormalities will be printed. Full electronic disclosures will be maintained as part of the subject's source documents and will be reviewed in detail. Start date and time, stop date and time, and nature of abnormality, if any, will be captured in the eCRF.

6.2.5. Clinical Laboratory Assessments

Any abnormal laboratory results that are considered clinically significant must be repeated. Clinical observation of the subject must be continued until the laboratory value returns to normal or in the opinion of the investigator is no longer clinically significant. The reference ranges and values of potential clinical concern (including INR correction factor) of the local laboratory will be used in this study. Timings of clinical laboratory blood draws in Parts A and B are provided in the Time and Events Tables (Section 3.6).

Samples collected for hematology, clinical chemistry, urinalysis, or hormone assays will be analysed at the unit's local laboratory under the relevant SOPs, GUIs and user manuals for details on methodology, processing, handling of specimens, and analyses.

Hematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below:

Hematology

Platelet Count	*RBC Indices*:	*Automated WBC Differential:*
RBC Count	MCV	Neutrophils
WBC Count (absolute)	MCH	Lymphocytes
Reticulocyte Count	MCHC	Monocytes
Hemoglobin	Prothrombin time (with and without INR)	Eosinophils
Hematocrit	Activated partial thromboplastin time	Basophils

Clinical Chemistry

BUN	Potassium	AST (SGOT)	Total and direct bilirubin
Creatinine	Chloride	ALT (SGPT)	Uric Acid
Glucose	Total CO_2	GGT	Albumin
Sodium	Calcium	Alkaline phosphatase	Total Protein
			Creatine Phosphokinase (Total)

Routine Urinalysis

Specific gravity
pH, glucose, protein, blood and ketones by dipstick
Microscopic examination (if blood or protein is abnormal)

Other screening tests

Prostate specific antigen
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) should be reflexively performed **on the same sample** to confirm the result)
Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines).

6.3. Pregnancy

6.3.1. Time period for collecting pregnancy information

All pregnancies in female partners of male subjects will be collected after the start of dosing and until follow-up.

6.3.2. Action to be taken if pregnancy occurs

Female subjects are excluded from this study.

6.3.3. Action to be taken if pregnancy occurs in a female partner of a male study subject

The investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. 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. The 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 premature termination of the pregnancy will be reported.

6.4. Pharmacokinetics

6.4.1. Blood Sample Collection

Blood samples for PK analysis of GSK2849466 will be collected at the time points indicated in Section 3.6, Time and Events Table. The actual date and time of each blood 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.

Approximately 2 mL of whole blood will be obtained for each time point.

Blood will be collected into K2 EDTA tubes, mixed gently, and placed on wet ice in an upright position. Blood samples will be centrifuged (for 10 minutes at approximately 1500g at 4^{o}C) and 0.5mL of the harvested plasma transferred into a labelled 1.4 mL Matrix tube and the remaining plasma will be placed into a labelled 1.8mL NUNC cryotube and frozen at approximately -20^{o}C within no more than 1 hour after collection of a blood sample.

Details of PK blood sample storage and shipping procedures are provided in the Study Procedures Manual (SPM).

6.4.2. Urine Sample Collection

In Part B urine samples for PK analysis of GSK2849466 will be collected at the timepoints listed in Section 3.6, Time and Events Table. The timing of urine samples may be altered and/or samples may be obtained at additional time points to ensure thorough PK monitoring.

Immediately prior to dosing on Day 14, each subject will be instructed to void their bladder. Urine collection for all other time points listed in the time and events table will begin immediately following dose administration. The volume and time will be recorded for each urine sample collected and for each subject. Samples within each time period (0-4 hours and 4-25 hours) will be pooled and a 100 mL aliquot urine sample for each time period will be transferred to a plastic container and stored at -20°C prior to shipment.

Details of PK urine sample storage and shipping procedures are provided in the SPM.

6.4.3. Sample Analysis

Plasma and urine analysis will be performed under the management of Worldwide Bioanalysis, DMPK, GlaxoSmithKline. Concentrations of GSK2849466 will be determined in plasma and urine samples using the currently approved analytical methodology. Raw data will be stored in the GLP Archives, GlaxoSmithKline. Once the plasma has been analyzed for GSK2849466, any remaining plasma may be analyzed qualitatively for other circulating metabolites and the results reported under a separate DMPK protocol. The urine samples may be analyzed for compound-related metabolites and the results will be reported under a separate DMPK protocol.

