TITLE PAGE

Protocol Title: A double blind, placebo-controlled first time in human study to evaluate the safety, tolerability and pharmacokinetics of single and repeat doses of GSK3036656 in healthy adult volunteers

Protocol Number: 201040 / Amendment 1

Short Title: A double blind, placebo-controlled first time in human study to evaluate the safety, tolerability and pharmacokinetics of single and repeat doses of GSK3036656 in healthy adult volunteers

Compound Number: GSK3036656

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

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): 2015-003654-41

Medical Monitor Name and SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Site Address
Primary Medical Monitor	PPD PPD	PPD P P D Telephone: PPD	Mobile: PPD	1250 South Collegeville Road (UP-4310) Collegeville, PA 19426 USA
Secondary Medical Monitor	PPD PPD	PPD PP D Telephone: PPD	Mobile: PP D	Iron Bridge Road Stockley Park West Uxbridge Middlesex UB11 1BT UK
SAE contact information	Medical monitor as above	PPD P P D AND cc: PPD	Mobile: PPD	1250 South Collegeville Road (UP-4310) Collegeville, PA 19426 USA

Approval Date: 27-FEB-2017

SPONSOR SIGNATORY:

PPD

FEB 27, 2017

Geo Derimanov
Medical Director, Medicines Development Centre,
DDM

Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 1 (27-February-2017)

DOCUMENT HISTORY	
Document	**Date**
2014N202803_01	27-FEB-2017
2014N202803_00	13-JAN-2017

Amendment 1 27-February-2017

Overall Rationale for the Amendment:

To address comments from the UK regulatory authority, Medicines and Healthcare Products Regulatory Agency (MHRA), on the initial protocol (GlaxoSmithKline Document Number GSK2014N202803_00).

Section # and Name	Description of Change	Brief Rationale
Section 1, Overall Design, Treatment Arms and Duration	From: "The two cohorts in Part A may be dosed sequentially (i.e., dosing in Cohort 2 starts after dosing in Cohort 1 is completed) or in an overlapping/interlocking fashion. The exact sequence of dosing will be determined together with the site investigator based on emerging information about the half-life of GSK3036656 in humans and logistical considerations." To: "The two cohorts in Part A will be dosed sequentially (i.e., dosing in Cohort 2 starts after dosing in Cohort 1 is completed). If it is considered desirable to dose Cohorts 1 and 2 in an overlapping/interlocking fashion (for example, if the half-life of GSK3036656/washout period makes sequential dosing impractical), approval for such dosing will be sought from the Regulatory Agency. Dosing in an overlapping/interlocking fashion will only take place if such approval is obtained."	To address the concern from the MHRA about the possibility of overlapping/ interlocking dosing.
Section 4.1, Study Design	From: The two cohorts in Part A may be dosed sequentially (i.e., dosing in Cohort 2 starts after dosing in Cohort 1 is completed) or in an overlapping/interlocking fashion. The exact sequence of dosing will be determined together with the site investigator based on emerging information about the half-life of GSK3036656 in humans and logistical considerations." To: The two cohorts in Part A will be dosed sequentially (i.e.,	To address the concern from the MHRA about the possibility of overlapping/ interlocking dosing.

Section # and Name	Description of Change	Brief Rationale
	dosing in Cohort 2 starts after dosing in Cohort 1 is completed). If it is considered desirable to dose Cohorts 1 and 2 in an overlapping/interlocking fashion (for example, if the half-life of GSK3036656/washout period makes sequential dosing impractical), approval for such dosing will be sought from the Regulatory Agency. Dosing in an overlapping/interlocking fashion will only take place if such approval is obtained." Figure 1, footnote (bullet 3) updated. From: Cohorts may be dosed in an overlapping fashion, the exact sequence of dosing will be determined together with the investigator based on emerging information about the half life of GSK3036656 in humans and logistical consideration To: Cohorts 1 and 2 will be dosed sequentially. If it is considered desirable to dose Cohorts 1 and 2 in an overlapping/interlocking fashion, approval will be sought from the Regulatory Agency first	
Section 5.1, Inclusion Criteria	From: "Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until follow up." To: "Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until 90 days after the last dose of study treatment (i.e. one sperm cycle)."	To allow the completion of one sperm cycle before possible pregnancy.

TABLE OF CONTENTS

PAGE

1. PROTOCOL SYNOPSIS FOR STUDY [201040]

Rationale

This study is the first time into human study (FTIH) for GSK3036656. The study will evaluate the safety, tolerability and pharmacokinetics (PK) of single ascending and repeat oral doses of GSK3036656 in healthy adult volunteers.

The results of this study are intended to be used to identify appropriate and well tolerated doses of GSK3036656 to be used in further studies. A food effect assessment will also be undertaken to investigate the influence of food on the pharmacokinetics of GSK3036656.

Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of GSK3036656 after single ascending and repeat oral doses in healthy adult subjects	• Safety and tolerability of GSK3036656: o Adverse Events o Clinically relevant changes in safety parameters: 12-lead electrocardiogram (ECG), telemetry, vital signs (systolic and diastolic blood pressure, heart rate, temperature), clinical laboratory data (haematology, clinical chemistry, urinalysis)
• To determine the pharmacokinetics of single and repeat doses of GSK3036656 in healthy subjects	• Derived pharmacokinetic parameters for GSK3036656 including area under the plasma drug concentration versus time curve (AUC(0-t), AUC(0-∞), AUC(0-τ)), maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (tmax), and apparent terminal half-life (t1/2) as appropriate
Secondary	
• To assess the effect of food on the pharmacokinetics of GSK3036656 following an oral dose in healthy subjects	• Derived pharmacokinetic parameters for GSK3036656 including AUC(0-t), AUC(0-∞), Cmax, tmax, and apparent terminal half-life (t1/2)
• To assess preliminary dose proportionality of GSK3036656 following single and	• AUC(0-t), AUC(0-∞), and Cmax following single dose and AUC(0-τ) and Cmax following repeat dose for the assessment

Objectives	Endpoints
repeat oral doses, as data permit	of dose proportionality
• To examine the extent of accumulation and achievement of steady-state following repeat oral doses of GSK3036656, as data permit	• Observed accumulation ratio based on AUC(Ro) and Cmax (RCmax) and steady-state ratio (Rss) following repeat dosing • Trough plasma concentrations at the end of the dosing interval (Cτ) to assess the achievement of steady-state of GSK3036656 following repeat oral doses
• To define the metabolic profile of GSK3036656 by identifying and quantifying, where possible and appropriate, GSK3036656-related material in plasma and urine following a single and repeated oral administration of GSK3036656	• Structure and concentration of GSK3036656-related material in plasma and urine

Overall Design

Treatment Arms and Duration

Part A:

For the single dose part, there will be up to 2 cohorts with up to 4 treatment (dosing) periods in each cohort (including a food effect treatment period). Initially, there will be a 14 day wash out period for individual subjects between each dose level which is considered sufficient in light of the predicted half-life of GSK3036656 [on average, approximately 30 hours (range: 12 to 72 hours) based on the various preclinical extrapolation methods], however this may be revised once relevant PK data is obtained. 9 subjects per cohort will be enrolled and randomised to ensure adequate safety, tolerability and PK information is gained and a balanced randomisation is achieved across all treatment (dosing) periods.

During each treatment (dosing) period, GSK3036656 will be administered to 6 subjects and placebo will be administered to 3 subjects. As this is a FTIH study, each treatment (dosing) period will be staggered over 2 days. On Day 1, one subject will receive GSK3036656 and one subject will receive placebo. The remaining subjects will be dosed one day later provided satisfactory safety and tolerability is demonstrated for the subjects dosed on Day 1. A treatment (dosing) period does not have to be staggered if the dose administered is equal to or lower than a dose that has been already tested and found to be safe and well tolerated.

Subjects will attend the unit on Day -1 for assessments and a meal. The subjects will then fast overnight (at least 8 hours) and be dosed the following morning (Day 1). Dosing with food may also be used in Part A once results from the food effect analysis are available. Dividing the total dose for the treatment (dosing) period into 2 or 3 smaller doses administered within 24 hours may also be done. The decision to divide the total dose into smaller doses will be made by the GSK study team in conjunction with the Principal Investigator. Post-dose, subjects will undergo safety and PK assessments. All subjects will remain in the unit until the 72 hour PK sample has been taken since this will enable a better assessment of their safety and will reduce the risk of subjects not returning for their visits. Subjects will be released at the discretion of the investigator following completion of the assessments provided there are no safety concerns identified from review of the clinical safety data. Approximately 14 days after their last dose, subjects will return to the unit for a follow-up visit.

The starting dose in Part A will be 5 mg. The dose will then be escalated up to a dose (no higher than 1500 mg) at which PK exposures do not exceed predefined limits determined from preclinical safety data (individual AUC[0-24]<4.9 µg.h/ml, individual Cmax<0.443 µg/ml). Dose escalation will only take place provided GSK3036656 is well tolerated and following review of all available safety, tolerability and pharmacokinetic data from the previous treatment (dosing) period by the Dose Escalation Committee.

The two cohorts in Part A will be dosed sequentially (i.e., dosing in Cohort 2 starts after dosing in Cohort 1 is completed). If it is considered desirable to dose Cohorts 1 and 2 in an overlapping/interlocking fashion (for example, if the half-life of GSK3036656/washout period makes sequential dosing impractical), approval for such dosing will be sought from the Regulatory Agency. Dosing in an overlapping/interlocking fashion will only take place if such approval is obtained. In any case, a wash out period of at least 4 half-lives will be required before the same group of subjects is dosed again.

Part A - Food Effect:

An assessment of the effect of food on the exposure to GSK3036656 will be incorporated into the single dose part of the study (Part A). This assessment will be done by administering a single dose of GSK3036656/placebo with a high fat meal provided this dose was well tolerated in a previous treatment (dosing) period in the same cohort when administered in the fasted state. The dose to be administered with food will be selected such that, when administered in the fasted state, it provides exposure no higher than 50% of the highest exposure allowed in the study, in the eventuality that the presence of food unexpectedly enhances absorption.