6.5. Pharmacodynamic and Biomarker Samples

6.5.1. Pharmacodynamic Samples

6.5.1.1. Reproductive Hormone Blood Samples

Fasting blood samples for hormones will be drawn in Part B of the study. A fasting pre-dose baseline sample will be collected on Day 1 prior to subjects receiving study treatment. A second fasting sample will be drawn on Day 15. Subjects should fast overnight for at least 8 hours prior to collection of these samples. Instructions on the shipment of hormone samples are provided in the SPM. The hormone blood samples will be analyzed for:

Hormone Assays[1]

Luteinizing hormone	Sex hormone binding globulin
Follicle stimulating hormone	Prolactin
Testosterone (total)	Inhibin B
Dihydrotestosterone	

1. Hormone samples will be analyzed with a third party, see SPM for shipment instructions.

6.5.1.2. Lipid Blood Panel

Fasting lipid blood panels will be drawn in Part B of the study. A fasted pre-dose baseline sample will be collected or Day 1 prior to subjects receiving study treatment. A second fasted sample will be drawn on Day 15. A follow-up draw is only required for subjects with abnormal values on Day 15 at the discretion of the investigator. Subjects should fast overnight for at least 8 hours prior to collection of these samples. Instructions on the shipment of lipid samples are provided in the SPM. The lipid samples will be analyzed for:

Lipid Blood Panel[1]

Total Cholesterol	Very Low-density Lipoprotein
Low-density Lipoprotein	Triglycerides
High-density Lipoprotein	

1. Lipid panel samples will be analyzed with a third party, see SPM for shipment instructions.

6.5.2. Biomarker Samples

Two samples will be drawn for biomarker analyses at each of the time points provided in the Time and Events Tables (see Section 3.6).

6.5.2.1. Adrenal, Metabolic, and Cardiovascular Biomarker Samples

Fasting samples will be drawn in Part B to determine changes in biomarkers of the adrenal and metabolic axes as well as cardiovascular biomarkers. Samples will be drawn on Day 1 prior to the first study treatment dosing as baseline and again on Day 15 for all biomarkers listed below. An additional fasting sample will be drawn on Day 7 for the cardiovascular biomarkers only. Subjects should fast overnight for at least 8 hours prior to collection of these samples.

As defined in Table 2, subjects will be monitored for unexpected effects of perturbations to these hormonal axes. These samples will be used to analyze subject levels of the following hormones:

Biomarker Panel[1]

Biomarkers of the Adrenal Axis	Biomarkers of the Metabolic Axis	Cardiovascular Biomarkers
Corticotropin (ACTH)	Insulin-like growth-factor-1	Brain natriuretic peptide
Cortisol	Insulin-like growth-factor Binding-protein 3	Troponin
Dehydroepiandrosterone sulfate	Fasting insulin	
	Fasting glucose	

1. Biomarker samples will be analyzed by a third party, see SPM for shipment instructions.

6.5.2.2. Exploratory Biomarkers

Fasted serum and plasma samples will be stored for analysis of potential biomarkers of anabolic, safety, or metabolic effects induced by GSK2849466. The exploratory biomarker sample will be drawn on Day 1 prior to the first study treatment dosing as baseline and on Day 15. Additional sample collection and handling information is available in the SPM.

7. LIFESTYLE AND/OR DIETARY RESTRICTIONS

7.1. Contraception Requirements

7.1.1. Male Subjects

Male subjects with female partners of child-bearing potential must use one of the following contraceptive methods after the first dose of study treatment until the follow-up contact:

- Condom plus partner use of a highly effective contraceptive such as occlusive cap (diaphragm or cervical/vault cap) plus spermicidal agent (foam/gel/ film/cream/suppository), oral contraceptive, injectable progesterone, implant of etonogestrel or levonorgestrel, estrogenic vaginal ring, percutaneous contraceptive patches, or intrauterine device.

  OR

- Abstinence, defined as sexual inactivity consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

7.2. Meals and Dietary Restrictions

Please see the time and events table for meal timings (Section 3.6). Meals will be provided following the completion of all other study assessments scheduled at the same nominal time.

Subjects should avoid 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.

In Part A, and in Part B prior to PK sampling on Days 1 and 14, subjects will fast overnight prior to dosing; no food will be allowed for at least 2 hours post-dose. Water will be allowed as desired. If, prior to 2 hours post-dosing a subject experiences nausea; this may be treated with a small amount of food (e.g., crackers) at the discretion of the investigator.