Part B:

Part B (Cohorts 3, 4, 5, and 6) will comprise up to 4 cohorts of 10 (8 active: 2 placebo) healthy adult subjects to examine the safety, tolerability and PK of a repeated daily dose of GSK3036656 over a period of up to 14 days. Progression to Part B from Part A will be based on an acceptable safety, tolerability and PK profile in Part A. Appropriate doses and dose regimens for Part B will be selected by the Dose Escalation Committee based

on available safety, tolerability and PK data from Part A and/or any preceding repeat dose cohorts from Part B. A decision to proceed to a higher dose in Part B will be based on the review of safety data from at least the first week of dosing and PK data from at least the first 48 hours of dosing at the preceding dose.

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). Dosing with food may also be done if there are PK or tolerability reasons making it preferable to dose in a fed state. Dividing the total daily dose into 2 or 3 smaller doses administered over 24 hours may also be done. The decision to divide the total dose into smaller doses will be made by the GSK study team in conjunction with the Principal Investigator. Post-dose, subjects will undergo safety and PK assessments. Subjects will remain in the unit for at least 72 hours after the initial dosing. If they are released after that, it would be done at the discretion of the investigator following completion of the assessments on Day 4 and provided there are no safety concerns. If released, subjects will then return to the clinical unit each morning to receive their daily dose and assessments for the duration of Part B. Dosing will be scheduled to occur at approximately the same time each day for each individual subject. Subjects will be required to spend at least the last 24 hours at the end of the dosing period in the unit in order to complete the necessary safety assessments and PK sampling. The subjects may then be discharged from the unit but, if discharged, will be required to return for additional PK sampling at 36, 48 and 72 hours post dosing. Approximately 14 days after their last dose, subjects will return to the unit for a follow-up visit.

The total duration of the study for each subject recruited into Part A will be approximately 12 weeks. For subjects recruited into Part B the total study duration will be approximately 8 weeks.

Type and Number of Subjects

Up to 18 subjects (excluding possible replacements) will be recruited into the single ascending dose part of the study and up to 40 subjects (excluding possible replacements) will be recruited for the repeat dose. Both males and females of non child-bearing potential will be included.

Analysis

The focus of this FTIH study, both single and repeat dose phases, is to evaluate the safety, tolerability and pharmacokinetics of GSK3036656. No formal statistical hypotheses will be tested.

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.

Pharmacokinetic Analyses

From the plasma concentration-time data, the following pharmacokinetic 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), AUC(0-τ), and AUC(0-∞)], and apparent terminal phase half-life (t1/2). 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 for AUC (Ro) and Cmax (RCmax) may be determined. To estimate the pharmacokinetic linearity, the state ratio (Rss) may be determined. From the urine concentration data, the following pharmacokinetic parameters will be determined, as data permit: urinary excretion of unchanged drug (Ae), fraction of the dose excreted in the urine (fe), and the renal clearance (CLr).

2. INTRODUCTION

2.1. Study Rationale

This study is the first time into human study (FTIH) for GSK3036656. The study will evaluate the safety, tolerability and pharmacokinetics (PK) of single ascending and repeat oral doses of GSK3036656 in healthy adult volunteers.

The results of this study are intended to be used to identify appropriate and well tolerated doses of GSK3036656 to be used in further studies. A food effect assessment will also be undertaken to investigate the influence of food on the pharmacokinetics of GSK3036656.

2.2. Brief Background

GSK3036656 is being developed by GSK for the treatment of tuberculosis (TB) as part of a future combination regimen.

GSK3036656 suppresses protein synthesis in *Mycobacterium tuberculosis*, the causative agent of TB, by inhibiting the enzyme Leucyl t-RNA synthetase. It has activity not only against laboratory strains of M. tuberculosis, but also against a selection of drug-sensitive –TB (DS-TB), multi-drug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB) clinical isolates. The compound is a selective anti-tubercular agent as it is inactive against a panel of common bacterial pathogens and a panel of mammalian cell lines.

Animal models of TB infection have shown that GSK3036656 is very potent *in vivo*, with doses around 1 mg/kg providing maximum anti-TB effect in acute and chronic mouse models of TB. The compound possesses good chemical and metabolic stability, excellent physicochemical properties, and a low estimated potential for drug-drug interactions. The toxicological profile of GSK3036656 indicates an acceptable therapeutic window.

The clinical development program will evaluate the safety and efficacy of GSK3036656 in humans and aim for fast registration if successful. The FTIH trial described in this protocol is the first study where GSK3036656 will be administered to humans. A successful FTIH study would be followed by subsequent clinical studies investigating the efficacy of GSK3036656, alone as well as in combination with other compounds, in patients with TB.

3. OBJECTIVE(S) AND ENDPOINT(S)

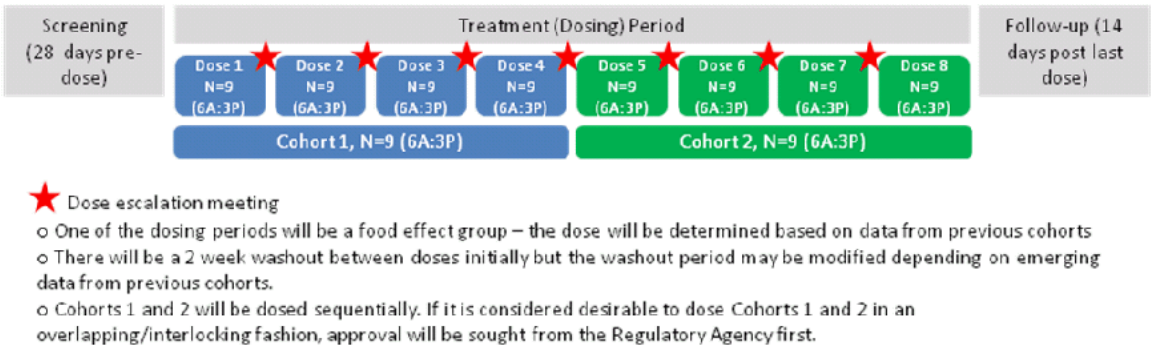
Objectives	Endpoints
Primary	
• To investigate the safety and tolerability of GSK3036656 after single ascending and repeat oral doses in healthy adult subjects	• Safety and tolerability of GSK3036656: o Adverse Events o Clinically relevant changes in safety parameters: 12-lead electrocardiogram (ECG), telemetry, vital signs (systolic and diastolic blood pressure, heart rate, temperature), clinical laboratory data (haematology, clinical chemistry, urinalysis)
• To determine the pharmacokinetics of single and repeat doses of GSK3036656 in healthy subjects	• Derived pharmacokinetic parameters for GSK3036656 including area under the plasma drug concentration versus time curve (AUC(0-t), AUC(0-∞), AUC(0-τ)), maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (tmax), and apparent terminal half-life (t1/2) as appropriate
Secondary	
• To assess the effect of food on the pharmacokinetics of GSK3036656 following an oral dose in healthy subjects	• Derived pharmacokinetic parameters for GSK3036656 including AUC(0-t), AUC(0-∞), Cmax, tmax, and apparent terminal half-life (t1/2)
• To assess preliminary dose proportionality of GSK3036656 following single and repeat oral doses, as data permit	• AUC(0-t), AUC(0-∞), and Cmax following single dose and AUC(0-τ) and Cmax following repeat dose for the assessment of dose proportionality
• To examine the extent of accumulation and achievement of steady-state following repeat oral doses of GSK3036656, as data permit	• Observed accumulation ratio based on AUC(Ro) and Cmax (RCmax) and steady-state ratio (Rss) following repeat dosing • Trough plasma concentrations at the end of the dosing interval (C_τ) to assess the achievement of steady-state of GSK3036656 following repeat oral doses
• To define the metabolic profile of GSK3036656 by identifying and quantifying, where possible and appropriate,	• Structure and concentration of GSK3036656-related material in plasma and urine

Objectives	Endpoints
GSK3036656-related material in plasma and urine following a single and repeated oral administration of GSK3036656	

4. STUDY DESIGN

4.1. Part A (Single Dose)

Figure 1 Part A Schematic



Up to two cohorts will be included in the single dose part (Part A). Each cohort will participate in up to 4 treatment (dosing) periods (including a food effect treatment period). Initially, there will be a 14 day wash out period for individual subjects between each dose level which is considered sufficient in light of the predicted half-life of GSK3036656 [on average, approximately 30 hours (range: 12 to 72 hours) based on the various preclinical extrapolation methods], however this may be revised once relevant PK data is obtained. Nine subjects per cohort will be enrolled and randomised to ensure adequate safety, tolerability and PK information is gained and a balanced randomisation is achieved across all treatment (dosing) periods.

During each treatment (dosing) period, GSK3036656 will be administered to 6 subjects and placebo will be administered to 3 subjects. As this is a FTIH study, each treatment (dosing) period will be staggered over 2 days. On Day 1 of each dose level, one subject will receive GSK3036656 and one subject will receive placebo. The remaining subjects within the dosing group will be dosed one day later provided satisfactory safety and tolerability is demonstrated for the subjects dosed on Day 1. A treatment (dosing) period does not have to be staggered if the dose administered is equal to or lower than a dose that has been already tested and found to be safe and well tolerated.

Subjects will attend the unit on Day -1 for assessments and a meal. The subjects will then fast overnight (at least 8 hours) and be dosed the following morning (Day 1). Dosing with food may also be done in Part A once results from the food effect analysis are available. Dividing the total dose for the treatment (dosing) period into 2 or 3 smaller doses administered within 24 hours may also be done. The decision to divide the total dose into

smaller doses will be made by the GSK study team in conjunction with the Principal Investigator. Post-dose, subjects will undergo safety and PK assessments. All subjects will remain in the unit until the 72 hour PK sample has been taken since this will enable a better assessment of their safety and will reduce the risk of subjects not returning for their visits. Subjects will be released at the discretion of the investigator following completion of the assessments provided there are no safety concerns identified from review of the clinical safety data. Approximately 14 days after their last dose, subjects will return to the unit for a follow-up visit.