At any time a meal is provided during the study, the same meals will be provided to all subjects. All meals shall be composed of 30% protein, 30% fat, and 40% carbohydrates. On Day 7 of Cohort 4 (and/or another cohort(s) as determined based on Part A PK data), the meal provided to subjects prior to dosing will be:

- Provided according to the site's standard procedures,
- Composed of 30% protein, 30% fat, and 40% carbohydrates
- Identical meal for all subjects,
- Provided approximately 30 minutes prior to dosing.

7.3. Caffeine, Alcohol, and Tobacco

- During each dosing session, subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g. coffee, tea, cola drinks, chocolate) for 24 hours prior to the start of dosing until collection of the final pharmacokinetic and or pharmacodynamic sample during each session.
- 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.
- Use of tobacco products is not allowed from screening until after the final follow-up visit.

7.4. Activity

Subjects will abstain from strenuous exercise for 48 hours prior to each blood collection for clinical laboratory tests. Subjects may participate in light recreational activities during studies (e.g., watch television, read).

8. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

8.1. Permitted Medications

Naproxen, at a dose of 1 tablet (220mg) twice-daily or less is permitted for use. Other concomitant medication may be considered on a case by case basis by the GSK Medical Monitor.

8.2. Prohibited Medications

Except as permitted in Section 8.1,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.

8.3. Non-Drug Therapies

Subjects must abstain from taking any vitamins, herbal and dietary 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.

9. COMPLETION OR EARLY WITHDRAWAL OF SUBJECTS

9.1. Subject 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.

9.2. Subject Withdrawal Criteria

Refer to Section 3.5 for dose adjustment/stopping criteria based on safety and tolerability, and PK criteria.

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, behavioral or administrative reasons.

9.3. Subject Withdrawal Procedures

If a subject decides to withdraw or is withdrawn by the physician responsible, the reasons for withdrawal and the results of any relevant tests will be recorded in the CRF and the planned follow-up procedures will be performed, where possible. A subject may voluntarily discontinue participation at any time.

The Investigator may also, at his/her discretion; withdraw the subject from participating in this study at any time. If a subject is prematurely withdrawn from the study for any reason, the Investigator must make every effort to perform the follow-up visit.

9.4. Treatment After the End of the Study

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

The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition, whether or not GSK is providing specific post-study treatment.

9.5. Screen and Baseline Failures

Data for screen and baseline failures will be collected in source documentation at the site but will not be transmitted to GSK.

10. STUDY TREATMENT

Study treatment dosage and administration details are listed in Section 3.4.

10.1. Blinding

This will be a double-blind study with subjects, investigator and site staff (with the exception of the site pharmacist) blinded. The Sponsor, GSK, will be unblinded.

The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. Whenever possible, the investigator must first discuss options with the GSK Medical Monitor or appropriate GSK study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the investigator must notify GSK as soon as possible. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

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 eCRF.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment to the site 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 clinical investigators in accordance with local regulations and/or GSK policy.

10.2. Packaging and Labeling

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

10.3. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of capsules containing GSK2849466 are provided in the Study Procedures Manual.

Study treatment must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study treatment. Only authorized site staff may supply or administer study treatment. All study treatment must be stored in a secure area with access limited to the investigator and authorized site staff. The recommended storage conditions and expiry date (as appropriate) for study treatment are stated on the product label. Maintenance of a temperature log (manual or automated) is required.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance. The investigator or the head of the medical institution (where applicable), or designated site staff (e.g., storage manager, where applicable) must maintain study treatment

accountability records throughout the course of the study. The responsible person(s) will document the amount of study treatment received from and returned to GSK and the amount supplied and/or administered to and/or returned by subjects. The required accountability unit for this study will be capsule. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused study treatment are listed in the SPM.

Investigational product is not expected to pose significant occupational safety risk to site staff under normal conditions of use and administration. 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.

However, precautions are to be taken to avoid direct skin contact, eye contact, and generating aerosols or mists. In the case of unintentional occupational exposure notify the monitor, medical monitor and/or study manager.

10.4. Assessment of Compliance

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 study 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 participant 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.

10.5. Treatment of Study Treatment Overdose

For this study, any dose of GSK2849466 greater than the dose specified for the treatment period, within a 24 hour time period [± 1 hour], will be considered an overdose.

GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

11. ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of Study Treatment and until the follow-up contact.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed as related to study participation (e.g. study treatment, 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. All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 11.6.

Investigators are not obligated to actively seek AEs or SAEs in former study participants. 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 would promptly notify GSK.

11.1. Definition of Adverse Events

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 meeting the definition of an AE **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 that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that 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.

11.2. Definition of Serious Adverse Events

If an event is not an AE per Section 11.1, 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).

An SAE is 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, or

   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. 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 **and** 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.

- Refer to Section 12 for the required liver chemistry follow-up instructions.

h. All grade 4 laboratory abnormalities.

11.3. 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?"

11.4. Recording of AEs and SAEs

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 appropriate data collection tool.

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 data collection tool. However, 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.

11.5. Evaluating AEs and SAEs

11.5.1. 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.

11.5.2. 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 GlaxoSmithKline Document Number 2012N138676_00 (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.

11.6. 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 AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

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 data collection tool. The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

11.7. Prompt Reporting of SAEs to GSK

Once the investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to GSK **within 24 hours**. Any follow-up information on a previously reported SAE will also be reported to GSK within 24 hours.

If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying GSK of the event and completing the appropriate data collection tool. The investigator will always provide an assessment of causality at the time of the initial report as described in Section 11.5.2, Assessment of Causality.

The 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 GSK Medical Monitor. Then the site will enter the serious adverse event data into the electronic system as soon as it becomes available.

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 participant 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 their GSK protocol contact by telephone.

GSK contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

11.8. Regulatory Reporting Requirements For SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects 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 regulatory authorities, IRBs/IECs 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 an SAE(s) or other specific safety information (e.g., summary or listing of

SAEs) from GSK will file it with the GlaxoSmithKline Document Number 2012N138676_00 and will notify the IRB/IEC, if appropriate according to local requirements.

12. LIVER CHEMISTRY FOLLOW-UP PROCEDURES

Refer to the diagram in Appendix 1 for a visual presentation of the procedures listed below.

The procedures listed below are to be followed if a subject meets the liver chemistry stopping criteria defined in Section 3.5.1.1:

- Immediately withdraw the subject from study treatment
- Notify the GSK medical monitor within 24 hours of learning of the abnormality to confirm the subject's study treatment cessation and follow-up.
- Complete the "Safety Follow-Up Procedures" listed below.
- Complete the liver event case report forms. If the event also meets the criteria of an SAE (see Section 11.2), the SAE data collection tool will be completed separately with the relevant details.
- Upon completion of the safety follow-up permanently withdraw the subject from the study, unless further safety follow up is required, and do not rechallenge with study treatment.

Safety Follow-Up Procedures for subjects with ALT ≥ 3xULN:

- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Safety Follow-Up Procedures for subjects with ALT ≥3xULN and total bilirubin ≥2xULN (>35% direct bilirubin); or ALT ≥ 3xULN and INR[1] > 1.5:

- This event is considered an SAE (see Section 11.2). Serum bilirubin fractionation should be performed if testing is available. If fractionation is unavailable, urinary bilirubin is to be measured via dipstick (a measurement of direct bilirubin, which would suggest liver injury).
- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries, additional testing, and close monitoring (with specialist or hepatology consultation recommended).
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

[1] INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants.

In addition, for <u>all</u> subjects with ALT ≥ 3xULN, every attempt must be made to also obtain the following:

- Viral hepatitis serology including:
  - 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.
- Blood sample for pharmacokinetic (PK) analysis, obtained within **48 hours** of last dose. 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 <u>OR</u> 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 included in the SPM.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥ 2xULN.
- Assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis (fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia) on the AE CRF.
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications CRF.
- Record alcohol use on the Liver Events CRF.

The following are required for subjects with ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- 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 computerized tomography) to evaluate liver disease.

- The Liver Imaging and/or Liver Biopsy CRFs are also to be completed if these tests are performed.

13. STUDY CONDUCT CONSIDERATIONS

13.1. 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.

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

The study will be conducted in accordance with all applicable regulatory requirements.

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 2008 Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval to conduct the study and of any subsequent relevant amended documents
- Written informed consent (and any amendments) to be obtained for each subject before participation in the study
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)

Written informed consent must be obtained from each subject prior to participation in the study.