The starting dose in Part A will be 5 mg. The dose will then be escalated up to a dose (no higher than 1500 mg) at which PK exposures do not exceed predefined limits determined from preclinical safety data (individual AUC[0-24] <4.9 µg.h/ml, individual Cmax <0.443 µg/ml). Dose escalation will only take place provided GSK3036656 is well tolerated and following review of all available safety, tolerability and pharmacokinetic data from the previous treatment (dosing) period by the Dose Escalation Committee (Section 6.3).

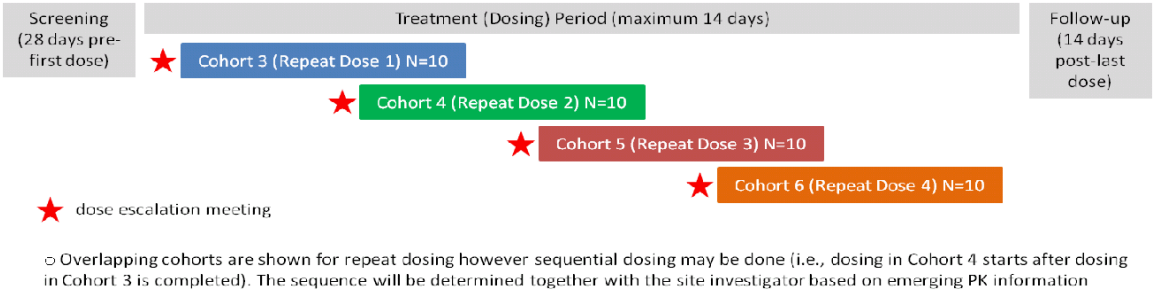
The two cohorts in Part A will be dosed sequentially (i.e., dosing in Cohort 2 starts after dosing in Cohort 1 is completed). If it is considered desirable to dose Cohorts 1 and 2 in an overlapping/interlocking fashion (for example, if the half-life of GSK3036656/washout period makes sequential dosing impractical), approval for such dosing will be sought from the Regulatory Agency. Dosing in an overlapping/interlocking fashion will only take place if such approval is obtained. In any case, a washout period of at least 4 half-lives will be required before the same group of subjects is dosed again.

4.1.1. Food Effect

An assessment of the effect of food on the exposure to GSK3036656 will be incorporated into Part A. This assessment will be done by administering a single dose of GSK3036656/placebo with a high fat meal provided this dose was well tolerated in a previous treatment (dosing) period in the same cohort when administered in the fasted state. The dose to be administered with food will be selected such that, when administered in the fasted state, it provides exposure no higher than 50% of the highest exposure allowed in the study, in the eventuality that the presence of food unexpectedly enhances absorption.

4.2. Part B (Repeat Dose)

Figure 2 Part B Schematic



Part B (Cohorts 3, 4, 5, and 6) will comprise up to 4 cohorts each containing 10 (8 active: 2 placebo) healthy adult subjects to examine the safety, tolerability and PK of a repeated daily dose of GSK3036656 over a period of up to 14 days. Progression to Part B from Part A will be based on an acceptable safety, tolerability and PK profile in Part A. Appropriate doses and dose regimens for Part B will be selected by the Dose Escalation Committee based on available safety, tolerability and PK data from Part A and/or any preceding repeat dose cohorts from Part B (Section 6.3). A decision to proceed to a higher dose in Part B will be based on the review of safety data from at least the first week of dosing and PK data from at least the first 48 hours of dosing at the preceding dose.

On Day –1 of each cohort, 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). Dosing with food may also be done if there are PK or tolerability reasons making it preferable to dose in a fed state. Dividing the total daily dose into 2 or 3 smaller doses administered over 24 hours may also be done. The decision to divide the total dose into smaller doses will be made by the GSK study team in conjunction with the Principal Investigator. Post-dose, subjects will undergo safety and PK assessments. Subjects will remain in the unit for at least 72 hours after the initial dosing. If they are released after that, it would be done at the discretion of the investigator following completion of assessments on Day 4 and provided there are no safety concerns. If released, subjects will then return to the clinical unit each morning to receive their daily dose and assessments for the duration of Part B. Dosing will be scheduled to occur at approximately the same time each day for each individual subject. Subjects will be required to spend at least the last 24 hours at the end of the dosing period in the unit in order to complete the necessary safety assessments and PK sampling. The subjects may then be discharged from the unit but, if discharged, will be required to return for additional PK sampling at 36, 48 and 72 hours post dosing. Approximately 14 days after their last dose, subjects will return to the unit for a follow-up visit.

The total duration of the study for each subject recruited into Part A will be approximately 12 weeks. For subjects recruited into Part B the total study duration will be approximately 8 weeks.

4.3. Type and Number of Subjects

Up to 18 subjects (excluding possible replacements) will be enrolled into Part A and up to 40 subjects (excluding possible replacements) will be enrolled into to Part B.

If subjects prematurely discontinue the study, replacements will be permitted for the single ascending dose part of the study (Part A) and will be considered on a case by case basis for the repeat dose (Part B) by the Sponsor in consultation with the investigator.

4.4. Design Justification

The FTIH study with GSK3036656 will evaluate the safety of the compound in healthy volunteers in order to avoid confounding factors resulting from the disease or concomitant drugs in patients with TB that may hinder the proper evaluation of safety. Also, ethical considerations dictate exploration of safety and tolerability in healthy volunteers first as patients with TB may be more vulnerable to side effects caused by the compound.

A cross-over design is preferred for Part A as it would allow assessment of safety and PK in the same individual thus reducing the influence of inter-individual variability.

Based on the physicochemical properties of GSK3036656, no significant food effect is predicted. Nevertheless, the study will investigate the possibility of food effect in order to provide guidance for dosing in future studies. If the FTIH study with GSK3036656 is successful, the next study in humans is expected to be an efficacy study in patients with TB where the compound is dosed for up to 2 weeks. Therefore, the proposed dosing for up to 14 days in Part B of the FTIH study is an appropriate first step in evaluating the safety of GSK3036656.

4.5. Dose Justification

Dose selection of GSK3036656 for this FTIH study was based on no observed adverse effect level (NOAEL) data, predicted pharmacokinetics for humans using the pharmacokinetic data from various preclinical species, and a targeted therapeutic exposure based on efficacy data from a murine model of chronic lung infection. GSK3036656 PK parameters and exposure values were converted from whole blood values to plasma values when necessary. GSK3036656 suppresses protein synthesis in *Mycobacterium tuberculosis* by inhibiting the enzyme Leucyl t-RNA synthetase which is not a human target; thus, the minimum anticipated biological effect level (MABEL) in humans for GSK3036656 could not be determined.

The *in vivo* PK parameters obtained in preclinical species (CD-1 mouse, SD rat, and beagle dog) after 1 mg/kg intravenous administration and the *in vitro* parameters (intrinsic Cl from microsomes and hepatocytes, plasma protein binding, and blood to plasma ratio) were used for calculations. The GlaxoSmithKline software package PK Predictor Pro (GUI v1.1.45 Calculation Engine v1.4.4) was used for IVIVE, LBF, GFR and allometric scaling and the CloePK software (Cyprotex) for the physiologically based pharmacokinetic (PBPK) modelling.

Predicted human clearance values ranged from approximately 1.1 (allometric scaling with MLP) to 7.2 (PBPK) mL/min/kg while predicted volume of distribution ranged from 3.5 (PBPK) to 4.5 (simple allometry) L/kg. Preclinically, oral bioavailability ranged from approximately 60% to greater than 100%.

The NOAEL dose in the rat (the most sensitive species) was 30 mg/kg with an average AUC(0-24) and Cmax of 90.5 µg.h/mL and 7.59 µg/mL, respectively; the NOAEL dose in the dog was 20 mg/kg with an average AUC(0-24) and Cmax of 147.0 µg.h/mL and 13.3 µg/mL, respectively. Due to the presence of heart valvular and vascular lesions in dogs at higher doses, and based on discussions with the GSK Cardiovascular Safety panel, the maximum individual daily human exposure after single or repeat dose in the study will be limited to 4.9 µg.h/mL for AUC(0-24) and 0.443 µg/ml for Cmax (30-fold margins from the dog NOAEL exposures of 147.0 µg.h/mL and 13.3 µg/ml, respectively).

The minimum target therapeutic exposure to be achieved in human is a mean AUC(0-24) of 1.74 µg.h/mL (95% CI: 0.94 – 4.55 µg.h/mL) based on efficacy data from a murine model of chronic lung infection.

Maximum Recommended Starting Dose (MRSD)

Using the FDA Guidance for estimation of the maximum safe starting dose, the NOAEL in rats was converted to the Human Equivalent Dose (HED) based on surface body area. After applying an uncertainty safety factor of 10 (guideline default) to the HED, the maximum recommended starting dose is 31 mg.

Dose Predicted to Achieve the Therapeutic Exposure Target

Simulations were conducted to predict the dose that would provide a therapeutic exposure in 90% and 95% of simulated subjects (n=10,000). Based on the range of predicted human clearance (CL) and bioavailability values for GSK3036656, 50% CV for CL, and a mean efficacy target of 1.74 µg.h/mL, the human dose to achieve the therapeutic exposure target ranges from 12 to 170 mg.

Predicted Exposure of the Proposed Starting Dose Compared to Study Exposure Limits

Simulations (n=10000 subjects) were conducted to predict the probability of individual exposure for a starting dose of 5 mg to exceed the AUC exposure limit of 4.9 µg.h/mL. Based on the range of predicted human CL and bioavailability values for GSK3036656 and 50% CV for CL, there is a very low probability (<1%) of any individual subject exceeding the AUC limit of 4.9 µg.h/mL for a 5 mg dose.