In approving the clinical protocol the IEC/IRB and, where required, the applicable regulatory agency are also approving the optional assessments e.g., PGx assessments described in Appendix 2, unless otherwise indicated. Where permitted by regulatory authorities, approval of the optional assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the optional assessments is being deferred and the study, except for the optional assessments, can be initiated. When the optional assessments are not approved, then the approval for the rest of the study will clearly indicate this and therefore, the optional assessments will not be conducted.

13.3. 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 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

13.4. 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.

13.5. Study and Site Closure

Upon completion or premature discontinuation of the study, the monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK procedures.

In addition, 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. If GSK determines such action is needed, GSK will discuss this with the investigator or the head of the medical institution (where applicable), including the reasons for taking such action. When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform investigators or the head of the medical institution (where applicable) and the 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 IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

13.6. 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 by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and 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 assure 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, or GSK standards/procedures; otherwise, the retention period will default to 15 years.

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 leaves the site.

13.7. 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. Investigators 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 investigators with the full summary of the study results. Investigators are encouraged to share the summary results with the study subjects, as appropriate.

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

GSK aims to post a results summary to the GSK Clinical Study Register and other publicly available registers no later than 8 months after the last subject's last visit (LSLV) [this applies to each data analysis phase for studies with multiple phases, e.g., primary analysis, follow up analysis etc]. In addition, the aim is to submit a manuscript to a peer-

reviewed journal for publication within 18 months of LSLV. GSK also aims to publish the full study protocol on the GSK Clinical Study Register at the time the results of the study are published as a manuscript in the scientific literature.

When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

13.8. Data Management

For this study subject data will be entered into GSK defined electronic case report forms (eCRFs), 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 an internal validated medication dictionary, GSKDrug. eCRFs (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.

14. REFERENCES

Basaria, S; S; Collins, L; Dillon, EL; Orwoll, K; Storer, TW; Miciek, R; *et.al*. The Safety, Pharmacokinetics, and Effects of LGD-4033, a Novel Nonsteroidal Oral, Selective Androgen Receptor Modulator in Healthy Young Men," *J Gerontol A Biol Sci Med Sci*, 2012, Mar 28.

Dalton, JT; Barnette, KG; Bohl, CE; Hancock, ML; Rodriquez, D; Dodson, ST, *et.al*. "Selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: results of a double blind, placebo-controlled phase II trial," *J Cachexia Sarcopenia Muscle*, 2011, 2:153-161.

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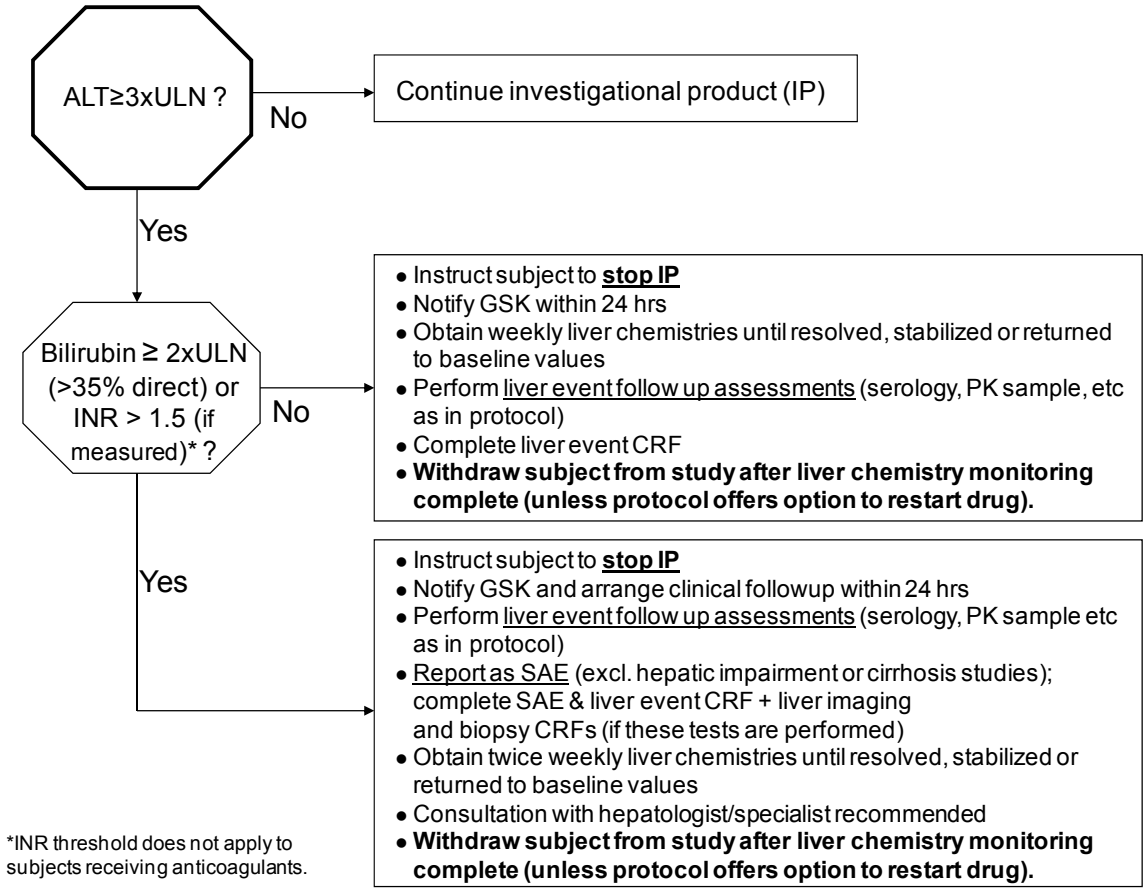
James LP. 2009. Pharmacokinetics of Acetaminophen - Protein Adducts **...** Liver Failure. Drug Metab Disp, 37:1779-1784.