Based on the large predicted human volume of distribution (242 – 315 L), Cmax is expected to be very low following oral absorption of a 5 mg dose.

Summary

The proposed starting dose is 5 mg which is less than the Food and Drug Administration (FDA) Maximum Recommended Starting Dose (MRSD) of 31 mg and has a very low probability of any individual subject exceeding the limits of 4.9 µg.h/mL for AUC(0-24) or 0.443 µg/ml for Cmax . Further dose escalation will be based on exposure, safety, and tolerability data from the previous dose level. The maximum dose that can be administered in the study is 1500 mg based on a Genotoxic Risk Assessment.

4.6. Benefit:Risk Assessment

Consistent with GlaxoSmithKline guidance for early phase studies, GSK3036656 will be administered in an in-patient setting (with sufficient overnight facilities) with appropriate monitoring.

In order to minimise the risk of the initial human administration of GSK3036656, at the beginning of each treatment (dosing) period in Part A, one subject will receive GSK3036656 and one subject will receive placebo. The remaining subjects from that cohort will be dosed on the next day only if satisfactory safety and tolerability is demonstrated for the subjects dosed on Day 1. A treatment (dosing) period does not have to be staggered if the dose administered is equal to or lower than a dose that has been already tested and found to be safe and well tolerated.

Summaries of findings from non-clinical studies conducted with GSK3036656 can be found in the Investigator's Brochure. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK3036656]		
Reduction in red blood cell count	In a 4-week rat study (doses 3, 10 & 30 mg/kg/d) - dose-dependent decline in reticulocytes (by up to 52% in males and 62% in females) at day 7 followed by normal levels by day 14 and increased levels by day 29/30 compared to controls. Hgb levels decreased by 10-13% compared to controls on day 14 and day 29/30. In a 4 week dog study (doses 5, 10 & 20 mg/kg/d) - mild dose-dependent decrease in Hgb on day 14 (by about 10% compared to controls) with recovery by week 4. Reticulocyte counts unaffected. Dogs not bled on day 7. No histopathological changes in bone marrow or other relevant histopathology in the 4-week studies.	Standard safety haematology and clinical chemistry assessments will be performed and both trends and changes outside normal range will be monitored as part of laboratory safety assessments. Subjects whose haemoglobin drops below pre-specified limits (<110 g/L for males, <100 g/L for females) will be withdrawn from the study and followed up until levels are not clinically significant (Section 6.4– Individual Withdrawal/Stopping Criteria). While women of non-childbearing potential are permitted in this study, women who are susceptible to periods or heavy vaginal bleeding or spotting will be excluded in order to minimize blood loss and avoid confounding effects on the interpretation of hematology parameters.
Reduction in white blood cell count	In the 4 week rat study, decrease of up to 37% in total leucocyte count on day 29/30 compared to controls. In the 4-week dog study, no reported effects on white	White blood cell count will be monitored as part of laboratory safety assessments. Any clinically significant changes will be followed up until levels are not clinically significant.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	blood cells.	Subjects developing neutrophil counts <1000/mm^3 (1.0x10^9/L) and lymphocyte counts <500/mm^3 (0.5x10^9/L) will be withdrawn from the study and followed up until levels are not clinically significant (Section 6.4 – Individual Withdrawal/Stopping Criteria).
Heart valvular and vascular pathology	In a 7-day dog dose range finding (DRF) study – minimal focal subendocardial hemorrhage on the atrial surface of the left atrioventricular valve observed in both animals at the top dose of 60 mg/kg/d. In a 10day dog investigative study at 65 mg/kg/d – vascular lesions (including minimal focal necrosis and inflammatory infiltrate) in 3 out of 8 dogs. In the 4-week dog GLP study - no heart or valve changes up to the top dose of 20mg/kg/day; no increased inflammatory markers. Valvular or vascular pathology not observed in rats. This pathological change is not commonly seen in animals, and its mechanism and significance to humans are not clear. A correlation between the presence of hemodynamic changes and the presence of this pathology is suspected, but currently unproven.	This pathology is not monitorable in humans. To avoid risk to humans, dosing in the FTIH study will be limited to doses at which individual exposures [AUC (0-24)] do not exceed of 4.9 µg.h/ml – 1/30 of the dog NOAEL exposure (from the 4-week GLP study) at which no heart pathology was seen. Echocardiograms will be done at screening and follow up in order to exclude subjects with pre-existing valve or other cardiac abnormalities from the study and detect the presence of abnormalities after completion of the study.
Hemodynamic changes	Hemodynamic changes in several studies at ≥100 mg/kg in rats and ≥20 mg/kg in dogs - increased heart rate (rats and dogs), increased (rats) or decreased	Vital signs monitoring and stopping criteria will be used.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	(dogs) blood pressure.	
Phototoxicity	As GSK3036656 absorbs light in the UVB wavelength range (>290 nm), there is a potential for phototoxicity in clinical populations. No pathology in the skin or eye has been observed in animals so far.	Subjects with a history of photosensitivity will be excluded from participating in the study (Exclusion Criteria, Section 6.2). All study subjects will be instructed to minimise exposure to sunlight and other sources of ultraviolet radiation (Section 6.2).

4.6.2. Benefit Assessment

This is a healthy volunteer study and subjects will not stand to directly benefit from administration of GSK3036656.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Consent for screening evaluations may be obtained using the information and consent form for the HMR healthy volunteer panel, which has been approved by the Health Research Authority's Generic Document Review Committee. The trial-specific information and consent form will be signed by the subject either before any study-specific screening evaluation or after the investigator confirms the eligibility of the subject for the trial and before the subject is randomised to receive the first administration of study drug.

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product that may impact subject eligibility is provided in the GSK3036656 Investigator's Brochure [GlaxoSmithKline Document Number 2016N305393_01].

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

5.1. Inclusion Criteria

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

[1] AGE
• Between 18 and 55 years of age inclusive, at the time of signing the informed consent.

[2] TYPE OF SUBJECT
• Healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. • A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied, may be included only if the investigator in consultation with the Medical Monitor, if required, agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.

[3] WEIGHT
• Body weight ≥60 kg and body mass index (BMI) within the range 19 to 29.9 kg/m2 inclusive.

[4] SEX

• Male
• Female subjects of non-child bearing potential are eligible to participate. Non-child bearing potential is defined as:
  • Pre-menopausal females with one of the following:
  • Documented tubal ligation
  • Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion or documented bilateral salpingectomy
  • Hysterectomy
  • Documented Bilateral Oophorectomy
  • Postmenopausal defined as 12 months of spontaneous amenorrhea. Post-menopausal status will be confirmed by a simultaneous FSH and estradiol levels test.
• Male subjects with female partners of child bearing potential must comply with the following contraception requirements from the time of first dose of study medication until **90 days** after the last dose of study treatment (i.e. one sperm cycle).
  • Vasectomy with documentation of azoospermia.
  • Male condom plus partner use of one of the contraceptive options below:
  • Contraceptive subdermal implant
  • Intrauterine device or intrauterine system
  • Highly effective oral contraceptive, either combined or progestogen alone (provided it's associated with inhibition of ovulation)
  • Injectable progestogen
  • Contraceptive vaginal ring
  • Percutaneous contraceptive patches
• These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception (Appendix 3).

[5] INFORMED CONSENT
• The subject is able to understand and comply with protocol requirements, instructions and protocol-stated restrictions.

5.2. Exclusion Criteria

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

[1] CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
• Alanine aminotransferase (ALT) and bilirubin >1.5xupper limit of normal (ULN) (isolated bilirubin >1.5xULN may be acceptable, after consultation with the GSK Medical Monitor, if bilirubin is fractionated and direct bilirubin <35%). • Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). • QTcF >450 msec. • Presence of moderate or severe valve disorder or any other clinically significant abnormality. • Subjects with a history of photosensitivity. • Females of non-childbearing potential who are susceptible to heavy periods or vaginal bleeding or spotting. • Pregnant females. A human chorionic gonadotrophin (hCG) test will be performed on Day-1 of each treatment (dosing) period in Part A and Part B for women for whom post-menopausal status has not been confirmed by follicle stimulating hormone (FSH)/estradiol testing. No pregnancy tests will be required for female subjects confirmed as post-menopausal by FSH/estradiol testing. • Lactating females.

[2] CONCOMITANT MEDICATIONS
• Use of prescription or non-prescription drugs, including high-dose 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, unless in the opinion of the Investigator and sponsor the medication will not interfere with the study procedures or compromise subject safety. Paracetamol for mild analgesia will be permitted.

[3] RELEVANT HABITS
• Breath carbon monoxide test indicative of smoking or history of current use of tobacco- or nicotine-containing products. • Current regular alcohol consumption defined as: • An average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits. • Subjects must not sunbathe or use a tanning device (e.g. sunbed or solarium) whilst taking the study medication and until at least 2 weeks after their last dose. Subjects are to be advised that they should wear protective clothing (e.g. sun hat, long sleeves) and use a broad spectrum UVA/UVB sunscreen (SPF ≥30) when outdoors.

[4] CONTRAINDICATIONS
• History of sensitivity to heparin or heparin-induced thrombocytopenia. • History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.

[5] DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
• Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. • A positive test for HIV antibody. • A positive pre-study drug/alcohol screen. • 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, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). • Exposure to more than four new chemical entities within 12 months prior to the first dosing day.

5.3. Screening/Baseline/Run-in Failures

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

5.4. Individual Withdrawal/Stopping Criteria

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

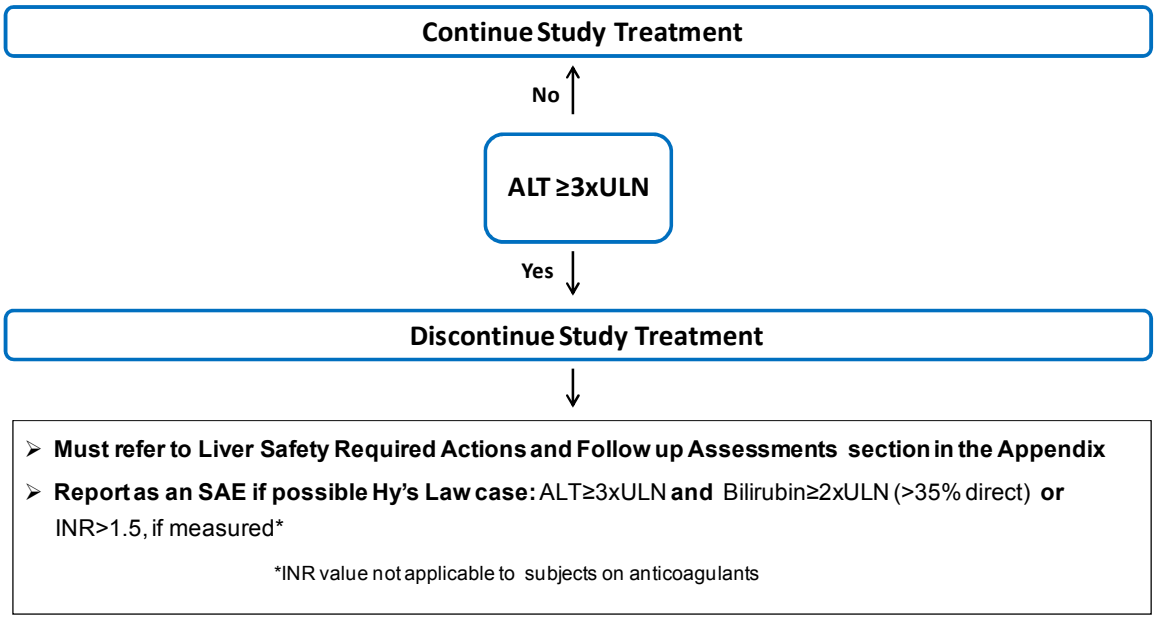
- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where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

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

5.4.1. Liver Chemistry Stopping Criteria

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

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 4.

5.4.1.1. Study Treatment Restart or Rechallenge

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

5.4.2. QTc Stopping Criteria

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

- QTcF >500 msec,
- Change from baseline: increase in QTcF >60 msec

Withdrawal of subjects is to be based on an average QTcF value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, obtain two more ECGs over a brief period of time and then use the averaged QTcF values of the three ECGs to determine whether the subject should be discontinued from the study.

5.4.3. Haematology Stopping Criteria

Study treatment will be discontinued for a subject if the following haematology stopping criteria are met and subjects should be followed up until values are not clinically significant.

- A reduction in haemoglobin to below 110 g/L in males and below 100 g/L in females
- A reduction in neutrophil count to below 1000/mm3 ($1.0x10^9$/L)
- A reduction in lymphocyte count to below 500/mm3 ($0.5x10^9$/L)

5.4.4. Vital Signs Stopping Criteria

Study treatment will be discontinued for a subject if the following vital signs stopping criteria are met:

- Clinically significant and sustained increase in resting heart rate (for example, >120 beats/minute for more than 2 hours)
- Clinically significant and sustained change in blood pressure (for example, systolic blood pressure >150 mm Hg or <85 mm Hg for more than 2 hours, or diastolic blood pressure >95 mm Hg for more than 2 hours)

5.4.5. Other Dose Adjustment/Stopping Safety Criteria

For an individual study participant, stopping criteria include, but are not limited to:

- Severe signs or symptoms, or significant changes in any of the safety assessments that put the safety of the individual at risk (e.g. ECG, vital signs,

laboratory tests etc), as judged by the Principal Investigator, in consultation with the Medical Monitor if necessary.

Any unacceptable adverse event that is thought to be related to the investigational product and any general safety finding that, in the opinion of the Investigator, gives cause for concern may result in the withdrawal of subject(s) and/or the study being paused or terminated and/or a dose adjustment.

5.5. Dose Escalation Stopping Criteria

Dose escalation in Part A or Part B will be stopped if any of the following occurs in a group/cohort:

1. There is substantially increased incidence and/or severity of clinically significant adverse events or withdrawals possibly related to GSK3036656 in the active treatment subgroup at the last dose level administered as compared to the placebo subgroup. The GSK Study Team in conjunction with the study investigator will determine the significance of the adverse events or withdrawals and make a decision about whether stopping further dose escalation is necessary.
2. At least one subject has a plasma AUC (0-24) higher than 4.9 µg.h/mL or a plasma Cmax higher than 0.443 µg/mL on any day.
3. For Part A, no meaningful increase in exposure is observed with increase in dose (i.e., a plateau in exposures is reached).

   Note: If dose escalation is stopped due to reasons 1 or 2 above occurring at the last dose, dosing at a lower level (e.g., an intermediate level between the last dose and a previous dose where dose escalation stopping criteria were not met) could be allowed. The GSK Study Team in conjunction with the study investigator will decide whether dosing at such level could be done and will select the dose to be administered.

5.6. Trial stopping criteria

The trial will be stopped if either of the following occurs:

- A serious adverse event that is considered to be at least possibly related to GSK3036656 in one or more subjects on active treatment
- Severe, clinically significant non-serious adverse events that are considered to be at least possibly related to GSK3036656 in 2 or more subjects on active treatment in the same group/cohort

If, following an internal safety review, it is appropriate to restart the trial, a substantial amendment will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) and Independent Ethics Committee (IEC). The trial will not restart until the amendment has been approved by the MHRA and IEC.

5.7. Subject and Study Completion

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

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

6. STUDY TREATMENT

6.1. Investigational Product

The term 'study treatment' is used throughout the protocol to describe products received by the subject as per the protocol design.

	Study Treatment	
Product name:	GSK3036656	Placebo
Formulation description:	GSK3036656 capsules containing 5 mg, 25 mg or 100 mg of GSK3036656 as free base equivalent	Matching capsule containing Avicel PH 102
Dosage form:	Capsule	Capsule
Unit dose strength(s)/Dosage level(s):	5 mg, 25 mg and 100 mg	N/A
Route of Administration	Oral	Oral
Dosing instructions:	See Study Reference Manual	See Study Reference Manual
Physical description:	Swedish Orange Size 0 capsule with no identifying markings containing a white to slightly coloured powder	Swedish Orange Size 0 capsule with no identifying markings containing a white to slightly coloured powder
Method for individualizing dosage:	Capsules packed in separate HDPE bottles	Capsules packed in separate HDPE bottles

6.2. Treatment Assignment

Eligible subjects will receive a unique subject number which will be assigned in chronological order. Once a subject number has been assigned to a subject, it cannot be reassigned to another subject.
A randomisation schedule will be generated by Clinical Statistics, prior to the start of the study, using validated internal software, which will assign subjects to GSK3036656 or placebo during a specific period. The pharmacist would be sent a copy of the randomisation schedule by the GSK randomisation co-ordinator, together with instructions as to which subjects to dose on Days 1 and 2 in the case of sentinel dosing. The pharmacist will assign randomisation numbers accordingly and communicate those back to the site to enter in the case report form (CRF).

6.3. Planned Dose Escalation and Adjustments

After the initial dose of GSK3036656, the decision to proceed to each subsequent dose level will be made by the Dose Escalation Committee (DEC) based on safety, tolerability and preliminary pharmacokinetic data from the prior lower dose level (Further details regarding dose escalation can be found in the 201040 Dose Escalation Charter). In Part A, safety data for at least 5 days post-dose and PK data for at least 2 days (48 hours) postdose from at least 4 subjects who received active treatment at the prior lower dose level will be reviewed before dose escalation. In Part B, safety data for at least the first 1 week (7 days) of dosing and PK data for at least the first 2 days (48 hours) of dosing from at least 4 subjects who received active treatment at the prior lower dose level will be reviewed before dose escalation. The actual doses to be administered will be selected by the DEC and may involve either an increase or a decrease in the dose, or repeating the same dose.

The exposures (AUC, Cmax) expected with the next selected dose will be predicted by pharmacokinetic assessment and modelling, and by calculating Bayesian predictive probabilities as data permit (more details in Section 10.3.1).

In toxicology studies in dogs, heart valvular and vascular lesions have been observed at relatively high doses and exposures; no such lesions have been seen in rats at similar exposures. To avoid the risk of this adverse event in the FTIH subjects, exposures in the FTIH study will be limited to predefined levels. Based on discussions with the GSK Cardiovascular Safety panel, the study will aim to limit the maximum individual daily plasma AUC(0-24) and Cmax after single or repeat dose to 4.9 µg.h/mL and 0.443 µg/ml, respectively - a 30-fold margin from the corresponding dog NOAEL exposures of 147.0 µg.h/mL and 13.3 µg/ml at which no valvular or vascular lesions have been detected.

Note: The term “mean” applied to group human exposure parameters (e.g., AUC) in this section refers to Geometric Mean of a dose cohort.

6.3.1. Dose escalation in Part A

In Part A, bigger dose escalation steps may be allowed at lower doses and systemic exposures as the expected risk of adverse events at these exposures is low. At higher doses, smaller dose escalation steps will be used to minimize the risk of adverse events and gastrointestinal intolerance.

The following rules will guide dose selection in Part A:

1. No dose escalation to the next dose will be higher than 6-fold.
2. Once the dose is ≥300 mg, any further dose escalation will be no higher than 3-fold irrespective of the observed exposures.
3. The highest dose in Part A will not exceed 1500 mg.
4. A proposed dose will be acceptable if the predicted probability of an individual exceeding a Day 1 plasma AUC (0-24) of 4.9 µg.h/mL or Cmax of 0.443 µg/mL, as estimated by PK modeling and Bayesian analysis (if feasible), is no more than 10%.

5. Based on prior PK data, individual doses may be adjusted, if needed, such that a predicted individual Day 1 AUC (0-24) or Cmax does not exceed 4.9 µg.h/mL or 0.443 µg/mL, respectively.

Dosing with food in Part A will be initiated after the exposures achieved with at least two dose levels administered in a fasted state are already known.

6.3.2. Dose escalation in Part B

Part B may be initiated after the safety and PK data of at least three doses from Part A are already known. The decision to initiate Part B will be made by the GSK Study team in conjunction with the investigator.

The following rules will guide dose selection in Part B:

1. The starting daily dose in Part B will be selected such that its expected exposure (mean AUC[0-24] or Cmax) on the last day of dosing is no higher than the Day 1 exposure of a dose that has been found to be safe and well tolerated in Part A. The expected daily exposures during the dosing period, including on the last day of dosing, will be predicted based on the PK parameters for GSK3036656 established in Part A. As the highest exposure with repeat dosing is expected on the last day of dosing (as a result of accumulation), this approach would select a daily dose which provides systemic concentrations that, at any time during the period of dosing, are not likely to be higher than the ones already found to be safe and well tolerated in Part A.
2. Subsequent doses in Part B may be selected using the criteria described above for the starting dose in Part B. The expected daily exposures during the dosing period, including on the last day of dosing, will be predicted based on available PK data from Part A and from prior cohorts in Part B. Alternatively, a dose may also be selected even if it does not meet these criteria provided it is no more than 4-fold higher than a previous dose that has been found to be safe and well tolerated upon repeat dosing in Part B.
3. The highest daily dose in Part B will not exceed the highest single dose that has been found to be safe and well tolerated in Part A.
4. A proposed dose will be acceptable if the predicted probability of an individual exceeding a daily plasma AUC (0-24) of 4.9 µg.h/mL or Cmax of 0.443 µg/mL on any day of the dosing period, as estimated by PK modeling and Bayesian analysis (if feasible), is no more than 10%.

6.4. Blinding

This will be a double blind (sponsor unblind) study where neither the study subjects nor the investigator are aware of the treatment received. The following will apply.

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.

- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding. The date and reason for the unblinding must be fully documented in the CRF.

If a subject's treatment is unblinded, subjects may continue in the study at the discretion of the sponsor. The primary reason for unblinding (the event or condition which led to the unblinding) will be recorded in the CRF.

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

6.5. Packaging and Labeling

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

6.6. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for preparation of GSK3036656 will be detailed in a Study Specific Technical Agreement/Memo (TTS).

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

6.7. Compliance with Study Treatment Administration

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

6.8. Treatment of Study Treatment Overdose

For this study, any dose of GSK3036656 greater than the dose specified for that treatment (dosing) period will be considered an overdose.

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

In the event of an overdose the investigator or treating physician should:

- contact the Medical Monitor immediately.
- closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities for at least 30 days.
- obtain a plasma sample for pharmacokinetic (PK) analysis, if requested by the Medical Monitor, within 2 days of that request (determined on a case-by-case basis).
- document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

In case of an overdose, decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.9. Treatment after the End of the Study

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

6.10. Concomitant Medications and Non-Drug Therapies

6.10.1. Permitted Medications and Non-Drug Therapies

Paracetamol at doses of ≤2 grams/day is permitted. Other concomitant medication may be considered on a case by case basis by the investigator in consultation with the GSK Medical Monitor.

6.10.2. Prohibited Medications and Non-Drug Therapies

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

7. STUDY ASSESSMENTS AND PROCEDURES

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1

The following points must be noted:

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

    Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The timing and number of planned study assessments, including safety 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 documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- **Part B outpatient visits:** If subjects are discharged on Day 4, they will be required to return to the unit daily for dosing and assessments. Safety assessments will include daily vital signs, AE and concomitant medication review and laboratory assessments on days 6, 10 and 15.
- The IEC and MHRA will be informed of any safety issues that require a protocol amendment or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time & Events Table

Table 1 Part A

Part A	**Screening**		**Day**					**Follow-up**
Days	**-28 to -2**		**–1**	**1**	**2**	**3**	**4**	**15**
Informed consent	X							
Inclusion/exclusion criteria[1]	X		X					
Medical/surgical history	X							X
Admission			X					
Inpatient stay			←	—	—	—	→	
Dose of GSK3036656[2]				X				
Echocardiogram[3]	X							X
Discharge							X	X
Outpatient visit[4]	X	X						X
Safety assessments								
Physical examination[5]	X		X		X		X	X
Height & weight[5]	X							
Vital signs[6]	X		X	X	X	X	X	X
12-lead ECG[7]	X			X	X	X	X	X
Holter monitoring[8]	←	→						
Telemetry[9]				←	—	→		
Clinical laboratory assessments								
Screening tests (incl blood FSH & estradiol for female subjects only)	X							
Haematology, biochemistry and urinalysis[10]	X		X		X		X	X
Pregnancy test (female only)[11]	X		X					
Urine drug screen, alcohol & smoking breath tests	X		X					
PK samples								
Blood for PK GSK3036656[12]				X	X	X	X	
Total urine collection[13]				X	X	X	X	
Concomitant therapy review[14]	←	—	—	—	—	—	—	→
Adverse events[14]	←	—	—	—	—	—	—	→

1. Inclusion/exclusion criteria will only be assessed at Day-1 of the first period.
2. In the event of a divided dose, alterations to event timepoints may be communicated in a filenote. For the food effect assessment, the selected dose will be given with a high fat meal.
3. Echocardiograms may be done at a separate screening visit.
4. When there is Holter monitoring at screening, subjects will return after 24 h to have the Holter removed.
5. Brief physical examination will be done at admission (Day–1) and in the morning on Days 2 and 4 in each treatment session. Full physical examination will be done at screening and follow-up (to include height and weight at screening only).
6. Blood pressure, heart rate, tympanic temperature and respiratory rate. Vital signs will be recorded: at pre-dose and at 0.5, 1, 2, 3, 4, 6, 12, 24, 48 and 72 h after dosing on Day 1.

7. ECGs will be recorded at pre-dose and at 0.5, 1, 2, 3, 4, 6, 12, 24, 48 and 72 h after dosing on Day 1. Triplicate measurements (about 2-5 mins apart) will be taken at pre-dose; single measurements will be taken at all other time points.
8. 24 h Holter monitoring at screening only.
9. Telemetry will be recorded from -1 h pre-dose until 24 h post-dose
10. Haematology, clinical chemistry, and urinalysis will be done at Day-1 and at 24 and 72 h post-dose.
11. Pregnancy testing of female subjects only. At screening pregnancy test will be done using the blood sample; urine pregnancy test will be done on admission.
12. Blood samples for assay of GSK3036656 will be taken: at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48 and 72 h after dosing on Day 1.
13. Total urine collections for GSK3036656 will be performed at the following time points: pre-dose and 0-6, 6-12, 12-24, 24-48 and 48-72 h after dosing on Day 1.
14. AEs and concomitant medications will be recorded collected from the start of informed consent until the follow-up contact.

Table 2 Part B

Part B	Screening		Day																		Follow-up
Days	**-28 to -2**		**–1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**28**
Informed consent	X																				
Inclusion/exclusion criteria	X		X																		
Medical/surgical history	X																				X
Admission			X																		
Inpatient stay			←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→	
Dose of GSK3036656[1]				X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Echocardiogram[2]	X																				X
Discharge																		X			X
Outpatient visit[3]	X	X																	X	X	X
Safety assessments																					
Physical examination[4]	X		X		X		X		X				X					X			X
Height & weight[4]	X																				
Vital signs[5]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[6]	X			X	X	X	X		X				X				X				X
Holter monitoring[7]	←	→																			
Telemetry[8]				←	→																
Clinical laboratory assessments																					
Screening tests (incl blood FSH & estradiol for female subjects only)	X																				
Haematology, biochemistry and urinalysis[9]	X		X				X		X				X					X			X
Serum pregnancy test (female only)[10]	X		X																		
Urine drug screen, alcohol & smoking breath tests	X		X																		
PK samples																					
Blood for PK GSK3036656[11]				X	X	X	X								X	X	X	X	X	X	
Total urine collection[12]				X	X												X	X			
Concomitant therapy review[13]	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→	
Adverse events[13]	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→	

1. Dosing of GSK3036656 should be at approximately the same time each day. In the event of a divided dose, alterations to event timepoints may be communicated in a filenote.
2. Echocardiograms may be done at a separate screening visit.
3. When there is Holter monitoring at screening, subjects will return after 24 h to have the Holter removed.
4. Brief physical examination will be done on Days-1, 2, 4, 6, 10, and 15. Full physical examination will be done at screening and follow-up (to include height and weight at screening only).
5. Blood pressure, heart rate, tympanic temperature and respiratory rate. Vital signs will be recorded: at pre-dose and at 0.5, 1, 2, 3, 4, 6, 12, 24, 48 and 72 h after dosing on Days 1 and 14; and at pre-dose on Days 5-13.
6. ECGs will be recorded at pre-dose and at 0.5, 1, 2, 3, 4, 6, 12, 24, 48 and 72 h after dosing on Days 1 and 14; and at pre-dose on Days 6 and 10. Triplicate measurements (about 2-5 mins apart) will be taken at pre-dose; single measurements will be taken at all other time points.
7. 24 h Holter monitoring at screening only.
8. Telemetry will be recorded from -1 h pre-dose until 24 h post-dose on Day 1.
9. Haematology, clinical chemistry and urinalysis will be done on Day-1 and in the morning (pre-dose if feasible) on Days, 4, 6, 10, and 15.
10. Pregnancy testing of female subjects only. At screening pregnancy test will be done using the blood sample; urine pregnancy test will be done on Day-1.
11. Blood samples for assay of GSK3036656 will be taken: at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36, 48 and 72 h after dosing on Day 1; and at pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 15, 24, 36 48 and 72 h after dosing on Day 14. PK samples will also be taken pre-dose on Days 12 and 13.
12. Total urine collections for GSK3036656 will be performed at the following time points: pre-dose and 0-6, 6-12 and 12-24 h after dosing on Days 1 and 14.
13. AEs and concomitant medications will be recorded collected from the start of informed consent until the follow-up contact.

7.2. Safety Assessments

Planned time points for all safety assessments are provided in the Time and Events table (Section 7.1).

7.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded (at screening only).
- A brief physical examination will include, at a minimum, assessments of the lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.2.2. Vital Signs

- Tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed supine with a completely automated device. Manual techniques will be used only if an automated device is not available or in the case of an emergency.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Pulse rate and blood pressure will be measured in triplicate at screening and pre-dose. The readings should be averaged to give the measurement to be recorded in the CRF.

7.2.3. Electrocardiograms

- Triplicate 12-lead ECG will be obtained at screening and predose using an ECG machine that calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Refer to Section 5.4.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, three individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 to 5 minutes apart.

7.2.4. Cardiac Telemetry

- Continuous cardiac telemetry will be performed from approximately 1 hr pre-dose to 24 hours post dosing in both Parts A and B. Full disclosures will be maintained as part of the participant's source documents and will be reviewed in detail.

7.2.5. Holter Monitoring

- Holter monitoring will be performed in Parts A & B at screening for the duration of 24 hours.

7.2.6. Echocardiography

- Echocardiography will be performed at screening and at follow-up in a blinded fashion. This assessment will be done only for subjects who have undergone all other screening assessments, have been found eligible for the study, and are willing to enrol into the study.

7.2.7. Clinical Safety Laboratory Assessments

- The tests will be performed by the local laboratory.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with an underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or at follow-up should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual and the Time and Events table (Section 7.1).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g. SAE or AE or dose modification), then the results must be recorded in the CRF.

Table 3 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count		*RBC Indices*:	*WBC count with Differential:*
	RBC Count		MCV	Neutrophils
	Hemoglobin		MCH	Lymphocytes
	Hematocrit			Monocytes
	Reticulocytes			Eosinophils
				Basophils
Clinical Chemistry	BUN	Potassium	AST (SGOT)	Total and direct bilirubin

Laboratory Assessments	Parameters
	Creatinine | Sodium | ALT (SGPT) | Total Protein Glucose | Calcium | Alkaline phosphatise | Albumin Cholesterol | Triglycerides | Cardiac troponin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)
Screening Tests	• HIV • Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol (as needed in women of non-child bearing potential only) • Pregnancy (hCG) – serum or urine • Urine drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Alcohol and smoking breath tests
NOTES : • Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.4.1 and Appendix 4	

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

7.3. Pharmacokinetics

7.3.1. Blood Sample Collection

Blood samples for plasma PK analysis of GSK3036656 will be collected into K3 EDTA tubes at the time points indicated in the Time and Events Table (Section 7.1). The actual date and time of each blood sample collection will be recorded. In the repeat dose part of the study on days 12 and 13, PK samples will be taken pre-dose to assess the achievement of steady-state of GSK3036656 following repeat oral doses. On the last dosing day of the repeat dose, subjects will undergo the same assessments as on Day 1. Subjects may then be discharged but will be required to return for the 36, 48 and 72 hour PK sampling. PK samples obtained on pre-dose and 24 hours post-dose on day 14 will also be used as part of the assessment to see if steady-state has been achieved.

The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

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

7.4. Non-Pharmacokinetic Sample Collection and Processing

7.4.1. Urine Sample Collection

Urine samples will be collected from each subject prior to dosing (the pre-dose sample can be collected up to 48 hours prior to dosing) and over the time period listed in the Time and Events Table to investigate any GSK3036656 related material excreted via this route. Details of urine sample collection, processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

7.4.2. Sample Analysis

Plasma analysis will be performed under the control of Platform Technologies and Science (PTS), GlaxoSmithKline, the details of which will be included in the SRM. Concentrations of GSK3036656 will be determined in plasma samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma has been analyzed for GSK3036656, any remaining plasma may be analyzed for other compound-related metabolites and the results reported under a separate PTS, GlaxoSmithKline protocol.

The urine samples may be analysed qualitatively and quantitatively for compound-related material and the results will be reported under a separate PTS, GlaxoSmithKline protocol.

8. SAFETY

Planned time points for all safety assessments are listed in the Time and Events Table (Section 7.1). Additional time points for safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

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

The definitions of an AE or SAE can be found in Appendix 2.

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

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

- AEs and SAEs will be collected from the start of informed consent until the follow-up contact, at the time points specified in the Time and Events Table (Section 7.1).
- AEs and SAEs collected before the start of study treatment will be recorded as pre-treatment AEs/SAEs.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
    - All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstances should this exceed 24 hours, as indicated in Appendix 2. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 2.

8.1.2. Method of Detecting AEs and SAEs

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

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”

- "Have you taken any new medicines, other than those provided in this study, since your last visit/contact?"

8.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up. Further information on follow-up procedures is given in Appendix 2.

8.1.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

9. DATA MANAGEMENT

- For this study data will be double-entered into a clinical database management system (ClinPlus Version 3.3).
- 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 Medical Dictionary for Regulatory Activities (MedDRA) and an internal validated medication dictionary, GSKDrug by GSK.

Original CRFs will be retained by GSK, while the investigator will retain a copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

10. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

10.1. Hypothesis and Treatment Comparisons

Given this is the first time in human trial for GSK3036656, no formal statistical hypotheses are to be tested. Where appropriate, an estimation approach will be taken, and point estimates and confidence intervals (CIs) will be constructed.

10.2. Sample Size Considerations

The planned sample size is 18 subjects for Part A of this study (9 subjects per cohort) and up to 40 subjects for Part B (10 subjects per cohort). Additional subjects may be recruited as replacement for withdrawn subjects.

No statistical techniques were used to calculate the sample size, and because this is a FTIH study, no information on PK variability is available to allow any precision estimate.

10.2.1. Sample Size Re-estimation

No sample size re-estimation is currently planned for this study.

10.3. Data analysis Considerations

Statistical analyses will be performed by, or under the direct auspices of, Statistics, Programming and Data Sciences (SPDS), GlaxoSmithKline.

Complete details of the planned statistical analyses will be provided in the RAP.

10.3.1. Interim Analysis

No formal interim analyses are planned for this study. However, safety, tolerability, and pharmacokinetic data will be reviewed before each dose escalation in Part A (single dose) and Part B (repeat dose), and prior to the investigation of the food effect.

The relationship between dose and plasma GSK3036656 exposure, and associated variability will be characterized by a power model once data are available from 3 dose levels. Prior to that, prediction of the human exposure at the next dose will be based on population PK modelling (if feasible) or on the assumption of dose–exposure proportionality (i.e., doubling the dose gives an approximate doubling of exposure). If prior PK results show less than proportional increase in exposure with increasing dose, the prediction will be based on the assumption that the fold exposure increase to fold dose increase ratio will be the same with the current dose escalation as it was with the previous one. If prior PK results show more than proportional increase in exposure with dose, subsequent dose escalations will not be higher than 3-fold. The power model will be updated as data become available throughout the study. During dose escalation, and once data is available from 3 doses, a Bayesian predictive probability that an individual will have AUC(0-24) greater than 4.9 µg.h/mL or a Cmax greater than 0.443 µg/mL,

will be calculated for the next dose level and used together with safety and tolerability data to aid the next dose selection.

The Bayesian predictive probability will be based on Whitehead's model [Whitehead, 2001]:

$\log(yij) = \theta 1 + \theta 2 \cdot \log(dij) + \varepsilon ij$

where

- y_{ij} is the observed or predicted log-AUC variable (AUC[0-24]) or log-Cmax of the j-th dose d_{ij} administered to the i-th subject
- θ_1, θ_2 are population intercept and slope, respectively.
- ε_{ij} is a random error term, with mean zero and variance σ^2.

10.3.2. Final analyses

10.3.2.1. 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.

10.3.2.2. Pharmacokinetic Analyses

Pharmacokinetic analysis will be the responsibility of the Clinical Pharmacology Modeling and Simulation Department, (CPMS), GlaxoSmithKline. Plasma GSK3036656 concentration-time data will be analyzed by non-compartmental methods with WinNonlin 5.2 or higher. Calculations will be based on the actual sampling times recorded during the study.

From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit:

- maximum observed blood concentration (Cmax),
- time to Cmax (tmax),
- area under the plasma concentration-time curve [AUC(0-t), AUC(0-∞) and AUC(0-τ)],
- apparent terminal phase half-life (t1/2)
- trough concentration (Cτ).

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 will be used to assess attainment of steady state and the steady state ratio (Rss) will be calculated (Day 14 AUC(0-τ)/Day 1 AUC(0-∞)). To estimate the extent of

accumulation after repeat dosing, the observed accumulation ratio (Ro: Day 14 AUC(0-τ)/Day 1 AUC(0-τ); and RCmax: Day 28 Cmax/Day 1 Cmax) will be determined.

From the urine concentration data, the following pharmacokinetic parameters will be determined, as data permit: urinary excretion of unchanged drug (Ae), fraction of the dose excreted in the urine (fe), and the renal clearance (CLr).

Pharmacokinetic data will be presented in graphical and/or tabular form and will be summarized descriptively.

Statistical analyses of the pharmacokinetic parameter data will be the responsibility of SPDS, GlaxoSmithKline. Distributional assumptions underlying the statistical analyses will be assessed by visual inspection of residual plots. Normality will be examined by normal probability plots, while homogeneity of variance will be assessed by plotting the residuals against the predicted values for the model. Alternative analyses of the data will be performed if any of the model assumptions appear to be violated. Full details on the statistical aspects will be detailed in the Reporting and Analysis Plan (RAP).

Dose Proportionality (Single and Repeat Dose Study Phases)

Dose proportionality will be assessed following single doses of GSK3036656 (Part A) via analyses of AUC(0-t), AUC(0-∞), and Cmax. Dose proportionality following repeated dosing (Part B) will be assessed using AUC(0-τ) and Cmax.

A statistical analysis will be performed using the power model. The analysis will be performed on $\log_e$-transformed data. For each of these parameters a mixed effects model will be fitted with $\log_e$(dose) as a fixed effect and individual subject fitted as random effects. Estimates of the mean slopes of $\log_e$(dose) will be reported along with corresponding 90% confidence intervals (slope≈1 implies dose proportionality).

Food Effect (Single Dose Study)

The effect of food on the pharmacokinetics of GSK3036656 will be examined. AUC(0-t), AUC(0-∞), Cmax, and $t_{1/2}$ of GSK3036656 will be analysed after a $\log_e$-transformation of the data. An analysis of variance model will be fitted along with 90% confidence intervals using a mixed effects model, with fed/fasted condition as a fixed effect and subject as a random effect. Point estimates and corresponding 90% confidence intervals will be constructed for the comparisons of interest of GSK3036656 fed – GSK3036656 fasted, using the residual variance. These will then be back-transformed to provide point estimates and corresponding 90% confidence intervals for the geometric mean ratios fed:fasted.

Tmax will be analyzed non-parametrically using a Wilcoxon matched pairs test to compute the point estimate and 90% confidence interval for the median difference (fed – fasted).

Accumulation (Repeat Dose Study Phase)

The extent of accumulation of GSK3036656 will be based on AUC (Ro) and Cmax (RCmax).

The focus of the statistical analysis will be to estimate the accumulation ratio, Ro, on the pharmacokinetics of GSK3036656. Following $\log_e$-transformation, AUC(0-τ) on Day 14 and AUC(0-τ) on Day 1 will be analysed by a mixed effect model, fitting fixed effect terms for dose, day, and day by dose interaction, and fitting subject as a random effect. For each dose, point estimates and 90% confidence intervals for the differences "Day 14-Day 1" will be constructed using the appropriate error term. The point estimates and associated 90% confidence intervals will then be exponentially back-transformed to provide point and 90% confidence interval estimates for the ratios "Day 14: Day 1" for each active dose. If both the dose and day by dose interaction terms are not significant, a single point estimate and confidence interval pooled across all doses will also be constructed.

Similarly, the accumulation ratio, RCmax will be estimated, using Cmax calculated on Day 14 and on Day 1. The analysis will be analogous to that described above for the estimation of Ro, replacing AUC by Cmax.

Time Invariance

The time invariance ratio will be calculated as the ratio of AUC(0-τ) on Day 14 over AUC(0-inf) on Day 1. The time invariance ratio will be listed and summarized along with other PK parameters. An analysis of variance (ANOVA) with subject as a random effect and day as a fixed, categorical effect will be conducted by dose on the log-transformed AUC. The time invariance of GSK3036656 will be assessed by calculating the ratio of the generalized least square means of AUC(0-τ) on Day 14 to AUC(0-inf) on Day 1, along with the corresponding 90% CI at each dose level. AUC(0-inf) on Day 1 will be the reference phase in the analysis, while AUC(0-τ) on Day 14 will be the test phase.

Achievement of Steady State (Repeat Dose Study Phase)

Trough concentration levels, Cτ, collected pre-morning dose will be plotted by collection day and dose.

To evaluate whether steady state was achieved, statistical analysis of Cτ will be performed after a log-transformation of the dose data. A mixed effect model will be fitted with dose, day and dose-by-day interaction as fixed effects (with dose as a factor and day as a continuous covariate) and subject as a random effect. The coefficients of the slopes for the day effect for each dose, along with corresponding 90% confidence intervals, will be used to determine whether steady state was achieved. If the day-by-dose interaction were not significant, then the point estimates and 95% CIs for the individual dose levels will also be pooled across all doses for a single D14/D1 ratio.

10.3.3. Non-Pharmacokinetic Sample Analysis

Aliquots of any remaining plasma and urine will be transferred to a separate protocol for metabolite profiling investigations. The results of these investigations will be reported separately.

11. STUDY GOVERNANCE CONSIDERATIONS

11.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (e.g. advertisements) must be submitted to an IEC by the investigator and reviewed and approved by the IEC before the study is initiated.
- Any amendments to the protocol will require IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC
  - Notifying the IEC of SAE or other significant safety findings as required by IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

11.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

11.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

11.5. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

11.6. Dissemination of Clinical Study Data

11.6.1. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g. laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.6.2. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Source Document Agreement (SDA).

11.7. Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12. REFERENCES

GlaxoSmithKline Document Number 2016N305393_01, GSK3036656 Investigator's Brochure, dated 03-Jan-2017

GlaxoSmithKline Document Number 2014N202803_00, A double blind, placebo-controlled first time in human study to evaluate the safety, tolerability and pharmacokinetics of single and repeat doses of GSK3036656 in healthy adult volunteers, dated 13-Jan-2017.

Whitehead J, Patterson S, Webber D, Francis S, Zhou Y. Easy-to-implement Bayesian methods for dose-escalation studies in healthy volunteers. Biostatistics. 2001 Mar;2(1):47-61

13. APPENDICES

13.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

µg	Microgram
AE	Adverse Event
Ae	Excretion of unchanged drug
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 from time zero (pre-dose) during a dosage interval
AUC(Ro)	Observed Accumulation Ratio for AUC observed accumulation ratio for AUC
AUC[0-24]	Area under the concentration-time curve from time zero (pre-dose) to 24 hours post dose
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CL	Clearance
CLr	Renal Clearance
Cmax	Maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CPMS	Clinical Pharmacology Modelling and Simulation
CPSSO	Clinical Pharmacology Sciences and Study Operations
CRF	Case Report Form
Cτ CτCτ Cτ	Trough Concentration (Cτ) Trough concentration (Cτ) Trough concentration (Cτ) Trough concentration (Cτ)
DEC	Dose Escalation Committee
DRF	Dose Range Finding
DS-TB	Drug-Sensitive-Tuberculosis
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
FDA	Food and Drug Administration
fe	Fraction of the dose excreted in urine
FRP	Females of Reproductive Potential
FSH	Follicle Stimulating Hormone
FTIH	First Time In Human

GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
h	Hour
HBsAg	Hepatitis B surface antigen
hCG	Human Chorionic Gonadotrophin
HED	Human Equivalent Dose
Hep B	Hepatitis B
Hep C	Hepatitis C
Hg	Mercury
Hgb	Haemoglobin
HIV	Human Immunodeficiency Virus
HMR	Hammersmith Medicines Research
HPLC	High Performance Liquid Chromatography
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
Ig	Immunoglobulin
INR	International Normalised Ratio
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IVIVE	In vitro in vivo extrapolation
kg	Kilogram
L	Litres
LBF	Liver Blood Flow
LDH	Lactate dehydrogenase
MABEL	Minimum Anticipated Biologically Effective Level
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MDR-TB	Multi-Drug-Resistant-Tuberculosis
MedRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
mIU/mL	Milli-international units per millilitre
mL	Millilitre
mm	Millimetre
MRSD	Maximum Recommended Starting Dose
MSDS	Material Safety Data Sheet
nm	Nanometer
NOAEL	No Observed Adverse Effect Level
PBPK	Physiologically Based Pharmacokinetic

PK	Pharmacokinetic
PTS	Platform Technologies and Science
QTc	Electrocardiogram QT interval corrected for heart rate
QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
RCmax	Cmax Ratio
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RNA	Ribonucleic acid
Rss	Steady-State Ratio
SAE	Serious adverse event(s)
SDA	Source Document Agreement
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SPDS	Statistics, Programming and Data Sciences
SPF	Sun Protection Factor
SRM	Study Reference Manual
t½	Terminal phase half-life
TB	Tuberculosis
tmax	Time of occurrence of Cmax
t-RNA	Transfer-Ribonucleic acid
ULN	Upper Limit of Normal
UV	Ultraviolet
WBC	White blood cells
XDR-TB	Extensively Drug-Resistant-Tuberculosis

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
ClinPlus
CloePK
WinNonlin

13.2. Appendix 2: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • 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 study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • 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 before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant'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 participant's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which 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.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant 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 outpatient setting. Complications that occur during hospitalization are AE. 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 persistent disability/incapacity

- 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 with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE 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 participant or may require medical or surgical intervention to prevent

one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include 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.

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment

administration will be considered and investigated.

- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK

- The SAE CRF should be transmitted to the SAE coordinator by e-mail.
- In rare circumstances and in the absence of other options, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page, and in the SRM.

13.3. Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Females of Reproductive Potential (FRP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered FRP

- Premenarchal
- Premenopausal female with ONE of the following:
- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year as described in the table below when having penile-vaginal intercourse with a female reproductive potential.

- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.
- Refrain from donating sperm for duration of study and for 5 half-lives + 90 days after the last dose of drug.

Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the FRP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used).*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant).*

NOTES:

a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Pregnancy Testing

- Pregnancy testing, with a sensitivity of 25 mIU/mL will be performed and assayed in a certified laboratory in accordance with instructions provided in its package insert.

Collection of Pregnancy Information

Male participants with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK
- Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

13.4. Appendix 4: Liver Safety: Required Actions and Follow-up Assessments Guidelines

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN

If ALT≥3xULN AND bilirubin[1,2] ≥2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.

See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)

MONITORING:

If ALT≥3xULN AND bilirubin ≥2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended

If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 3 days of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form

If ALT≥3xULN AND bilirubin ≥2xULN or INR >1.5:
• Anti-nuclear antibody, anti-smooth muscle</td></tr>
</table>

Liver Chemistry Stopping Criteria	
liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]. **NOTE: not required in China**. • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

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

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

13.5. Appendix 5: Protocol Amendment History

Not Applicable