Appendices

Appendix 1: Liver Safety Algorithms



Appendix 2: Pharmacogenetic Research

Pharmacogenetics - Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in populations. There is increasing evidence that an individual's genetic composition (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Collection of whole blood samples, even when no a priori hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation response to GSK2849466.

Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a relationship between genetic factors and response to GSK2849466. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with GSK2849466 that may be attributable to genetic variations of subjects, the following objectives may be investigated – the relationship between genetic variants and study treatment with respect to:

- Pharmacokinetics of study treatment
- Safety and/or tolerability

Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

Study Population

Any subject who is enrolled in the clinical study can participate in PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study.

Study Assessments and Procedures

Blood samples can be taken for Deoxyribonucleic acid (DNA) extraction and used in PGx assessments.

In addition to any blood samples taken for the clinical study, a whole blood sample (~10 ml) will be collected for the PGx research using a tube containing EDTA. It is

recommended that the blood sample be taken at the first opportunity after a subject has been randomized and provided informed consent for PGx research, but may be taken at any time while the subject is participating in the clinical study.

The PGx sample is labelled (or "coded") with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or a set of studies) of GSK2849466 has been completed and the clinical study data reviewed.

In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to GSK2849466.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

Subject Withdrawal from Study

If a subject who has consented to participate in PGx research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the PGx sample, if already collected:

- Retain the sample for PGx research
- Destroy the PGx sample

If a subject withdraws consent for PGx research or requests sample destruction, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK, and maintain the documentation in the site study records.

Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is then determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator should instruct the participant that their PGx sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent

and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Pharmacogenetics Analyses

The need to conduct PGx analysis may be identified after a study (or set of studies) has been completed. For this reason, samples may be kept for up to 15 years after the last subject completes the study. GSK may destroy the samples sooner.

Generally, GSK will utilize one of two approaches to explore genetic variation in drug response.

1. Specific genes may be studied that encode the drug targets, or drug mechanism of action pathways, drug metabolizing enzymes, or drug transporters which may underpin adverse events, disease risk or drug response. These candidate genes may include a common set of ADME (Absorption, Distribution, Metabolism and Excretion) genes that are studied to determine the relationship between gene variants or treatment response and/or tolerance.

   In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response GSK2849466. The genes that may code for these proteins may also be studied.

2. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) at defined locations in the genome, often correlated with a candidate gene, may be studied to determine the relationship between genetic variants and treatment response or tolerance. This approach is often employed when a definitive candidate gene(s) does not exist and/or the potential genetic effects are not well understood.

If applicable and PGx research is conducted, appropriate statistical analysis methods will be used to evaluate pharmacogenetic data in the context of the other clinical data. Results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. Endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. A detailed description of the analysis to be performed will be documented in the study reporting and analysis plan (RAP) or in a separate pharmacogenetics RAP, as appropriate

Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarize the PGx research results in the clinical study report separately or may publish the results in scientific journals.

GSK does not inform the investigator, subject, or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is because the information generated from PGx studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined.