TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase I, Randomized, Double-Blind (Sponsor Unblinded), Single-Center, Placebo-Controlled, Three-Part Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Ascending Single and Repeat Intravenous Doses of GSK3342830 in Healthy Adult Subjects

Compound Number: GSK3342830

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Author (s):

GSK: PPD (Clinical Statistics), PPD (Infectious Disease Medicines Development), PPD (Preclinical Safety Assessment), PPD (Bioanalysis), PPD (Clinical Pharmacology Modeling and Simulation), PPD (PCPS Therapy Area Delivery)

PPD: PPD (Global Product Development), PPD (Biostatistician), PPD (Regulatory Affairs), PPD (Pharmacokineticist), PPD (Medical Writer)

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2015N257523_00	2016-FEB-18	Original
2015N257523_01	2016-NOV-01	Amendment No. 1
The purpose of this amendment is to add 1 cohort to this study. This cohort will consist of Japanese subjects who will receive a single IV dose of GSK3342830. Testing GSK3342830 in this specific population will provide pharmacokinetic data and enable future pivotal Phase III studies in the respective country.		

SPONSOR SIGNATORY

PPD

01-Nov-2016

David Gardiner, MD, FACP
Medical Director
Infectious Disease Medicines Development

Date

PPD

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor and SAE Contact Information	PPD MD	PPD PPD PPD	PPD PPD	Safety fax number: PPD	PPD Level 8, Pavilion KL 168, Jalan Bukit Bintang 55100 Kuala Lumpur Malaysia
Secondary Medical Monitor	PPD MD	PPD PPD PPD	PPD	PPD	GlaxoSmithKline 1250 South Collegeville Road Collegeville, PA 19426, USA
Secondary GSK Medical Monitor	PPD PPD MD	PPD (Office)	PPD (Cell)	PPD	GlaxoSmithKline 1250 South Collegeville Road Collegeville, PA 19426, USA

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:

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 204847

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	

Investigator Signature	Date

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Rationale

This study represents the first administration of GSK3342830 in humans. It will be conducted to define the safety, tolerability, and pharmacokinetics of GSK3342830 after administration of single and repeat IV doses in healthy adult subjects, and after administration of a single IV dose in healthy adult Japanese subjects.

Objectives/Endpoints

Objectives	Endpoints
Part 1	
Primary	
• To investigate the safety and tolerability of GSK3342830 after administration of single IV doses in healthy adult subjects	• Clinical safety data from adverse events (AEs), clinical laboratory tests, vital signs (blood pressure, heart rate, temperature, and respiration rate), and 12-lead electrocardiogram (ECG) readings
Secondary	
• To determine the pharmacokinetics of GSK3342830 after administration of single IV doses in healthy adult subjects	• Plasma and urine concentrations and pharmacokinetic (PK) endpoints include AUC(0-t), AUC(0-∞), Cmax, Tmax, CL, Vss, t1/2, Feu(t1-t2), Ae, and CLr of GSK3342830, as data permit
• To assess dose proportionality of GSK3342830 after administration of single IV doses in healthy adult subjects	• Pharmacokinetic endpoints include AUC(0-t), AUC(0-∞), and Cmax of GSK3342830 after administration of single IV doses for the assessment of dose proportionality, as data permit
Exploratory	
• To correlate PK parameters (AUC[0-t], AUC[0-∞], and Cmax) of GSK3342830 with safety findings after administration of single IV doses in healthy adult subjects	• Exposure-response analyses, as data permit
• To evaluate the production of any GSK3342830 metabolites in plasma and urine and determine the need to perform a more detailed analysis of any metabolites	• Metabolite characterization in plasma and urine and estimation of observed drug-related material in plasma to determine the presence of any metabolite >10%, and estimate the percentage dose eliminated via urine
Part 2	
Primary	
• To investigate the safety and tolerability of GSK3342830 after administration of repeat IV doses in healthy adult subjects	• Clinical safety data from AEs, clinical laboratory tests, vital signs (blood pressure, heart rate, temperature, and respiration rate), and 12-lead ECG readings
Secondary	
• To determine the pharmacokinetics of GSK3342830 after administration of repeat IV doses in healthy adult subjects	• Plasma and urine concentrations and PK endpoints include AUC(0-t) and AUC(0-∞) on Day 1 only, AUC(0-τ), Cmax, Tmax, CL, Vss, t1/2, Cτ, Feu(t1-t2), Ae, and CLr of GSK3342830, as data permit

Objectives	Endpoints
• To assess dose proportionality of GSK3342830 after administration of repeat IV doses in healthy adult subjects	• Pharmacokinetic endpoints include AUC(0-τ) and Cmax of GSK3342830 after administration of repeat IV doses for the assessment of dose proportionality, as data permit
• To examine the extent of accumulation, time invariance, and achievement of steady-state of GSK3342830 after administration of repeat IV doses in healthy adult subjects	• Observed accumulation ratio (Ro) based on AUC and Cmax of GSK3342830 after administration of repeat IV doses, as data permit • Steady-state ratio (Rss) of GSK3342830 to assess time invariance, as data permit • Trough plasma concentrations at the end of the dosing interval (Cτ) to assess the achievement of steady-state of GSK3342830 after administration of repeat IV doses, as data permit
Exploratory	
• To correlate PK parameters (AUC[0-t], AUC[0-∞], AUC[0-τ], and Cmax) of GSK3342830 with safety findings and evaluate urine discoloration after administration of repeat IV doses in healthy adult subjects	• Exposure-response analyses, as data permit
• To evaluate the production of any GSK3342830 metabolites in plasma and urine and determine the need to perform a more detailed analysis of any metabolites	• Metabolite characterization in plasma and urine and estimation of observed drug-related material in plasma to determine the presence of any metabolite >10%, and estimate the percentage dose eliminated via urine
Part 3	
Primary	
• To investigate the safety and tolerability of GSK3342830 after administration of a single IV dose in healthy adult Japanese subjects	• Clinical safety data from AEs, clinical laboratory tests, vital signs (blood pressure, heart rate, temperature, and respiration rate), and 12-lead ECG readings
Secondary	
• To determine the pharmacokinetics of GSK3342830 after administration of a single IV dose in healthy adult Japanese subjects	• Plasma and urine concentrations and PK endpoints include AUC(0-t), AUC(0-∞), Cmax, Tmax, CL, Vss, t1/2, Feu(t1-t2), Ae, and CLr of GSK3342830, as data permit
Exploratory	
• To correlate PK parameters (AUC[0-t], AUC[0-∞], and Cmax) of GSK3342830 with safety findings after administration of a single IV dose in healthy adult Japanese subjects	• Exposure-response analyses, as data permit
• To evaluate the production of any GSK3342830 metabolites in plasma and urine and determine the need to perform a more detailed analysis of any metabolites	• Metabolite characterization in plasma and urine and estimation of observed drug-related material in plasma to determine the presence of any metabolite >10%, and estimate the percentage dose eliminated via urine

Overall Design

This is a Phase I, first-time-in-human (FTIH), randomized, double-blind (sponsor unblinded), single-center, placebo-controlled, dose-escalation study to determine the safety, tolerability, and pharmacokinetic (PK) profile of GSK3342830 after administration of single (Part 1) and repeat (Part 2) IV doses in healthy adult subjects, and a single IV dose in healthy adult Japanese subjects (Part 3).

For Parts 1 and 2, on Day 1, before study drug administration, subjects who meet the criteria for study entry will be assigned to the current dose level cohort and randomized to receive GSK3342830 or placebo. For Part 3, on Day 1, before study drug administration, subjects who meet the criteria for study entry will be randomized to receive GSK3342830 or placebo. All doses of GSK3342830 or placebo are planned to be administered as a 1-hour infusion.

Dose escalation will be conducted only if it is supported by the preliminary safety, tolerability, and PK results from the preceding dose levels in the study. This is the first administration of GSK3342830 in humans; therefore, as preliminary safety, tolerability, and PK results are reviewed internally at GSK and with the clinical study site, study design adjustments may be made based on emerging data from each dose cohort.

The repeat dose escalation component (Part 2) of this study is planned to be initiated after completion and evaluation of the all single dose cohorts up to and including 4000 mg. Initiation of Part 2 will be based on the evaluation of preliminary safety, tolerability, and PK data from the single dose escalation (Part 1) cohorts once safety at an exposure that exceeds the daily exposure predicted for the Part 2 planned starting dose of 1000 mg TID is demonstrated, which is predicted to occur at the 4000 mg single dose.

The single dose administration in Japanese subjects (Part 3) is planned to be conducted in parallel with Part 2. The dose for the Part 3 cohort will be based on preliminary safety and tolerability results of doses determined to be safe and well tolerated in subjects of non-Japanese heritage after completion of the single escalation dose cohorts (Part 1).

Treatment Arms and Duration

Part 1: Single Dose Escalation in Healthy Adult Subjects

The planned starting GSK3342830 dose in Part 1 is 250 mg administered as a single IV infusion. The dose is planned to increase in subsequent cohorts to 500, 1000, 2000, 4000, and ≤6000 mg. As a safety precaution, all Part 1 dose cohorts will be split into 2 sub-cohorts for sentinel dosing. In each cohort, the first 2 subjects will receive either GSK3342830 or placebo (1 active/1 placebo). Dosing in the remaining 6 subjects (5 active/1 placebo) in that cohort will occur at least 24 hours later based on the safety results from the first sub-cohort. Doses are planned to escalate in a sequential fashion contingent on the safety, tolerability, and PK profile of approximately 4 subjects who received active treatment in the previous cohort. Dose escalations or reductions will progress with modifications based on the safety, tolerability, and preliminary PK data from the preceding cohorts.

In Part 1, subjects will remain confined to the clinical unit from admission on Day –1 until after all scheduled safety and PK assessments have been completed on Day 3. The duration of study (from Screening to the Follow-up visit) for each subject will be up to approximately 43 days.

Part 2: Repeat Dose Escalation in Healthy Adult Subjects

The planned starting GSK3342830 dose in Part 2 is 1000 mg administered as a single IV infusion on Day 1, TID IV infusions on Days 2 through 14, and a single IV infusion on Day 15. The dose is planned to increase in subsequent cohorts to 2000 and 4000 mg following the same dosing schedule as the 1000 mg dose cohort. The starting dose and maximum dose may be changed based on clinical safety and PK findings in Part 1 or earlier doses in Part 2 and consideration of the area under the concentration-time curve (AUC) from time zero to 24 hours after dosing (AUC[0-24]) and maximum plasma concentration (Cmax) exposures based on the no observed adverse effect level (NOAEL).

Doses are planned to escalate in a sequential fashion contingent on the preliminary safety, tolerability, and PK data from Part 1 and at least 14 days of repeat dosing in approximately 5 subjects who received active treatment in the previous cohort in Part 2. The dosing frequency, duration of dosing, and decision to dose in the next dose level may be changed based on the safety, tolerability, or PK findings in Part 1 or earlier doses in Part 2.

In Part 2, subjects will remain confined to the clinical unit from admission on Day –1 until after all scheduled safety assessments have been completed on Day 16. The duration of study (from Screening to the Follow-up visit) for each subject will be up to approximately 56 days.

Part 3: Single Dose in Healthy Adult Japanese Subjects

The planned GSK3342830 dose in Part 3 will be either 250, 500, 1000, 2000, 4000, or ≤6000 mg based on preliminary safety and tolerability results of doses determined to be safe and well tolerated in subjects of non-Japanese heritage after completion of the single escalation dose cohorts (Part 1). The dose in Part 3 will be administered as a single IV infusion on Day 1.

In Part 3, subjects will remain confined to the clinical unit from admission on Day –1 until after all scheduled safety and PK assessments have been completed on Day 3. The duration of study (from Screening to the Follow-up visit) for each subject will be up to approximately 43 days.

Type and Number of Subjects

For Part 1, approximately 48 healthy adult subjects will be enrolled with approximately 8 subjects in each of the 6 planned cohorts. In each Part 1 cohort, approximately 6 subjects will be assigned to active treatment and approximately 2 subjects will be assigned to placebo. For Part 2, approximately 30 healthy adult subjects will be enrolled with approximately 10 subjects in each of the 3 planned cohorts. For Part 3, approximately 10 healthy adult Japanese subjects will be enrolled. In each Part 2 cohort

and the Part 3 cohort, approximately 8 subjects will be randomized to receive active treatment and approximately 2 subjects will be randomized to receive placebo. Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels. Subjects may only be randomized to one cohort and may only participate in one part of the study.

Analysis

Safety endpoints will include monitoring adverse events (AEs), clinical laboratory test results (chemistry [including liver function parameters], hematology, and urinalysis), vital signs (blood pressure, heart rate, respiratory rate, and body temperature), and 12-lead electrocardiogram (ECG) readings.

All safety data will be presented in the data listings. Subject demographics, medical history, and prior and concomitant medications will be summarized for each dose level using descriptive statistics. For continuous variables, these summaries will include number of subjects, mean, median, standard deviation, minimum, and maximum. For categorical variables, the summaries will include frequencies and corresponding percentages. No inferential hypothesis testing will be performed on the safety variables.

Plasma and urine concentrations of GSK3342830 will be analyzed by non-compartmental methods to determine the following PK parameters: AUC from time zero to the last quantifiable concentration after dosing (AUC[0-t]), AUC extrapolated from time zero to infinity (AUC[0-∞]; estimated for single dose and on Day 1 for repeat dose), AUC over the dosing interval τ (AUC[0-τ]), total systemic clearance (CL), Cmax, trough concentration (Cτ), terminal elimination half-life (t1/2), time to Cmax (Tmax), steady-state volume of distribution (Vss), amount excreted in urine (Ae), renal clearance (CLr), and urinary excretion ratio relative to dose (Feu[t1-t2]).

Plasma GSK3342830 concentration data will be listed and summarized by time point for each dose level using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, maximum, and coefficient of variation). Urine GSK3342830 concentration and volume data will be listed for each collection interval. Mean, median, and individual plasma concentration versus time profiles will be presented graphically on linear and semi-logarithmic scales.

For dose proportionality, accumulation, time invariance, and assessment of steady-state, an estimation approach will be taken, and point estimates and confidence intervals (CIs) will be constructed.

2. INTRODUCTION

GSK3342830 is a novel catechol-cephem antibiotic that is being developed by GlaxoSmithKline (GSK) for the treatment of infections caused by Gram-negative bacteria including multidrug-resistant isolates. GSK3342830 has demonstrated potent *in vitro* activity against Enterobacteriaceae including resistant strains of *Klebsiella pneumoniae*, *Escherichia coli*, and non-fermenting bacteria including *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, as well as efficacy in a range of murine

bacterial infection models including septicemia, respiratory tract infection, urinary tract infection, and abscess. GSK3342830 has a predicted efficacious dose of 1 to 2 grams TID.

2.1. Study Rationale

This study represents the first administration of GSK3342830 in humans. It will be conducted to define the safety, tolerability, and pharmacokinetics of GSK3342830 after administration of single and repeat IV doses in healthy adult subjects, and after administration of a single IV dose in healthy adult Japanese subjects.

2.2. Brief Background

The number of infections and deaths caused by drug-resistant strains of Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* is increasing and the current antibacterial pipeline for novel therapeutics is especially ill-equipped to treat these infections. GSK3342830 contains a catechol group on the 3-position side chain that facilitates entry into the bacterial cell via iron uptake mechanisms, and it shows antibacterial activity by inhibiting synthesis of cell walls. As such, GSK3342830 has the potential to meet the current and future threat of multidrug-resistant Gram-negative infections and to treat patients where no current treatment options exist.

GSK3342830 is a β-lactam-containing antibiotic with two differentiating enhancements expected to be of clinical significance. First, the multiple-decorated β-lactam core of GSK3342830 is demonstrated to significantly improve stability to β-lactamase resistance mechanisms. Second, it has been engineered to utilize the bacterial iron transport system and enhance penetration into Gram-negative bacteria through the addition of a catechol group on the 3-position side chain that acts as a siderophore mimetic. This siderophore moiety binds iron outside the bacteria, is subsequently imported through the bacterial iron transport system, and thereby enhances delivery of the cephalosporin into the periplasmic space of the bacteria where it is available to bind to penicillin binding proteins and inhibit cell wall synthesis.

Although the strategy of incorporation of catechol subunits as siderophore mimetics has been widely exploited, the early studies identified compounds with preclinical toxicology issues and recent efforts have investigated compounds with potency and spectrum of activity issues. These issues have prevented β-lactams with this functionality from successfully advancing to market. GSK3342830 incorporates chemical characteristics within the molecule that enhance stability against multiple classes of β-lactamases and differentiate its activity from commercially available molecules, including ceftazidime and the carbapenems.

Based on the results of preclinical studies of GSK3342830 as well as clinical adverse events (AEs) previously associated with cephalosporin antibiotics and antibiotics in general, the following areas of interest have been identified for safety monitoring in the early clinical development program for GSK3342830: potential effects on heart rate, blood pressure, and body temperature; potential effects on the respiratory cycle; injection

site reactions, potential effects on kidney function, chromaturia and colored stool, and hematologic findings; and potential interactions with 5-hydroxytryptamine, serotonin (5-HT)-3 receptors. All of these effects showed evidence of reversibility after a 1-month recovery period and were considered non-adverse, except for the injection site reactions, which were considered adverse. In 4-week Good Laboratory Practice (GLP) studies, local irritation and inflammation occurred at the two higher doses (1000 and 2000 mg/kg/day) tested and irritation occurred at the 50 and 100 mg/mL doses in rat and monkey, respectively. It is uncertain whether these local effects were due to the GSK3342830 itself or to the high osmolalities (≥740 mOsm) of the dosing formulations, or both. The results of these studies suggest that limiting the concentrations to no greater than 25 mg/mL is expected to reduce or eliminate the irritation potential in clinical formulations.

The findings for GSK3342830 in the toxicology and safety pharmacology studies support the proposed clinical trial. The only adverse findings were irritation and injury at the injection sites that were believed to be due to the high concentrations (50 - 200 mg/mL) and/or osmolalities (740 - 2164 mOsm) of the formulations (Stranz, 2002). Use of lower concentrations should avoid this issue in the clinic. The other findings in the 4-week GLP studies were non-adverse, secondary to the local irritation, or were of slight severity. Hemodynamic findings in monkey and respiratory findings in rat were relatively slight, have acceptable safety margins at clinically predicted doses and, if required, are able to be monitored.

Refer to GSK3342830 Investigator's Brochure (IB) [GSK Document Number 2015N255155_00] for complete information regarding GSK3342830.

Details of the required monitoring including the specific plan to monitor for and manage likely AEs or adverse reactions, and individual subject withdrawal/stopping criteria and the procedures and responsibilities for modifying or stopping the trial, if necessary, are specified in Section 4.6 and Section 5.4, respectively.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Part 1	
Primary	
• To investigate the safety and tolerability of GSK3342830 after administration of single IV doses in healthy adult subjects	• Clinical safety data from adverse events (AEs), clinical laboratory tests, vital signs (blood pressure, heart rate, temperature, and respiration rate), and 12-lead electrocardiogram (ECG) readings
Secondary	
• To determine the pharmacokinetics of GSK3342830 after administration of single IV doses in healthy adult subjects	• Plasma and urine concentrations and pharmacokinetic (PK) endpoints include AUC(0-t), AUC(0-∞), Cmax, Tmax, CL, Vss, t1/2, Feu(t1-t2), Ae, and CLr of GSK3342830, as data permit
• To assess dose proportionality of GSK3342830 after administration of single IV doses in healthy adult subjects	• Pharmacokinetic endpoints include AUC(0-t), AUC(0-∞), and Cmax of GSK3342830 after administration of single IV doses for the assessment of dose proportionality, as data permit

Objectives	Endpoints
Exploratory	
• To correlate PK parameters (AUC[0-t], AUC[0-∞], and Cmax) of GSK3342830 with safety findings after administration of single IV doses in healthy adult subjects	• Exposure-response analyses, as data permit
• To evaluate the production of any GSK3342830 metabolites in plasma and urine and determine the need to perform a more detailed analysis of any metabolites	• Metabolite characterization in plasma and urine and estimation of observed drug-related material in plasma to determine the presence of any metabolite >10%, and estimate the percentage dose eliminated via urine
Part 2	
Primary	
• To investigate the safety and tolerability of GSK3342830 after administration of repeat IV doses in healthy adult subjects	• Clinical safety data from AEs, clinical laboratory tests, vital signs (blood pressure, heart rate, temperature, and respiration rate), and 12-lead ECG readings
Secondary	
• To determine the pharmacokinetics of GSK3342830 after administration of repeat IV doses in healthy adult subjects	• Plasma and urine concentrations and PK endpoints include AUC(0-t) and AUC(0-∞) on Day 1 only, AUC(0-τ), Cmax, Tmax, CL, Vss, t1/2, Cτ, Feu(t1-t2), Ae, and CLr of GSK3342830, as data permit
• To assess dose proportionality of GSK3342830 after administration of repeat IV doses in healthy adult subjects	• Pharmacokinetic endpoints include AUC(0-τ) and Cmax of GSK3342830 after administration of repeat IV doses for the assessment of dose proportionality, as data permit
• To examine the extent of accumulation, time invariance, and achievement of steady-state of GSK3342830 after administration of repeat IV doses in healthy adult subjects	• Observed accumulation ratio (Ro) based on AUC and Cmax of GSK3342830 after administration of repeat IV doses, as data permit • Steady-state ratio (Rss) of GSK3342830 to assess time invariance, as data permit • Trough plasma concentrations at the end of the dosing interval (Cτ) to assess the achievement of steady-state of GSK3342830 after administration of repeat IV doses, as data permit
Exploratory	
• To correlate PK parameters (AUC[0-t], AUC[0-∞], AUC[0-τ], and Cmax) of GSK3342830 with safety findings and evaluate urine discoloration after administration of repeat IV doses in healthy adult subjects	• Exposure-response analyses, as data permit
• To evaluate the production of any GSK3342830 metabolites in plasma and urine and determine the need to perform a more detailed analysis of any metabolites	• Metabolite characterization in plasma and urine and estimation of observed drug-related material in plasma to determine the presence of any metabolite >10%, and estimate the percentage dose eliminated via urine

Objectives	Endpoints
Part 3	
Primary	
• To investigate the safety and tolerability of GSK3342830 after administration of a single IV dose in healthy adult Japanese subjects	• Clinical safety data from AEs, clinical laboratory tests, vital signs (blood pressure, heart rate, temperature, and respiration rate), and 12-lead ECG readings
Secondary	
• To determine the pharmacokinetics of GSK3342830 after administration of a single IV dose in healthy adult Japanese subjects	• Plasma and urine concentrations and PK endpoints include AUC(0-t), AUC(0-∞), Cmax, Tmax, CL, Vss, t1/2, Feu(t1-t2), Ae, and CLr of GSK3342830, as data permit
Exploratory	
• To correlate PK parameters (AUC[0-t], AUC[0-∞], and Cmax) of GSK3342830 with safety findings after administration of a single IV dose in healthy adult Japanese subjects	• Exposure-response analyses, as data permit
• To evaluate the production of any GSK3342830 metabolites in plasma and urine and determine the need to perform a more detailed analysis of any metabolites	• Metabolite characterization in plasma and urine and estimation of observed drug-related material in plasma to determine the presence of any metabolite >10%, and estimate the percentage dose eliminated via urine

4. STUDY DESIGN

4.1. Overall Design

This is a Phase I, first-time-in-human (FTIH), randomized, double-blind (sponsor unblinded), single-center, placebo-controlled, dose-escalation study to determine the safety, tolerability, and pharmacokinetic (PK) profile of GSK3342830 after administration of single (Part 1) and repeat (Part 2) IV doses in healthy adult subjects, and after administration of a single IV dose in healthy adult Japanese subjects (Part 3). Part 1 will investigate escalating single IV doses of GSK3342830. Part 2 will investigate escalating repeat IV doses of GSK3342830 with repeat dosing for 14 days and multiple dosing per day for 13 days as follows: a single IV infusion on Day 1, TID IV infusions on Days 2 through 14 (approximately every 8 hours), and a single IV infusion on Day 15. Part 3 will investigate a single IV dose of GSK3342830 in Japanese subjects.

For Parts 1 and 2, on Day 1, before study drug administration, subjects who meet the criteria for study entry will be assigned to the current dose level cohort and randomized to receive GSK3342830 or placebo. For Part 3, on Day 1, before study drug administration, subjects who meet the criteria for study entry will be randomized to receive GSK3342830 or placebo. All doses of GSK3342830 or placebo are planned to be administered as a 1-hour infusion.

This is the first administration of GSK3342830 in humans; therefore, the study design may change based on emerging data from each cohort. As preliminary safety, tolerability,

and PK results are reviewed internally at GSK and with the clinical study site, the following adjustments may be made to the proposed study design:

- The proposed dose levels, dosing frequency, infusion duration, and/or infusion volume of GSK3342830 may be adjusted during the course of Part 1 and/or Part 2 of the study.
- The duration of repeat dose administration planned for Part 2 may be adjusted.
- Cohorts may be added to or removed from either study Part 1 or Part 2 depending on findings from previous cohorts.
- Pharmacokinetic sampling and/or study assessment schedules may be changed.

This study will aim to explore the safety, tolerability, and pharmacokinetics of a wide range of exposures in healthy adult subjects. The exposures observed in animal toxicology studies will be used to guide dose escalation. Systemic exposures as measured by AUC in the human subjects in this study may exceed the systemic no observed adverse effect level (NOAEL) animal exposures from 4-week GLP toxicology studies as long as the doses administered in the study are safe and well tolerated. This approach is based on the following considerations:

- In the 4-week GLP studies, there was no dose-limiting organ toxicity in the animals (rats and monkeys) with exposures up to 2000 mg/kg/day, the highest dose tested.
- This study will incorporate a risk mitigation strategy (see Section 4.6.1).
- In the 4-week GLP studies, all observed systemic findings in the animals were mild to moderate and readily monitored in the clinic.
- Bayesian predictive probabilities of area under the concentration-time curve (AUC) from time zero to 24 hours after dosing (AUC[0-24]) and maximum plasma concentration (Cmax) meeting criteria defined in Section 9.3.2, along with safety data will be used to drive decision making for dose escalation. The dose will be escalated only if it is supported by the safety, tolerability, and preliminary PK results from the preceding dose levels in the study.
- The planned maximum duration of repeat dosing in the study is 14 days.

As the efficacious exposure levels of GSK3342830 are uncertain, this approach provides the best chance of success in reaching therapeutic levels and establishing a sufficient margin of safety.

Planned Cmax exposures in humans will not exceed the Cmax exposure of the NOAEL as determined by the preclinical safety studies.

The repeat dose escalation component (Part 2) of this study is planned to be initiated after completion and evaluation of all single dose cohorts up to and including 4000 mg. Initiation of Part 2 will be based on the evaluation of preliminary safety, tolerability, and PK data from the single dose escalation (Part 1) cohorts once safety at an exposure that

exceeds the daily exposure predicted for the Part 2 planned starting dose of 1000 mg TID is demonstrated, which is predicted to occur at the 4000 mg single dose.

The single dose administration in Japanese subjects component (Part 3) of this study is planned to be conducted in parallel with Part 2. The dose for the Part 3 cohort will be based on preliminary safety and tolerability results of doses determined to be safe and well tolerated in subjects of non-Japanese heritage after completion of the single escalation dose cohorts (Part 1).

The relationship between dose and plasma GSK3342830 exposure will be determined as part of dose escalation as described in Section 9.3.2.

4.2. Treatment Arms and Duration

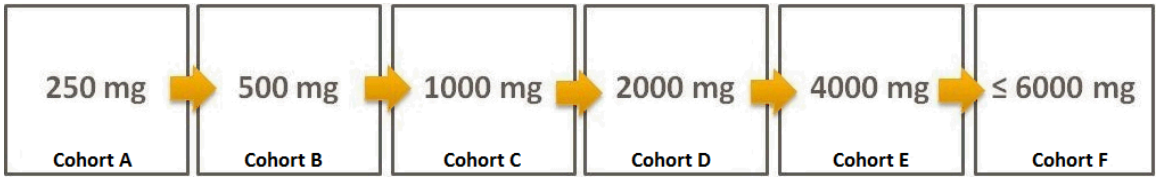
Part 1: Single Dose Escalation in Healthy Adult Subjects

Part 1 is planned to include 6 dose level cohorts. Additional doses (1 per cohort) may be evaluated to further understand the study drug. The planned starting GSK3342830 dose in Part 1 is 250 mg administered as a single IV infusion. The dose is planned to increase in subsequent cohorts to 500, 1000, 2000, 4000, and ≤6000 mg IV as shown in Figure 1. Doses >6000 mg may be administered if the predicted Cmax exposures will not exceed the NOAEL.

On Day 1, before study drug administration, subjects will be randomized to treatment with either GSK3342830 or placebo in a 3:1 ratio. As a safety precaution, all Part 1 cohorts will be split into 2 sub-cohorts for sentinel dosing. In each cohort, the first 2 subjects will receive either GSK3342830 or placebo (1 active/1 placebo). Dosing in the remaining 6 subjects (5 active/1 placebo) in that cohort will occur at least 24 hours later based on the safety results from the first sub-cohort. Study assessments will be performed as indicated in the Time and Events Tables (Section 7.1).

Doses are planned to escalate in a sequential fashion contingent on the safety, tolerability, and PK profile of approximately 4 subjects who received active treatment in the previous cohort. The evaluated subjects should be followed for a minimum of 48 hours after dosing. Dose escalations or reductions will progress with modifications based on the preliminary safety, tolerability, and PK data from the preceding cohorts.

Figure 1 Part 1 Single Dose Escalation Study Design Schematic



Note: Figure shows illustration of the planned doses, which may be switched, changed, or cancelled based on preliminary safety, tolerability, and pharmacokinetic data from preceding cohorts.

The AUC from time zero to the last quantifiable concentration after dosing (AUC[0-t]) and Cmax observed in the human subjects in this study at each single dose will be compared with the systemic NOAEL animal exposure values in order to determine the magnitude of dose escalation.

The dose escalation strategy is based on the following 2 principles:

- Bigger dose escalation steps will be allowed at lower systemic exposures as the expected risk of AEs at these exposures is low. The magnitude of dose escalation steps will be progressively restricted at higher exposures.
- Once a certain dose is reached, the magnitude of dose escalation steps will be restricted regardless of systemic exposure.

The following algorithm will be used for dose escalation in Part 1:

For each dose level, the human AUC and Cmax values after a single dose will be calculated as percentage of the NOAEL animal exposures. The next dose level will then be determined as described in Table 1.

Table 1 Single Dose Escalation Scheme

Human exposure at current dose as percentage of rat NOAEL	Dose escalation to next dose will be no higher than	Predicted human exposure at next dose as percentage of NOAEL will be no higher than[1,2]
≤2%	10-fold	N/A
>2 and ≤5%	8-fold	30%
>5 and ≤15%	6-fold	60%
>15 and ≤30%	4-fold	90%
>30%	3-fold	N/A

N/A = not applicable, NOAEL = no observed adverse effect level.
NOTES:
1. The relationship between dose and plasma GSK3342830 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 pharmacokinetic (PK) modeling (if feasible) or on the assumption of dose-exposure proportionality. 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.
2. Human exposure may exceed the NOAEL exposures based on acceptable safety and tolerability data. Initial exposure targets will be based on NOAEL exposures.

Both conditions (dose escalation to the next dose level and predicted human exposure at next dose as percentage of NOAEL) will be met when determining a dose escalation step based on Table 1 (i.e., the condition allowing a smaller dose escalation step will limit the maximum dose escalation).

- Once the dose is ≥500 mg, any further dose escalation will be no higher than 3-fold irrespective of the observed exposures.
- The targeted mean AUC and Cmax in Part 1 are NOAEL exposures for AUC(0-24) (2875 h•µg/mL) and Cmax (2270 µg/mL). Human exposure may

exceed the NOAEL exposures based on acceptable safety and tolerability data. Initial exposure targets will be based on NOAEL exposures.

In Part 1, subjects will remain confined to the clinical unit from admission on Day –1 until all scheduled safety and PK assessments have been completed on Day 3. The duration of study (from Screening to the Follow-up visit) for each subject will be up to approximately 43 days.

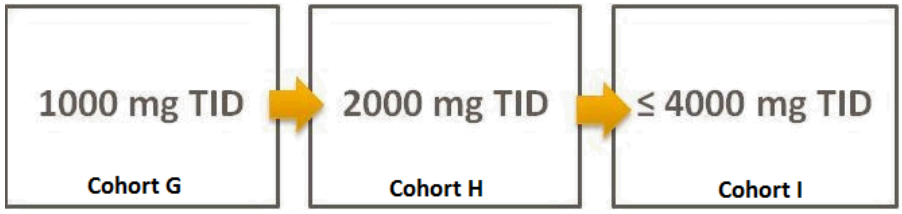
Part 2: Repeat Dose Escalation in Healthy Subjects

Part 2 is planned to include a sequential panel of up to 3 dose level cohorts. Additional repeat dose cohorts may be evaluated to further assess the safety, tolerability, and pharmacokinetics of GSK3342830. The planned starting GSK3342830 dose in Part 2 is 1000 mg administered as a single IV infusion on Day 1, TID IV infusions on Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14, and a single IV infusion on Day 15. The dose is planned to increase in subsequent cohorts to 2000 and 4000 mg TID as shown in Figure 2. The starting dose and maximum dose may be changed based on clinical safety and PK findings in Part 1 or earlier doses in Part 2 and consideration of the AUC(0-24) and Cmax exposures based on the NOAEL.

On Day 1, before study drug administration, subjects will be randomized to treatment with either GSK3342830 or placebo in a 4:1 ratio. Study assessments will be performed as indicated in the Time and Events Tables (Section 7.1).

Doses are planned to escalate in a sequential fashion based on the preliminary safety, tolerability, and PK data from Part 1 and at least 14 days of repeat dosing in approximately 5 subjects who received active treatment in the previous cohort in Part 2. The evaluated subjects should be followed for a minimum of 24 hours after dosing on Day 15. The dosing frequency, duration of dosing, and decision to dose in the next dose level may be changed based on the safety, tolerability, or PK findings in Part 1 or earlier doses in Part 2.

Figure 2 Part 2 Repeat Dose Escalation Study Design Schematic



Note: Figure shows illustration of the planned doses, which may be switched, changed, or cancelled based on preliminary safety, tolerability, and pharmacokinetic data from preceding cohorts.

The following rules will guide dose selection in Part 2:

- The starting daily dose in Part 2 will be selected such that its predicted AUC(0-24) and Cmax on the last day of dosing (i.e., account for any drug accumulation) is no higher than the exposure of a dose that has been found to be safe and well tolerated in Part 1.
- Subsequent doses in Part 2 may be selected using the previously described criteria for the Part 2 starting dose. Alternatively, a dose may 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 2.
- The targeted mean AUC(0-24) and Cmax in Part 2 are the NOAEL exposures (AUC[0-24] of 2875 h•µg/mL and Cmax of 2270 µg/mL). Human exposure may exceed the NOAEL animal exposures based on acceptable safety and tolerability data. Initial exposure targets will be based on NOAEL exposures.

In Part 2, subjects will remain confined to the clinical unit from admission on Day –1 until after all scheduled safety assessments have been completed on Day 16. The duration of study (from Screening to the Follow-up visit) for each subject will be up to approximately 56 days.

Part 3: Single Dose in Healthy Adult Japanese Subjects

Part 3 is planned to include 1 cohort (Cohort J). The planned GSK3342830 dose in Part 3 will be either 250, 500, 1000, 2000, 4000, or ≤6000 mg based on preliminary safety and tolerability results of doses determined to be safe and well tolerated in subjects of non-Japanese heritage after completion of the single escalation dose cohorts (Part 1). The dose in Part 3 will be administered as a single IV infusion on Day 1.

On Day 1, before study drug administration, subjects will be randomized to treatment with either GSK3342830 or placebo in a 4:1 ratio. Study assessments will be performed as indicated in the Time and Events Tables (Section 7.1).

In Part 3, subjects will remain confined to the clinical unit from admission on Day –1 until all scheduled safety and PK assessments have been completed on Day 3. The duration of study (from Screening to the Follow-up visit) for each subject will be up to approximately 43 days.

4.3. Type and Number of Subjects

For Part 1, approximately 48 healthy adult subjects will be enrolled with approximately 8 subjects in each of the 6 planned cohorts. In each Part 1 cohort, approximately 6 subjects will be assigned to active treatment and approximately 2 subjects will be assigned to placebo. For Part 2, approximately 30 healthy adult subjects will be enrolled with approximately 10 subjects in each of the 3 planned cohorts. For Part 3, approximately 10 healthy adult Japanese subjects will be enrolled. In each Part 2 cohort and the Part 3 cohort, approximately 8 subjects will be randomized to receive active treatment and approximately 2 subjects will be randomized to receive placebo.

Additional subjects/cohorts may be enrolled to allow for evaluation of additional dose levels.

Decisions regarding replacement of subjects prematurely discontinued from study drug in any cohort will be made by the investigator and the GSK medical monitor on a case-by-case basis. Subjects may only be randomized to one cohort and may only participate in one part of the study.

4.4. Design Justification

The design of this FTIH study is consistent with global regulatory guidelines for protocol design including subject selection, estimation of starting dose, precautions that are applied within and between dosing cohorts, dose escalation scheme, risk mitigation, and stopping rules [EMEA, 2007 and DHHS, 2005].

Scheduled assessments of subjective symptoms, and objective clinical laboratory tests, vital signs, and 12-lead electrocardiograms (ECGs) will be obtained to monitor subject safety. In order to further mitigate the risks to subjects who participate in this study, subjects will be specifically monitored for findings observed in animal species with GSK3342830, findings identified with similar catechol cephalosporin compounds, as well as known risks common to cephalosporin antibiotics. These potential risks and their mitigations are presented in Section 4.6.1.

Part 2 of this study is planned to include 14 days of repeat dosing based on the following 2 factors:

- An objective of this study is to establish the safety and tolerability of the medication for a dosing duration that will be clinically relevant in future efficacy studies of acute bacterial infection. Most acute bacterial infections for which GSK3342830 may be developed will need to permit up to 14 days of treatment.
- Non-adverse hematologic changes were observed in the 4-week preclinical safety studies after 14 days of dosing. In this FTIH study, 14 days of dosing will provide additional reassurance of hematologic safety specifically for future subjects with acute bacterial infection requiring up to 14 days of therapy.

4.5. Dose Justification

Dose selection of GSK3342830 for this FTIH study was based on NOAEL data from animal toxicology studies, predicted pharmacokinetics for humans using PK data from preclinical species, and a targeted therapeutic exposure based on efficacy data from a rat pneumonia model. GSK3342830 is a catechol cephalosporin antibiotic that utilizes the bacterial iron transport system to facilitate transport into bacteria and disrupts the synthesis of the peptidoglycan layer of bacterial cell walls. This is not a human target; therefore, the minimum anticipated biological effect level in humans for GSK3342830 was not determined.

As described in the following sub-sections,

- While the maximum recommended starting dose is 1935 mg, the proposed starting dose is 250 mg, which is predicted to have AUC(0-t) and Cmax values 45-fold and 83-fold lower than the NOAEL values, respectively.
- The predicted dose to achieve the therapeutic exposure target ranges from 500 to 2000 mg, which is predicted to have AUC(0-t) values 5.6- to 22-fold lower and Cmax values 10- to 42-fold lower than the NOAEL values after administration of single doses, and AUC(0-24) values 1.9- to 7.5-fold lower and Cmax values 10- to 42-fold lower than the NOAEL values after administration of repeat doses.
- The anticipated maximum 6000 mg single dose will provide an AUC exposure of 1933 h•µg/mL (predicted AUC encompassing 95% of the simulated population) with a safety margin of 1.48-fold and a Cmax of 849 µg/mL (predicted Cmax encompassing 95% of the simulated population) with a safety margin of 2.67-fold.
- The anticipated maximum 4000 mg TID dose will provide an AUC exposure of 3846 h•µg/mL (predicted AUC[0-24] encompassing 95% of the simulated population) that may exceed the systemic NOAEL AUC(0-24) exposure of 2875 h•µg/mL (safety margin of 0.93-fold) and a Cmax of 569 µg/mL (predicted Cmax encompassing 95% of the simulated population) with a safety margin of 3.98-fold.
- Based on a concentration limitation of 25 mg/mL, IV solution volumes between 100 to 250 mL would support single doses of 2500 to 6000 mg (IV formulation work is ongoing. Formulation instructions will be available in the Pharmacy Manual before the start of the study).
- Importantly, dose escalation decisions will be based on observed exposure, safety, and tolerability data for GSK3342830 from the previous dose level.

Data Used for Dose Justification

No observed adverse effect level (NOAEL)

The primary AEs in the 4-week GLP toxicology studies were those at the infusion site. The NOAEL dose in both the rat and monkey for these local infusion site effects (ulcer, perivascular/vascular inflammation, thrombus) was 500 mg/kg; the formulation concentration at this dose was 25 mg/mL for rats and 50 mg/mL for monkeys. These local effects were considered secondary to the high concentrations and resultant high osmolalities of the formulations at doses higher than 500 mg/kg/day. The concentration of the clinical formulation will be limited to no greater than 25 mg/mL (the concentrations at the NOAEL dose for rats), which should preclude these local irritation effects. Based on a concentration limitation of 25 mg/mL, IV solution volumes between 100 to 250 mL would support single doses of 2500 to 6000 mg (IV formulation work is ongoing. Formulation instructions will be available in the Pharmacy Manual before the start of the study) as shown in Table 2.

Table 2 Single IV Infusion Doses, Concentrations, and Osmolality[1]

Dose (mg)	Concentration (mg/mL) for a 100 mL infusion	Concentration (mg/mL) for a 250 mL infusion	Final osmolality[2] (mOsm/kg)
250	2.5		302
500	5		314
1000	10		339
2000	20		388
4000		16	388
6000		24	407

NOTES:
1. Theoretically calculated osmolality values.
2. Based on 100 mL (250 to 2000 mg doses) and 250 mL (4000 and 6000 mg doses) infusion volumes.

Given that the infusion site reactions can be addressed by formulation, the 2000 mg/kg dose and exposures were selected to define the exposure limits. Slight decreases (10 to 20%) in red blood cell count, hemoglobin, and hematocrit, accompanied by an increase in reticulocytes, as well as other clinical pathology changes considered non-adverse were observed at 2000 mg/kg/day in male and female monkeys; these were considered secondary to the severe and ongoing inflammation induced by the infusion site effects. The hematological findings showed evidence of reversibility by week 4 of dose administration and showed recovery by 4 weeks post dosing. In summary, the hematologic findings were mild, reversible, and able to be monitored in the clinic. The NOAELs of 2000 mg/kg in the rat and monkey with NOAEL exposures of 2875 h•µg/mL (rat) and 2270 µg/mL (monkey) for AUC(0-t) and Cmax, respectively, were selected to define the exposure limits.

Scaling to human exposure

GSK3342830 is structurally similar to another catechol cephalosporin compound with generally comparable *in vivo* PK profiles in preclinical species. Scaling using the dedrick monkey method was proven to accurately predict the human clearance and volume of distribution for the former compound (observed values within 20% of predicted values). Thus, the dedrick method, along with a single-point allometry method, was selected to predict human clearance and volume of distribution for GSK3342830. Both methods showed similar predicted human clearance values of approximately 0.82 mL/min/kg (single-point allometry) and 0.93 mL/min/kg (dedrick monkey), while predicted volume of distribution was 0.121 L/kg (dedrick monkey).

In vivo efficacy models

A major objective of this study is to establish safety across a clinically relevant dose range to enable a future Phase II efficacy study. *In vivo* efficacy models predict target therapeutic AUC(0-t) exposures of 112 to 467 h•µg/mL after administration of single doses and AUC(0-24) values of 336 to 1401 h•µg/mL after TID dose administration. Scaling of animal exposure to humans predicts GSK3342830 will achieve these exposures at doses between 500 to 2000 mg. Additional details on the *in vivo* efficacy calculations and animal to human scaling is available in Appendix 9.

Maximum Recommended Starting Dose

The systemic NOAEL dose level of 2000 mg/kg in the rat (most sensitive species) was converted to the human equivalent dose based on body surface area using the US Food and Drug Administration (FDA) Guidance for estimation of the maximum safe starting dose [DHHS, 2005]. After applying an uncertainty safety factor of 10 (the guideline default) to the human equivalent dose, the maximum recommended starting dose is 1935 mg.

- The proposed starting dose is 250 mg which is predicted to have AUC(0-t) and Cmax values 45-fold and 83-fold lower than the NOAEL values, respectively.
- Assuming an IV solution volume between 100 to 250 mL, the drug concentration of 1 to 2.5 mg/mL is well below the lower concentration limitation of 25 mg/mL.

Dose Predicted to Achieve the Therapeutic Exposure Target

Doses of 500 to 2000 mg are predicted to achieve the target therapeutic exposure (total AUC[0-t] values of 112 to 467 h•µg/mL after administration of single doses and AUC[0-24] values of 336 to 1401 h•µg/mL after administration of repeat TID doses). Comparisons of the therapeutic doses with the NOAELs from the 2000 mg/kg exposures suggest the following safety margins:

- AUC(0-t) values 5.6- to 22-fold lower and Cmax values 10- to 42-fold lower than the NOAEL values after administration of single doses.
- AUC(0-24) values 1.9- to 7.5-fold lower and Cmax values 10- to 42-fold lower than the NOAEL values after administration of repeat doses.

Predicted Maximum Dose Exposure Margins: Single Dose Escalation Cohorts

Based on the systemic NOAEL AUC(0-24) exposure of 2875 h•µg/mL and Cmax exposure of 2270 µg/mL, the anticipated maximum 6000 mg single dose will provide:

- An AUC exposure of 1933 h•µg/mL (predicted AUC encompassing 95% of the simulated population [Table 8, Appendix 9]) with a safety margin of 1.48-fold.
- A Cmax of 849 µg/mL (predicted Cmax encompassing 95% of the simulated population [Table 8, Appendix 9]) with a safety margin of 2.67-fold.

Predicted Maximum Dose Exposure Margins: Repeat Dose Escalation Cohorts

Given the evolving PK and pharmacodynamic data currently being generated through *in vivo* preclinical models, doses above 2000 mg TID may be required to adequately treat certain challenging bacteria in the clinic. With this in mind, the tolerability of repeat doses up to 4000 mg TID will be tested. Based on the systemic NOAEL AUC(0-24) exposure of 2875 h•µg/mL and Cmax exposure of 2270 µg/mL, the anticipated 4000 mg TID dose will provide:

- An AUC exposure of 3846 h•µg/mL (predicted AUC[0-24] encompassing 95% of the simulated population [Table 9, Appendix 9]) that may exceed the systemic NOAEL AUC(0-24) exposure of 2875 h•µg/mL.
    - As described previously, dose escalation would be predicated on safety and PK data observed at the preceding dose (2000 mg TID) administered for 14 days with at least 24 hours post-dose observation.
- A Cmax of 569 µg/mL (predicted Cmax encompassing 95% of the simulated population [Table 9, Appendix 9]) with a safety margin of 3.98-fold.

4.6. Benefit:Risk Assessment

Summaries of findings from non-clinical studies conducted with GSK3342830 can be found in the IB [GSK Document Number 2015N255155_00].

Section 4.6.1 outlines the risk assessment and mitigation strategy for this study.

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (GSK3342830)		

Death in preliminary monkey cardiovascular study	• **Preliminary monkey cardiovascular study:**
	  • No effect on corrected QT (QTc)
	  • 1 death
	  • 1/3 animals, single dose escalation design with 1-week washout; 4th dose at 1000 mg/kg
	  • Animal died at 2.5 hours post-dose
	  • No clear etiology
	  • No similar findings in definitive cardiovascular study
	  • 26 animals now dosed at and above 1000 mg/kg and at longer durations (4 weeks) without major adverse findings
		• Conduct study in inpatient clinical unit for first time in human (FTIH)
		• Normal vital signs on study entry
		• Frequent vital signs over the dosing interval
		• QTc <450 msec
		• 12-lead electrocardiograms (ECGs) across the initial exposure
		• Telemetry monitoring for Parts 1 and 3 and initial doses in Part 2

Blood pressure (BP), heart rate, and body temperature changes in monkey cardiovascular study	• **Blood pressure:**
	  • Maximum excursion of 29 mm Hg at 1000 mg/kg
	• **Heart rate:**
	  • Maximum excursion of 16 beats per minute at 1000 mg/kg
	• **Body temperature:**
	  • 0.5°C decrease at 1000 mg/kg
		• Conduct study in inpatient clinical unit for FTIH
		• Starting dose free Cmax margin: approximately 26×
		• Cmax at highest planned dose (6000 mg) similar to (1.1×) Cmax of the no observed effect level (NOEL) dose (250 mg/kg)
		• Normal vital signs on study entry
		• Frequent vital signs over the dosing interval
		• 12-lead ECGs across the exposures
		• Telemetry monitoring for Parts 1 and 3 and initial doses in Part 2
		• Blood pressure and heart rate stopping criteria:
		  • Systolic BP >160 mm Hg for >1 hour
		  • Diastolic BP >100 mm Hg for >1 hour
		  • Heart rate >120 beats per minute for >1 hour

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy

Renal findings	• **Kidney: hyaline droplets in proximal tubules, weight increase in both species**
	  • Hyaline droplets associates with absorption and secretion of the cephem antibiotics in lysosome
	  • No degenerative changes
	  • Probably mixture of drug and protein (stimulation of lysosomal turnover)
	  • Accompanied by increases in urinary N-acetyl-β-D-glucosaminidase (exploratory biomarker of lysosomal enzyme) at all doses and slight change in urinary albumin at 2000 mg/kg (relevance unclear)
		• **Inclusion/Exclusion**
		  • Healthy subjects
		  • Serum creatinine greater than the upper limit of normal (ULN)
		  • Estimated glomerular filtration rate (eGFR) <90 mL/min/1.73 m^2 as calculated by the Chronic Kidney Disease Epidemiology Collaboration formula
		  • Albumin to creatinine ratio (ACR) ≥0.03 mg/mg
		  • Urinalysis negative for blood/protein
		• **Monitor:**
		  • Serum blood urea nitrogen, creatinine, eGFR, electrolytes, urinalysis
		  • ACR during the study
		• **Criteria to pause Part 1 progression or interrupt Part 2 dosing**
		  • Creatinine change >0.3 mg/dL without alternative cause
		  • New blood in urinalysis confirmed by microscopy without alternative cause
		  • ACR ≥0.03 mg/mg

Injection site reactions	• **Local irritation**
	  • Gross: discoloration, hardening, wound, thrombosis
	  • Histology: ulcer, perivascular/vascular inflammation, thrombus (1000/2000 mg/kg/day; rats and monkeys)
	• **Considered due to high osmolality of the dosing formulations**
		• Reduced osmolality preparation
		• Monitor injection site including proximal limb for vascular change

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy

Hematologic findings	**Red Blood Cell (RBC) related changes**
	• **Decreases in RBC count, hemoglobin (Hgb), hematocrit (Hct; 2000 mg/kg/day in males and females)**
	  • Peaked at Week 2 (–10% to –20% versus pre-dosing values)
	  • Accompanied by increase in reticulocytes
	• **RBC findings considered secondary to:**
	  • Ongoing inflammation from infusion site reactions (above)
	  • Contribution from high osmolality infusion
	  • Hemolysis, iron depletion (catechol) or other direct mechanism of drug not considered present
	  • Evidence of recovery by end of follow-up
	Other hematologic findings
	• **Findings considered secondary to ongoing inflammation at the infusion site**
	• Increases in neutrophils and concomitant decreases in lymphocyte %
	• Decreased fibrinogen
	• Prolongation of activated partial thromboplastin time
	• Decreases in albumin and albumin/globulin ratio
	• Increase in total protein (due to globulin increase)
	• development of iliac lymph node germinal center
	• Findings were reversible in follow-up
		• Reduced osmolality infusions
		• Normal white blood cell (WBC) count, Hgb, Hct, and platelets on study entry
		• Follow for signs or symptoms of anemia
		• Follow regular clinical labs (WBC, Hgb, Hct, reticulocyte count, and platelets)
		Stopping criteria
		• Hemoglobin ≤9.9 g/dL (99 g/L)
		• White blood cell ≤1999/mm^3 (1.910 × 10^9/L)
		• Platelets ≤99.999 × 10^9/L

Increased tidal volume in rat respiratory study	• Only at high dose (2000 mg/kg)
	• 22.9% at 30 minutes after completion of infusion
	• Changes considered to be minimal
	  • Magnitude within the range of physiological changes
	  • No changes were seen in minute volume
	  • Not statistically significant
	  • May reflect high individual variability
		• Conduct study in inpatient Phase I clinical unit
		• Frequent vital sign capture during study
		• 6000 mg maximum dose maintains 2.1× margin relative to the NOEL of 1000 mg/kg

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy

Serotonin (5-HT)-3 *in vitro* binding assay	• "Moderately" positive with 39% effect at 100 mmol (78 μg/mL)
	• High dose Cmax will reach similar concentration
	• No clear *in vivo* correlation from toxicology studies
	  • Possible BP effect in monkey cardiovascular study
	  • Poor central nervous system penetration (approximately 3% blood)
		• Precautions c/w those indicated to mitigate the BP effect seen in monkey cardiovascular study
		• Enroll healthy subjects not on medications to avoid additive arrythmogenic potential

Other		
Neurologic findings (seizures)	• Known risk (seizures) for some β-lactams and cephalosporins • Seen pre-clinically with lead compound • No adverse findings to 2000 mg/kg/ day × 4 weeks in rats or monkeys • Central nervous system administration study in rats negative	• Specifically assess for negative history of seizures in past medical history at screening • Close monitoring during infusion in an acute care setting

Rash/Dermatologic toxicity	• Rash is a common adverse event (AE) of β-lactam antibiotics. Range of manifestations and severity from mild morbilliform drug eruption to hives, Erythema multiforme (EM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in rare cases	• Exclude individuals with history of rash to penicillins or cephalosporins
		• Exclude individuals with history of EM/SJS/TEN to any medication
		• Close monitoring
		• Discontinuation criteria
		  • Any rash of Grade 3 or greater severity
		  • Any rash characterized by:
		  • Hives
		  • Concomitant fever or other symptoms suggesting systemic manifestations
		  • Blistering
		  • Ocular or genital involvement
		• Access to standard interventions (antihistamines, steroids if indicated, intensive care unit/burn unit care in worst case)

Anaphylaxis/hypersensitivity	• Common to all β-lactam antibiotics
	  • Approximately 10% cross reaction between cephalosporins and penicillins
	  • Guinea pig immunotoxicity model negative
		• Conduct study in inpatient Phase I clinical unit
		• "Crash" cart availability
		• Exclude subjects with history of penicillin allergy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
***Clostridium difficile* (*C. difficile*) colitis**	• A general risk with all antibiotics • Cephalosporins generally considered moderate to high risk presumably due to broad effects on gut microbiome • No anaerobic activity may reduce propensity for *C. difficile* overgrowth	• Exclude subjects with a history of *C. difficile* colitis • Site chosen with experience in antibiotics studies • Importance of infection control procedures will be raised with the site

Liver findings	• No adverse findings to 2000 mg/kg/day × 4 weeks in rats or monkeys
	• Increase in liver weight (monkey)
	  • Mechanisms unclear
	  • No corresponding alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or histopathological change
		• Normal liver biomarkers on study entry with negative history of liver disease in past medical history
		• Frequent assessment of symptoms suggesting liver injury (nausea, vomiting, abdominal pain, etc.)
		• Frequent assessment of liver injury biomarkers (ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase)
		• Defined GSK liver stopping criteria

Catechol side chain binds free iron	• Catechol side chain binds free iron (part of the monoamine oxidase)	• Normal Hgb and Hct on study entry • Monitor Hgb and Hct with stopping criteria as above • Monitor iron binding studies (serum iron, ferritin, total iron binding capacity, reticulocytes)
Candidiasis (vaginal, oral thrush)	• A common AE of exposure to broad spectrum antibiotics	• Monitor clinically • Discontinue GSK 830 may be needed for treatment • Treat with topical antifungal medication as needed

4.6.2. Benefit Assessment

This Phase I study is being conducted in healthy subjects; therefore, there is no direct clinical benefit to study subjects. Participation in this study may contribute to the process of developing new therapies in an area of unmet need.

4.6.3. Overall Benefit:Risk Conclusion

The risk of AEs is minimized for the population being investigated in the proposed study by careful selection of subjects for the study and the extent of safety monitoring incorporated into the study.

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the IB [GSK Document Number 2015N255155_00].

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. A single repeat for clinical laboratory tests that meet the exclusion criteria may be conducted to confirm the value before the subject is excluded from the study.

5.1. Inclusion Criteria

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

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

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. Healthy as determined by a responsible and experienced physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. A subject with a clinical abnormality or laboratory parameter outside the reference range for the population being studied may be included only if the investigator feels and documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. 3. Additional inclusion criteria for Japanese subjects (Part 3 only): • The subject is a non-naturalized Japanese citizen and holds a Japanese passport. • The subject has 2 Japanese parents and 4 Japanese grandparents who are non-naturalized Japanese citizens, as confirmed by interview.

- The subject has been living outside of Japan for less than 10 years, as confirmed by interview.

WEIGHT
4. Body weight >50 kg (110 lb) for men and >40 kg (99 lb) for women and body mass index within the range of 18.5 to 30 kg/m^2, inclusive.
SEX

5. Male or Female
Males:
Male subjects with female partners of child-bearing potential must agree to use one of the highly effective contraception requirements listed in Appendix 8 from the time of first dose of study drug until completion of the Follow-up visit.
Females:
A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotropin [hCG] test), not lactating, and considered to be of non-reproductive potential.
Non-reproductive 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
  • Hysterectomy
  • Documented bilateral oophorectomy
• Postmenopausal defined as 12 months of spontaneous amenorrhea and in questionable cases a blood sample with simultaneous follicle-stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels).
• Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods listed in Appendix 8 if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrolment.

INFORMED CONSENT
6. Capable of giving signed informed consent as described in Section 10.2, which includes compliance with the requirements and restrictions listed in the consent form and in this protocol.

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. Alanine aminotransferase (ALT) not within normal limits; bilirubin >1.5× upper limit of normal (ULN; isolated bilirubin >1.5× ULN is acceptable if bilirubin is fractionated and direct bilirubin is <35%). 2. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). 3. Corrected QT (QTc) >450 msec. 4. Any clinically significant central nervous system (e.g., seizures), cardiac, pulmonary, metabolic, renal, hepatic, or gastrointestinal condition or history of such a condition that, in the opinion of the investigator, may place the subject at an unacceptable risk as a participant in this trial or may interfere with the absorption, distribution, metabolism, or excretion of drugs. 5. Use of a systemic antibiotic within 30 days of screening. 6. Ongoing febrile illness. 7. Confirmed history of *Clostridium difficile* diarrhea (see Appendix 10: *Clostridium difficile* Testing Procedure and Algorithm).

CONCOMITANT MEDICATIONS
8. Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the first dose of study treatment, unless in the opinion of the Investigator and the GSK medical monitor, the medication will not interfere with the study procedures or compromise subject safety.

RELEVANT HABITS
9. History of regular alcohol consumption within 6 months of screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or an average weekly intake of >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 270 mL of full strength beer, 470 mL of light beer, 30 mL of spirits, or 100 mL of wine. 10. Urinary cotinine level indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 3 months before screening.

CONTRAINDICATIONS

11. History of hypersensitivity attributed to β-lactam antibiotics (including cephalosporin, carbapenem, or penicillin antibiotics) or other drugs, a history of multiple antibiotic intolerances, or a history of serious adverse drug reactions.
12. Sensitivity to poison ivy or other catechol-related hypersensitivity (e.g., mango allergy).
13. History of sensitivity to heparin or heparin-induced thrombocytopenia.
14. History of latex allergy.
15. History of sensitivity to any of the study treatments or components thereof, or a history of drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in this study.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

16. Presence of hepatitis B surface antigen or positive hepatitis C antibody test result at screening or within 3 months before the first dosing day in this study.
17. Serum creatinine >ULN.
18. Glomerular filtration rate <90 mL/min/1.73m^2 as calculated by the Chronic Kidney Disease Epidemiology Collaboration formula (See Appendix 11).
19. Albumin to creatinine ratio (ACR) >0.03 mg/mg. In the event of an ACR above this threshold, eligibility may be confirmed by a second measurement.
20. Urinalysis positive for blood without other cause identified.
21. A positive pre-study drug or alcohol screen.
22. A positive test for human immunodeficiency virus antibody at or before screening.
23. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56-day period.
24. The subject has participated in a clinical trial and has received an investigational product within the following time period before the first dosing day in this study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
25. Exposure to more than 4 new chemical entities within 12 months before the first dosing day in this study.
26. Exclusion criteria for screening and baseline 12-lead ECG (a single repeat is allowed for eligibility determination):

	Males	**Females**
Heart rate	<40 and >100 beats per minute	<50 and >100 beats per minute
PR interval	<120 and >220 msec	
QRS duration	<70 and >120 msec	
QTcB or QTcF interval	>450 msec	
QTcB = corrected QT interval using Bazett's formula, QTcF = corrected QT interval using Fridericia's formula.		

a) Evidence of previous myocardial infarction (does not include ST segment changes associated with repolarization).
b) Subject has bundle branch block.
c) Any conduction abnormality (including but not specific to left or right complete bundle branch block, AV block [2nd degree or higher], Wolf-Parkinson-White

syndrome), sinus pauses more than 3 seconds, non-sustained or sustained ventricular tachycardia (≥3 consecutive ventricular ectopic beats), or any significant arrhythmia that, in the opinion of the investigator and the GSK medical monitor, will interfere with the safety of the individual subject.

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 publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including demography, screen failure details, eligibility criteria, and serious adverse events (SAEs; see Section 7.3.1.4).

5.4. Withdrawal/Stopping Criteria

The following actions must be taken in relation to a subject who fails to attend the clinical unit 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, behavioral, 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.

This protocol defines several clinical laboratory values, 12-lead ECG values, vital sign values, and additional safety criteria that, if observed and confirmed, mandate cessation of drug dosing and further evaluations. Any laboratory result that meets the stopping criteria should be repeated once to confirm the value before the subject is withdrawn from the study.

5.4.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to ensure subject safety and evaluate liver event etiology in alignment with the FDA guidance, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," [DHHS, 2009].

Study treatment will be discontinued for a subject who meets the following criterion:

- ALT ≥3 × ULN (Appendix 2)

Refer to Appendix 3, Liver Safety Required Actions and Follow-up Assessments, for details of the required assessments if a subject meets the above criterion.

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. Hematological Stopping Criteria

Study treatment will be discontinued for a subject who meets any of the following criteria:

- Hemoglobin ≤9.9 g/dL (99 g/L)
- White blood cells ≤1999/mm^3 (1.910 × 10^9/L)
- Platelets ≤99.999 × 10^9/L

5.4.3. Renal Stopping Criteria

Study treatment will be discontinued for a subject who meets any of the following criteria:

- Persistent (confirmed on recheck) elevation of serum creatinine (>0.3 mg/dL) without an alternative cause identified
- Albumin to creatinine ratio ≥0.03 mg/mg
- New blood in urinalysis confirmed by microscopy without an alternative cause identified

5.4.4. QTc Stopping Criteria

The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.

- For example, if a subject is eligible for the protocol based on corrected QT interval using Bazett's formula (QTcB), then QTcB must be used for discontinuation of this individual subject as well.

Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.

The QTc should be based on single or averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5 to 10 minute) recording period.

Study treatment will be discontinued for a subject who meets either of the following criteria:

- QTc >500 msec OR uncorrected QT >600 msec
- Change from baseline QTc of >60 msec

Withdrawal of subjects will be based on an average QTc value of triplicate ECGs. If an ECG demonstrates a prolonged QT interval, then 2 more ECGs will be obtained over a brief period of time (e.g., 5 to 10 minute) and then the averaged QTc values of the 3 ECGs will be used to determine whether the subject should be discontinued from the study.

5.4.5. Vital Signs Stopping Criteria

Study treatment will be discontinued for a subject who meets any of the following criteria:

- Systolic blood pressure (BP) >160 mm Hg for >1 hour
- Diastolic BP >100 mm Hg for >1 hour
- Heart rate >120 beats per minute for >1 hour

Vital signs should be taken with the subject in a semi-supine position, having rested in this position for at least 5 minutes. Repeat measurements should be taken within 5 minutes with the subject in the same physical position.

5.4.6. Other Safety Dose Adjustment/Stopping Criteria

For an individual study participant, additional 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 investigator in consultation with the medical monitor if necessary

5.4.7. Additional Safety Stopping Criteria

Individual subjects, dosed with GSK3342830 who have experienced the following should be considered for potential discontinuation in consultation with the GSK medical monitor:

- Any Grade 4 AE
- Grade 3 gastrointestinal AE (see Appendix 6)
    - *If a subject has 3 or more unformed stools in a 24-hour time frame, see Appendix 10 to determine if samples should be collected for Clostridium difficile testing.*
- Grade 3 renal or urinalysis finding (see Appendix 6)
- Severe hypersensitivity
- Anaphylaxis (see Appendix 7)
- Subjects with a systolic BP of <90 mm Hg or a change in systolic BP from baseline of 30 mm Hg with symptoms. Vital signs should be taken with the subject in a semi-supine position, having rested in this position for at least 5 minutes and findings are confirmed upon repeat measurements taken within 5 minutes with the subject in the same physical position.

Data will be reviewed by the investigator and sponsor for consideration of potential study stopping if:

- Two (2) or more subjects, within a dose level, receiving GSK3342830 experience a Grade 3 renal or urinary AE that is deemed possibly or probably related to study drug by the investigator.
- Two (2) or more subjects, within a dose level, receiving GSK3342830 experience Grade 3 hypersensitivity related AE that is deemed possibly or probably related to study drug by the investigator.
- Two (2) or more subjects, within a dose level, receiving GSK3342830 experience a Grade 3 AE of rash that is deemed possibly or probably related to study drug by the investigator.
- Two (2) or more subjects, within a dose level, receiving GSK3342830 experience a Grade 3 vital sign (heart rate or BP) abnormality that is considered an AE and is deemed possibly or probably related to study drug by the investigator. Vital signs should be taken with the subject in a semi-supine position, having rested in this position for at least 5 minutes and findings are confirmed upon repeat measurements taken within 5 minutes with the subject in the same physical position.
- One (1) or more subjects receiving GSK3342830 experience anaphylaxis that is deemed possibly or probably related to study drug by the investigator.

The grading for AEs is based on the US National Institute of Allergy and Infectious Diseases Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table (see Appendix 6).

5.4.8. Pharmacokinetic Dose Adjustment/Stopping Criteria

The exposures observed in animal toxicology studies will be used to guide dose escalation. Systemic exposures in the human subjects in this study may exceed the systemic NOAEL animal exposures from 4-week GLP toxicology studies as long as the doses administered in the study are safe and well tolerated.

For Part 1, the need to dose escalate will be evaluated if no meaningful increase in exposure is observed with an increase in dose (i.e., a plateau in exposures is reached).

5.5. 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 and Other Study Treatment

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

	Study Treatment	
Product name:	GSK3342830	Placebo
Formulation description:	A lyophilized formulation aseptically manufactured as a pyrogen-free, white to yellowish brown powder containing 1000 mg of GSK3342830A (as free base) per vial	A clear and colorless solution containing 0.9% sodium chloride
Dosage form:	Lyophile	IV solution
Unit dose strengths/Dosage levels:	Unit dose strength:1000 mg/vial as free base equivalent Dosage levels: Part 1: 250, 500, 1000, 2000, 4000, and ≤6000 mg Part 2: 1000, 2000, and ≤4000 mg Part 3: 250, 500, 1000, 2000, 4000, or ≤6000 mg	Not applicable
Route of Administration:	IV infusion over 1 hour	IV infusion over 1 hour

	Study Treatment	
Product name:	GSK3342830	Placebo
Dosing instructions:	Parts 1 and 3: Single IV infusion. Part 2: Single IV infusion on Day 1, TID IV infusions (approximately every 8 hours) on Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14, and a single IV infusion on Day 15. Instructions for the preparation of the IV drug are included in the Pharmacy Manual.	Parts 1 and 3: Single IV infusion. Part 2: Single IV infusion on Day 1, TID IV infusions (approximately every 8 hours) on Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14, and a single IV infusion on Day 15. Instructions for the preparation of the IV drug are included in the Pharmacy Manual.
Physical description:	The lyophilized powder cake has a white to yellowish brown color. The reconstituted solution is a clear, colorless to yellow or brownish yellow liquid, free from visible particulate matter.	A clear colorless solution

6.2. Treatment Assignment

Eligible subjects will be assigned to study treatment in accordance with the randomization schedule generated by PPD, before the start of the study, using validated internal software. Within each cohort, subjects will be randomly assigned to receive either GSK3342830 or placebo in a ratio of 3:1 in Part 1 and 4:1 in Part 2.

Each subject scheduled to receive study treatment will receive a treatment allocation number when randomized. The treatment number will indicate if the subject is to receive the scheduled dose of GSK3342830 or placebo.

6.3. Planned Dose Adjustments

- This protocol allows some alteration from the currently outlined dosing schedule. The maximum daily dose is planned to not exceed 6000 mg in Parts 1 and 3, and 4000 mg in Part 2.

- The decision to proceed to the next dose level of GSK3342830 will be made by the GSK study team and the investigator based on preliminary safety, tolerability, and PK data obtained in approximately 4 subjects for Part 1 and approximately 5 subjects for Part 2 that received active study treatment in the prior dose level. The actual doses to be administered may be adjusted based on the preliminary safety, tolerability, and PK data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose. A schematic of the planned study design is presented in Figure 3.

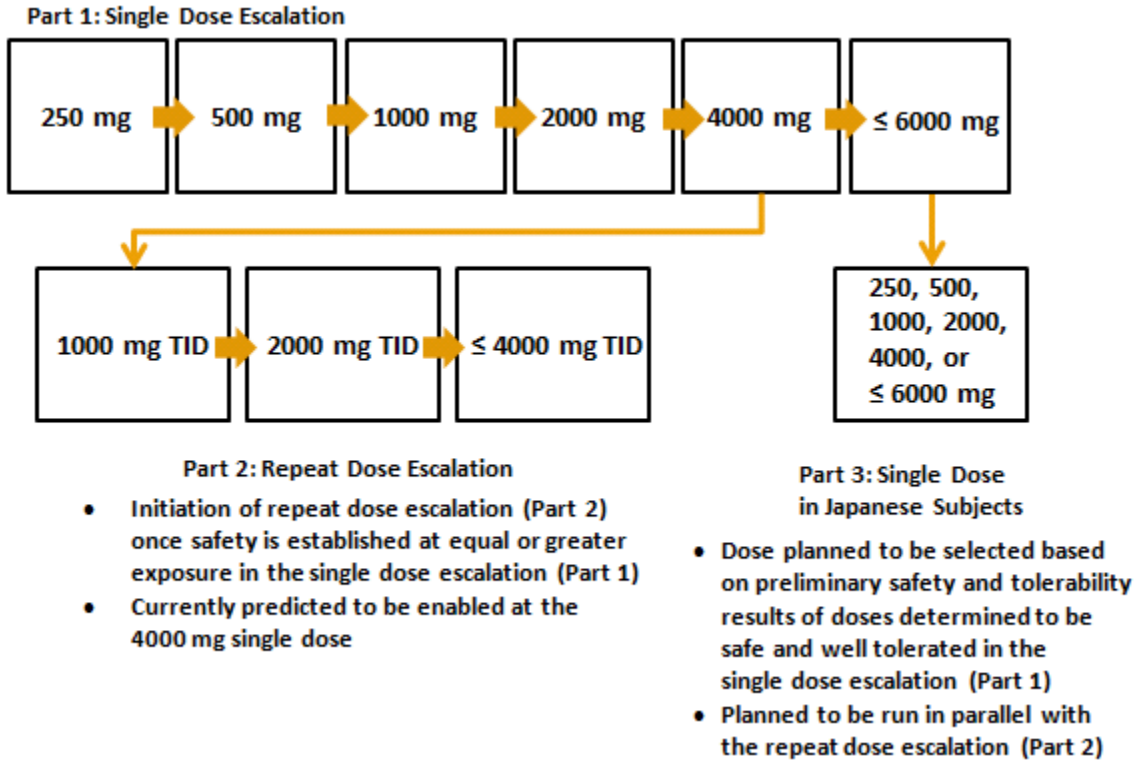
- The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety and PK findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as those described for other study subjects.

- If AEs, which are of severe intensity or greater and are consistent across subjects in a given dose level, or if unacceptable pharmacological effects, reasonably attributable in the opinion of the investigator to dosing with GSK3342830, are observed in 2 or more subjects in a dose level, further dose escalation will be temporarily halted and no further subject in subsequent cohorts will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the medical monitor, relevant GSK personnel, and with the Ethics Committee will then take place before any resumption of dosing.

- If the same SAE occurs in more than 1 subject, further dose escalation will be temporarily halted and no further subject in subsequent cohorts will be dosed until a full safety review of the data has taken place.

- The previously mentioned criteria will apply even if measured PK parameters are below the PK stopping criteria, and every effort will be made to take a blood sample at the time of the event for PK analysis in the presence of any of the above events.

Figure 3 Planned Study Schematic



6.4. Blinding

This will be a double-blind (sponsor unblinded) study. The subjects will be completely blinded and the site staff will be blinded to subject-specific treatment assignment. The GSK study team will be unblinded at the aggregate level for decision making throughout the study (e.g. to support dose escalations and use of Bayesian predictive techniques). Where possible, the GSK/clinical research organization personnel will not have access to subject-specific treatment assignment so as to not potentially introduce bias in discussions with the study site. The pharmacokineticists, statisticians, programmers, and data managers, however, will need access to subject randomization during the course of the single dose escalation and repeat dose escalation portions of the study for analysis purposes to support dose adjustments and escalations. Other GSK staff may be included in discussions around dose adjustments and progression if it is deemed necessary and relevant by the above mentioned GSK study team members.

During dosing of a specific cohort, the investigator or treating physician may unblind a subject's treatment assignment only in the case of an emergency, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. Whenever possible, the investigator must first discuss options with the GSK medical monitor or appropriate GSK study personnel before unblinding the subject's treatment assignment. If this is impractical, the investigator must notify GSK as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the electronic data capture system. *In this situation, the subject will be withdrawn from further treatment if the subject's treatment code is unblinded by the investigator or treating physician.* The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the electronic data capture system. GSK's Global Clinical Safety and Pharmacovigilance staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to the investigator in accordance with local regulations and/or GSK policy.

During the dose escalation safety review, the GSK clinical team and the investigator will review safety data in a blinded aggregate form. In the event of concern over a potential safety signal, the GSK clinical team and the investigator may review unblinded treatment assignments for the purposes of safety review and dose selection without study interruption. If a safety signal is determined to indicate findings in subjects who received GSK3342830, the findings will be escalated for assessment by the GSK safety team and actions taken as appropriate including review of study for possible halting of further dosing.

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 GSK3342830 infusion and placebo infusion will be detailed in a Pharmacy Manual which will be accompanied by a Quality Agreement.

- 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 Pharmacy Manual.
- 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 or 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.

Subjects will be dosed at the clinical unit and receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinical unit will be recorded in the source documents. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

GSK3342830 and placebo will be administered intravenously to subjects at the site. Administration will be documented in the source documents and recorded in the electronic case report form (eCRF).

6.8. Treatment of Study Treatment Overdose

GSK3342830 will be administered at the clinical unit, thus limiting the risk of overdose. In the unlikely event that an overdose with GSK3342830 should occur, the investigator must notify the sponsor promptly. There is no specific antidote for overdose with GSK3342830. In the event of a suspected overdose, it is recommended that the appropriate supportive clinical care should be instituted, as dictated by the subject's clinical status.

GSK does not recommend specific treatment for an overdose.

In the event of a suspected overdose the investigator should:

1. Contact the medical monitor
2. Closely monitor the subjects for AEs/SAEs and laboratory abnormalities until GSK3342830 can no longer be detected systemically (at least 1 day)
3. Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study treatment if requested by the medical monitor (determined on a case-by-case basis)
4. Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF

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 adult subjects are eligible for study participation.

6.10. Lifestyle and/or Dietary Restrictions

6.10.1. Meals and Dietary Restrictions

Standardized meals will be provided while the subject is confined to the clinical unit. At all mealtimes, food will be served only after completion of protocol-specified procedures.

Subjects will refrain from consumption of red wine, Seville oranges, grapefruit, or grapefruit juice (and/or pummelos, exotic citrus fruits, grapefruit hybrids, or fruit juices) from 7 days before the first dose of study drug until after the final dose.

Water will be allowed ad libitum except for 1 hour before the start of infusion and 1 hour after the end of infusion.

Subjects will fast from food and drink (except water) for at least 10 hours before dosing on Day 1 (Parts 1, 2, and 3) and Day 15 (Part 2 only). Meals at all other times will be provided at times that will not interfere with fasting required for clinical laboratory testing.

These fasting requirements may be removed or modified at the discretion of the sponsor in consultation with the investigator.

6.10.2. Caffeine, Alcohol, and Tobacco

Subjects will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 24 hours before the start of dosing on Day 1 until collection of the final PK sample.

Subjects will abstain from alcohol for 24 hours before the start of dosing on Day 1 until collection of the final PK sample.

Use of tobacco products is not allowed from 3 months before screening until after the final Follow-up visit.

6.10.3. Activity

Subjects will abstain from strenuous exercise during the course of the study through the Follow-up visit. Subjects may participate in light recreational activities during the study (e.g., watch television, read).

6.11. Concomitant Medications and Non-Drug Therapies

6.11.1. Permitted Medications and Non-Drug Therapies

Paracetamol or Acetaminophen at doses of ≤2 grams/day and HRT are permitted for use during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the medical monitor.

6.11.2. Prohibited Medications and Non-Drug Therapies

Subjects must refrain from the use of prescription or non-prescription drugs, including vitamins and 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) before the first dose of study drug, unless in the opinion of the investigator and GSK medical monitor, the medication will not interfere with the study procedures or compromise subject safety.

7. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Tables (Section 7.1) are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Tables (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
  2. vital signs
  3. 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.
  - The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form.
  - No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.1. Time and Events Tables

Table 3 Time and Events Table: Screening and Day –1; Single and Repeat Dose Escalation (Part 1 and Part 2) and Single Dose (Part 3)

Procedure	Screening (up to 30 days before Day 1)	Day –1	Notes
Informed consent	X		
Inclusion and exclusion criteria	X	X	
Demography	X		
Medical history (includes substance usage and family history of premature cardiovascular disease)	X	X	Substances: drugs, alcohol, tobacco and caffeine.
Past and current medical conditions including cardiovascular medical history	X	X	
Safety and Laboratory Assessments			
SAE review	X	X	Serious AEs will be collected from the signing of informed consent.
Concomitant medication review	X	X	
Full physical examination including height and weight	X		
Brief physical examination		X	
Vital signs (BP, HR, oral temperature, respiration rate)	X	X	
12-lead electrocardiogram	X	X	
Continuous cardiac monitoring		X	Continuous dual-lead telemetry will be initiated on Day –1 at least 8 hours before study drug administration on Day 1.
Urine cotinine and drug and breath alcohol screens	X	X	
β-hCG pregnancy test/estradiol/FSH	X	X	Pregnancy test (if female of child-bearing age; serum at screening and urine at Day –1); estradiol and FSH at screening as appropriate. Only women of non-child-bearing potential may participate.
Human immunodeficiency virus antibody, hepatitis B surface antigen, and hepatitis C antibody screen	X		
Clinical chemistry (including liver chemistries), hematology, and urinalysis	X	X	The albumin to creatinine ratio will be determined at Screening using the first morning void urine as described in Section 7.3.7. An aliquot of the urine sample will be collected for NGAL and KIM-1 at Day –1. These samples may be analyzed after the end of the study if a clinical signal is detected. Instructions for collection and storage of these urine samples are included in the Study Reference Manual. Hematology assessments on Day –1 will also include total iron, total binding iron capacity, ferritin, haptoglobin, ceruloplasmin and reticulocytes.

Procedure	Screening (up to 30 days before Day 1)	Day –1	Notes
Table is continued on the next page.			
Blood collection for additional iron tests		X	In Part 2 only. Samples will be collected for potential analysis of some or all of the additional iron tests at the end of the study if a clinical signal is detected.
Genetic sample		X	Collect a pharmacogenomics sample only if the subject has a signed consent specific for this purpose. The pharmacogenomics sample can be collected anytime, but Day –1 is recommended. Informed consent for optional sub-studies (e.g., genetics research) must be obtained before collecting a sample.
Admission to clinical unit		X	
β-hCG = beta human chorionic gonadotropin, BP = blood pressure, FSH = follicle-stimulating hormone, HR = heart rate, KIM-1 = kidney injury molecule 1, NGAL = neutrophil gelatinase-associated lipocalin, SAE = serious adverse event.			

Table 4 Time and Events Table: Part 1 - Single Dose Escalation and Part 3 - Single Dose

Procedure	Day 1																	Day 2		Day 3
	Hours relative to treatment administration																			
	Pre-dose	0	0.5	1	1.25	1.5	2	3	3.5	4	4.5	5	6	8	10	12	16	24	36	48
Randomization	X																			
12-lead ECG[1]	X		X	X		X	X	X		X			X			X		X		X
Vital signs (BP, HR, oral temperature, respiration rate)	X		X	X		X	X	X		X			X			X		X		X
Fasting clinical chemistry, hematology, and urinalysis[2]																		X		
Treatment administration[3]		X																		
Blood collection for pharmacokinetics[4]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection for pharmacokinetics[5]	X-- ---------X----------X----------X----------X----------X----------X----------X----------X																			
Continuous cardiac monitoring[6]	X←----------Continuous review----------→																			
AE review		X←----------Continuous review----------→																		
SAE review	X←----------Continuous review----------→																			
Concomitant medication review	X←----------Continuous review----------→																			
Discharge from inpatient unit[7]																				X

AE = adverse event, BP = blood pressure, ECG = electrocardiogram, HR = heart rate, SAE = serious adverse event.

NOTES:

1. Triplicate 12-lead ECGs to be obtained at least 5 minutes apart within 1 hour before dosing. Single ECGs will be obtained at all other time points.
2. An aliquot of the urine sample will be collected for neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1). These samples may be analyzed after the end of the study if a clinical signal is detected. Instructions for collection and storage of these urine samples are included in the Study Reference Manual. The albumin to creatinine ratio will be determined using the first morning void urine on Day 2.
3. GSK3342830 or placebo will be administered as a single IV infusion in the morning on Day 1. The planned infusion duration time is 1 hour.
4. Pharmacokinetic blood samples will be collected for GSK3342830 and potential metabolites. At the end of the study the saved blood samples from a predicted therapeutically-relevant dose level and higher dose level for plasma PK analysis of parent and the highest dose level completed for metabolite profile, will be transferred to a GSK specified laboratory. Details of PK sample collection and storage will be provided in the Study Reference Manual.
5. Pooled urine samples will be collected over the following time intervals: pre-dose (within a 24-hour period before dosing, may begin on Day –1) and 0 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48 hours post-dose. Two aliquots of urine samples for baseline analysis may be collected from any time after admission to just before dosing on Day 1. At the end of the study, the saved urine samples from a predicted therapeutically-relevant dose level and higher dose level for urinary PK analysis of parent and the highest dose level completed for potential metabolite profile, will be transferred to a GSK specified laboratory. Urine will be collected in opaque bottles to maintain blind of blinded study site personnel. Details of urine sample collection and storage will be provided in the Study Reference Manual.
6. Continuous dual-lead telemetry will be initiated on Day –1 at least 8 hours before treatment administration on Day 1 and will continue until 48 hours post dose.
7. Subjects will be discharged from the clinical unit after the 48-hour post-dose assessments are complete.

Table 5 Time and Events Table: Part 2 - Repeat Dose Escalation

Procedure	Study Day															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Randomization	X															
12-lead ECG[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, HR, oral temperature, respiration rate)[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fasting clinical chemistry, hematology, and urinalysis tests[3]		X			X					X					X	
Treatment administration[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood collection for pharmacokinetics[5]	X		X			X			X			X	X		X	
Urine collection for pharmacokinetics[6]	X	X													X	X
Continuous cardiac monitoring[7]	X←Continuous review→															
AE review	X←----------Continuous review----------→															
SAE review	X←----------Continuous review----------→															
Concomitant medication review	X←----------Continuous review----------→															
Discharge from inpatient unit[8]																X

AE = adverse event, BP = blood pressure, ECG = electrocardiogram, HR = heart rate, SAE = serious adverse event.

NOTES:

1. Triplicate 12-lead ECGs will be obtained at least 5 minutes apart within 1 hour before the start of infusion (pre-dose) on Day 1. Single ECGs will be obtained at 0.5, 1, 1.5, 2, 3, 4, 6, and 12 hours after the start of infusion on Day 1 and Day 15, within 1 hour before the start of the morning infusion on Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14, and in the morning on Day 16.
2. Vital signs will be measured within 1 hour before the start of infusion (pre-dose) and at 0.5, 1, 1.5, 2, 3, 4, 6, and 12 hours after the start of infusion on Days 1 and 15, within 1 hour before the start of the morning infusion and on Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14, and in the morning on Day 16.
3. An aliquot of the urine sample will be collected for neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1). These samples may be analyzed after the end of the study if a clinical signal is detected. Instructions for collection and storage of these urine samples are included in the Study Reference Manual. Hematology assessments on Days 5 and 15 will also include total iron, total iron binding capacity, ferritin, haptoglobin, ceruloplasmin and reticulocytes. The albumin to creatinine ratio will be determined using the first morning void urine on Days 5 and 15. Urinalysis assessments before dosing on Day 15 will also include urine color.
4. GSK3342830 or placebo will be administered as a single IV infusion in the morning on Day 1, TID IV infusions (approximately every 8 hours) on Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14, and as a single IV infusion in the morning on Day 15. The planned infusion duration time is 1 hour.
5. Pharmacokinetic samples for GSK3342830 and potential metabolites will be collected on Day 1 at the following time points: pre-dose (within 15 minutes before dosing) and 0.5, 1 (end of infusion), 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 16, and 24 hours after the start of infusion. Single pre-dose trough samples will be taken on the mornings of Days 3, 6, 9, 12, and 13. Serial samples will be collected on Day 15 at the following time points: pre-dose (within 15 minutes before dosing) and 0.5, 1 (end of infusion), 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, and 8 hours after the start of infusion. At the end of the study, the saved blood samples from a predicted therapeutically-relevant dose level and higher dose level for plasma PK analysis of parent and from the highest dose level completed for potential metabolite profile will be transferred to a GSK specified laboratory. Details of PK sample

collection and storage will be provided in the Study Reference Manual.

6. Pooled urine samples will be collected on Day 1 and Day 15 over the following time intervals: pre-dose (within a 24-hour period before dosing, may begin on Day –1) and 0 to 8 and 8 to 24 hours post-dose. Two aliquots of urine samples for baseline analysis may be collected from any time after admission to just before dosing on Day 1. At the end of the study, the saved urine samples from a predicted therapeutically-relevant dose level and higher dose level for urinary PK analysis of parent and from the highest dose level completed for potential metabolite profile, will be transferred to a GSK specified laboratory. Urine will be collected in opaque bottles to maintain blind of blinded study site personnel. Details of urine sample collection and storage will be provided in the Study Reference Manual.
7. Continuous dual-lead telemetry will be initiated on Day –1 at least 8 hours before treatment administration on Day 1 and will continue until 48 hours post dose.
8. Subjects will be discharged from the clinical unit after the Day 16 assessments are complete.

Table 6 Time and Events Table: Follow-up Visit; Single and Repeat Dose Escalation (Part 1 and Part 2) and Single Dose (Part 3)

Procedure	Follow-up Visit (7 to 10 days post last dose or early termination)
Adverse event/serious adverse event review	X
Concomitant medication review	X
Brief physical examination	X
12-lead electrocardiogram	X
Vital signs	X
Urine β-human chorionic gonadotropin pregnancy test (women of child-bearing age)	X
Clinical chemistry, hematology, and urinalysis tests[1]	X

NOTE:

1. An aliquot of the urine sample will be collected for neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1). These samples may be analyzed after the end of the study if a clinical signal is detected. Instructions for collection and storage of these urine samples are included in the Study Reference Manual. Hematology assessments will also include total iron, total iron binding capacity, ferritin, haptoglobin, ceruloplasmin and reticulocytes. The albumin to creatinine ratio will be determined using the first morning void urine as described in Section 7.3.7.

7.2. Screening and Critical Baseline Assessments

Cardiovascular medical history, family history, and risk factors (as detailed in the eCRF) will be assessed at screening.

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

Medical and medication history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed in the time frame of the study.

7.3. Safety

Planned time points for all safety assessments are listed in the Time and Events Tables (Section 7.1). Additional time points for safety tests such as vital signs, physical examinations, and laboratory safety tests may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

7.3.1. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 5.

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

7.3.1.1. Time Period and Frequency for Collecting AE and SAE Information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- Serious AEs will be collected from the signing of informed consent and AEs will be collected from the start of treatment until the follow-up contact (see Section 7.3.1.3) as indicated in the Time and Events Tables (Section 7.1).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 5.
- 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 5 and Appendix 6.

7.3.1.2. Method of Detecting AEs and SAEs

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

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

7.3.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Appendix 5.

7.3.1.4. Regulatory Reporting Requirements for SAEs

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

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

7.3.2. Pregnancy

Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of dosing and until the Follow-up visit (7 to 10 days post-last dose).

If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 8.

7.3.3. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, throat, skin, thyroid, neurological, lungs, cardiovascular system, gastrointestinal system, abdomen (liver and spleen), lymph nodes, and extremities. Height and weight will also be measured and recorded.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, gastrointestinal system, and abdomen (liver and spleen).

7.3.4. Vital Signs

Vital signs should be taken with the subject in a semi-supine position, having rested in this position for at least 5 minutes and will include temperature, systolic and diastolic BP, pulse rate, and respiratory rate. Refer to Section 5.4.5 for vital sign stopping criteria.

7.3.5. Electrocardiograms

Triplicate 12-lead ECGs will be obtained at least 5 minutes apart for the time points that are within 1 hour before dosing. Single 12-lead ECGs will be obtained at all other time points during the study. All 12-lead ECGs will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 5.4.4 for QTc stopping criteria.

7.3.6. Continuous Cardiac Monitoring

Continuous dual-lead telemetry will be initiated on Day –1 at least 8 hours before study drug administration on Day 1 and will continue until 48 hours post dose.

7.3.7. Clinical Safety Laboratory Assessments

All protocol required safety laboratory assessments, as defined in Table 7, must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events Tables (Section 7.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/center number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Study Reference Manual (SRM). Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

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

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

Hematology, clinical chemistry, urinalysis, and additional parameters to be tested are listed in Table 7.

Table 7 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count	Total iron[1]	*RBC Indices*:	*WBC count with Differential:*
	RBC Count	TIBC[1]	MCV	Neutrophils
	Hemoglobin	Ferritin[1]	MCH	Lymphocytes
	Hematocrit		MCHC	Monocytes
	Reticulocytes[1]			Eosinophils
				Basophils
Additional Iron Tests[2]	Transferrin (apotransferrin)	Ceruloplasmin	Haptoglobin/Hemopexin	
Clinical Chemistry[3]	Blood urea nitrogen	Potassium	AST	Total and direct bilirubin
	Creatinine	Sodium	ALT	Total protein
	Glucose	Calcium	Alkaline phosphatase	Albumin
	Bicarbonate	Chloride	Uric acid	
Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • ACR[4] • Microscopic examination (if blood or protein is abnormal) • NGAL[5] • KIM-1[5] • Urine color[6]			
Other Screening Tests	• Human immunodeficiency virus • Hepatitis B surface antigen • Hepatitis C antibody • Follicle-stimulating hormone and estradiol (as appropriate) • Alcohol, cotinine, and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • β-human chorionic gonadotropin pregnancy test (if female of child-bearing age; serum at screening and urine at Day –1 and follow-up)			

ACR = albumin to creatinine ratio, ALT = alanine aminotransferase, AST = aspartate aminotransferase, KIM-1 = kidney injury molecule 1, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, NGAL = Neutrophil gelatinase-associated lipocalin, RBC = red blood cell, TIBC = total iron binding capacity, WBC = white blood cell

Footnotes are on the next page.

NOTES:
1. In Parts 1 and 3, analyzed on Day –1 and at Follow-up visit. In Part 2, analyzed on Day –1, Day 5, Day 15, and at Follow-up visit.
2. Blood samples will be collected on Day –1, predose (at least 1 hour before dosing) on Days 5, and 15, and at Follow-up visit..
3. 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, Appendix 2, and Appendix 3.
4. The ACR on urine albumin and creatinine will be determined using the first morning void urine at Screening and Follow-up visit for all subjects in both parts of the study. In addition, the ACR will be determined on Day 2 in Parts 1 and 3, and Days 5 and 15 in Part 2. Screening ACR may be performed on urine during the screening visit. Subjects should be provided a sterile urine transport container and instructions on how to collect a first void urine at home for screening. In the event a subject fails by ACR, the subject should be contacted to bring back first void urine for recheck. For the Follow-up visit, subjects must be provided a sterile urine transport container on discharge from the clinical unit and instructed to bring back the first morning void urine on the day of their return Follow-up visit.
5. An aliquot of the remaining urine samples will be banked and may be analyzed for NGAL and KIM-1 after the end of the study if a clinical signal is detected. Instructions for collection and storage of these urine samples are included in the Study Reference Manual.
6. Assessed before dosing on Day 15 (Part 2) only.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study (from first dose of study treatment through the Follow-up visit) should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

7.4. Pharmacokinetics

7.4.1. Blood Sample Collection

Blood samples for PK analysis of GSK3342830 will be collected at the time points indicated in the Time and Events Tables (Section 7.1). The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

At the end of the study, the saved blood samples from a predicted therapeutically-relevant dose level and higher dose level for plasma PK analysis of parent and the highest dose level completed for metabolite profile, will be transferred to a GSK specified laboratory.

A total of 3 mL of blood will be collected from each subject.

Details of PK blood sample processing, storage, and shipping procedures are provided in the SRM.

7.4.2. Urine Sample Collection

Urine samples for PK analysis of GSK3342830 will be collected at the time points indicated in the Time and Events Tables (Section 7.1). The actual date and time of each urine sample collection will be recorded. The timing of urine samples may be altered and/or samples may be obtained at additional time points to ensure thorough PK monitoring.

At the end of the study, saved urine samples from a predicted therapeutically-relevant dose level and higher dose level for urinary PK analysis of parent and the highest dose level completed for potential metabolite profile, will be transferred to a GSK specified laboratory.

Urine will be collected in opaque bottles to maintain the blind of blinded study site personnel.

Details of PK urine sample processing, storage, and shipping procedures are provided in the SRM.

7.4.3. Sample Analysis

Concentrations of GSK3342830 will be determined in blood and urine samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma and urine have been analyzed for GSK3342830 any remaining blood and urine may be analyzed for other compound-related metabolites and the results reported under a separate protocol.

7.5. Genetics

Depending on the clinical study results, exploratory pharmacogenomics analyses may be performed to examine the potential relationship between genetic variants and clinical endpoints.

Information regarding genetic research is included in Appendix 4.

8. DATA MANAGEMENT

- For this study subject data will be entered via an eCRF into Oracle Clinical Remote Data Capture System (OC RDC). Subject data will be available for viewing through access to the OC RDC system. Data provided from other sources will be received, reconciled, combined, and transferred to GSK at predetermined time points.
- 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.
- The eCRFs (including queries and audit trails) will be sent at the end of the study in electronic format to GSK to be retained, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

All statistical analyses will be performed by PPD using SAS (SAS Institute Inc., Cary, North Carolina, USA), version 9.2 or higher. Pharmacokinetic parameters will be calculated using Phoenix WinNonlin (Certara, L.P., 1699 S Hanley Road, St Louis, Missouri 63144, USA), version 6.3 or higher.

Before database lock, a reporting and analysis plan (RAP) will be issued as a separate document, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described in a RAP addendum and justified in the final integrated clinical study report.

9.1. Hypotheses

The primary objective of this study is to investigate the safety and tolerability of GSK3342830 after administration of single and repeat IV doses in healthy adult subjects and after administration of single IV dose in adult Japanese subjects. The pharmacokinetics of GSK3342830 after administration of single and repeat IV doses in healthy subjects (and in adult Japanese subjects after administration of single IV dose) will also be determined. No formal statistical hypotheses are to be tested. For dose proportionality, accumulation, time invariance, and assessment of steady-state, an estimation approach will be taken, and point estimates and confidence intervals (CIs) will be constructed. For safety parameters, comparisons to placebo will be made based on descriptive statistics.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Sample size is based on feasibility. No formal calculation of power or sample size for Parts 1 or 2 of the study will be performed. A sample size of 6 to 10 subjects per dose level cohort should be sufficient to provide useful estimates of both inter- and intra-subject variability for GSK3342830 PK parameters, and initial safety assessment.

Although the sample size is not based on statistical criteria, general probabilities can be determined on the likelihood of observing AEs. With 6 subjects receiving each dose of active drug, if the true adverse outcome rate is 5%, the chance of observing at least 1 adverse outcome at a given dose is 26%. Similarly if the true adverse outcome rate is 20%, the chance of observing at least 1 adverse outcome at a given dose is 73%. This level of predictivity is deemed adequate within this FTIH setting before commencing to repeat dosing (Part 2) and Phase II studies.

9.2.2. Sample Size Sensitivity

Not applicable.

9.2.3. Sample Size Re-estimation or Adjustment

Not applicable.

9.3. Data Analysis Considerations

In general, descriptive summaries will include number of subjects, mean, standard deviation, median, minimum, and maximum for continuous variables; and percent for categorical variables. Summaries will present data by dose level and where appropriate, by assessment time.

9.3.1. Analysis Populations

The **Safety Population** will consist of all subjects who receive at least 1 dose of study drug and have at least on post-dose safety assessment.

The **PK Population** will consist of all subjects who receive at least 1 dose of GSK3342830 and for whom a PK sample is collected and analyzed.

The **PK Parameter Population** will consist of all subjects in the PK population for whom valid and evaluable PK parameters were derived.

9.3.2. Interim Analysis

No formal interim analysis is planned for this study. However, one may be conducted in the event of clinically significant safety or PK findings. All preliminary safety, tolerability, and available PK data will be reviewed internally at GSK and with the clinical study site before each dose escalation in Part 1, before initiation of Part 2, and before each dose escalation in Part 2. All preliminary safety and tolerability data from Part 1 will be reviewed internally at GSK and with the clinical study site before dose selection for and initiation of Part 3. Section 6.4 provides further detail on data access and the handling of treatment blinding.

The relationship between dose and plasma GSK3342830 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 modeling (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, a Bayesian predictive probability that a dose level will have mean AUC (AUC[0-t] or AUC[0-24] for single dose and AUC[0-24] for repeat dose) and Cmax values greater than 2875 h•µg/mL and 2270 µg/mL (mean exposures at the NOAEL dose in the rat and monkey), respectively, and Bayesian predictive probability that an individual will have AUC(0-24) and Cmax values greater than 3460 h•µg/mL and 2590 µg/mL (maximum

exposures at the NOAEL dose in the rat for AUC and the monkey for Cmax), respectively, may 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]:

$$y_{ij} = \theta_1 + \theta_2 d_{ij} + s_i + \epsilon_{ij}$$

where y_{ij} is log-PK of i-th subject to j-th dose, d_{ij} is j-th log-dose administered to i-th subject, θ_1 and θ_2 are population intercept and slope, respectively, s_i is random effect of i-th subject and ϵ_{ij} is random error of i-th subject in j-th dose.

9.4. Key Elements of Analysis Plan

9.4.1. Primary Analyses

Safety Analyses

The following safety evaluations will be performed:

- Monitoring for AEs
- Routine clinical laboratory tests including chemistry, hematology, and urinalysis
- Vital signs
- Twelve-lead ECG readings
- Continuous cardiac monitoring (dual-lead telemetry)

Safety endpoints will include AEs, clinical laboratory test results (chemistry [including liver function parameters], hematology, and urinalysis), vital signs (BP, heart rate, respiratory rate, and body temperature), and 12-lead ECG readings.

All safety data will be presented in data listings. Subject demographics, medical history, and prior and concomitant medications will be summarized for each dose level using descriptive statistics. For continuous variables, these summaries will include number of subjects, mean, median, standard deviation, minimum, and maximum.

For categorical variables, the summaries will include frequencies and corresponding percentages. No inferential hypothesis testing will be performed on the safety variables.

Adverse events will be coded using the MedDRA classification system. Treatment-emergent AEs will be defined as any AEs, regardless of relationship to study drug, that occur after the dose of study drug until the Follow-up visit. The treatment-emergent AEs will be summarized for each dose level at AE onset for the overall number of AEs and percentage of subjects who experience them. The total number of AEs will be summarized by dose level and overall. The AEs will be further summarized by severity and relationship to the study drug. If relationship information is missing, the AE will be considered treatment related. Listings for the subsets of SAEs

and treatment-related SAEs will be provided. The SAEs and number of AEs leading to discontinuation will be summarized. The incidence of AEs will also be summarized by system organ class and preferred term.

Clinical laboratory test results, vital signs, and 12-lead ECG results will be summarized by actual values and change from baseline. Clinical laboratory values that are outside of the reference ranges will be flagged and evaluated for clinical significance by the investigator. Any 12-lead ECG abnormalities will be summarized by each dose level. Physical examination findings and cardiac telemetry results will be listed.

Detailed descriptions of the analyses in this study will be presented in the RAP.

9.4.2. Secondary Analyses

Pharmacokinetic Analyses

Plasma GSK3342830 concentration versus time data will be analyzed by non-compartmental methods with WinNonlin Version 5.2 or higher. Calculations will be based on the actual sampling times recorded during the study. From the plasma and urine concentration versus time data, the following PK parameters will be determined, as data permit:

Plasma:

Cmax	Maximum plasma concentration
Tmax	Time to Cmax
AUC(0-t)	AUC from time zero to the last quantifiable concentration after dosing
AUC(0-∞)	AUC extrapolated from time zero to infinity (estimated for single dose in Parts 1 and 3, and on Day 1 for repeat dose in Part 2)
AUC(0-τ)	AUC over the dosing interval τ
t1/2	Terminal elimination half-life
CL	Total systemic clearance
Vss	Steady-state volume of distribution
Cτ	Trough concentration

Urine:

Feu(t1-t2)	Urinary excretion ratio relative to dose
CLr	Renal clearance
Ae	Amount excreted in urine

Plasma GSK3342830 concentration data will be listed and summarized by time point for each dose level using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, maximum, and coefficient of variation). Urine GSK3342830 concentration and volume data will be listed. Mean, median, and individual plasma

concentration versus time profiles will be presented graphically on linear and semi-logarithmic scales.

Actual sampling times, rather than scheduled sampling times, will be used in all calculations of PK parameters. However, for ease of presentation, scheduled sampling times will be used to present results in tables, listings, and figures.

Tmax of GSK3342830 will be separately analyzed using non-parametric Wilcoxon rank test to compute point estimates and associated 90% CIs for the median differences.

Detailed descriptions of the analyses in this study will be presented in the RAP.

Dose Proportionality

Dose proportionality of AUC(0-∞) and Cmax on Day 1 in Part 1 and for repeat dose groups AUC(0-τ) and Cmax of GSK3342830 on Day 15 in Part 2 will be assessed separately by day using the following power model:

$$y = \alpha * dose^{\beta}.$$

where y denotes the PK parameter being analyzed and α depends on the random error in the repeat dose phase where subjects take the study drug in a parallel-group fashion. Dose proportionality implies that β=1 and will be assessed by estimating β along with its 90% CI. The exponent, β, in the power model will be estimated by regressing the $\log_e$-transformed PK parameter on $\log_e$ dose.

$$\log(y) = \log(\alpha) + \beta * \log(dose)$$

The power model will be fitted by restricted maximum likelihood using Statistical Analysis Software (SAS) Proc Mixed, with a fixed effect term for dose. The PK parameter endpoint and the factor dose will be $\log_e$-transformed before the analysis. An estimate of slope (with corresponding 90% CI) will be provided as a measure of potential dose proportionality (i.e. a slope of approximately 1 implies dose proportionality). Dose proportionality is the prerequisite of the Bayesian predictive model.

In the case where dose proportionality is not established over the entire dosing range, secondary analysis of dose proportionality will be assessed for select doses over the higher dosing range with the power model or by pair-wise analysis of variance (ANOVA) using the SAS mixed models procedure. If the secondary analysis using the pair-wise ANOVA approach is performed, a reference dose would be chosen based on the lowest clinically relevant dose over which the pharmacokinetics can be adequately described and the other doses would be treated as test doses.

Time Invariance

For the repeat dose cohorts (Part 2), the time invariance ratio will be assessed by fitting a mixed effect model for AUC(0-∞) on Day 1 and AUC(0-τ) on Day 15 data with subject as a random effect and group (group=1 for AUC(0-∞) on Day 1, and group=2 for AUC(0-τ) on Day 15) as a fixed effect for each cohort. The time invariance ratio of GSK3342830 will be estimated by calculating the ratio of the geometric least squares

means of group 1 (AUC(0-τ) on Day 15) to group 2 (AUC(0-∞) on Day 1) and the corresponding 90% CI for each cohort. The time invariance ratio will be listed and summarized along with other PK parameters.

Accumulation Ratio

For the repeat dose cohorts (Part 2), the accumulation ratio (Ro) will be calculated as the ratio of AUC(0-τ) on Day 15 to AUC(0-τ) on Day 1 for each subject. The dosing interval (τ) will be equal to 8 hours. The accumulation ratio will be listed and summarized along with other PK parameters.

Following log-transformation, AUC(0-τ) of GSK3342830 on Days 1 and 15 will be analyzed by a mixed effect model, fitting dose, day, and dose-by-day interaction as fixed effects and subject as a random effect. For each dose, point estimate and 90% CI for the difference "AUC(0-τ) on Day 15 - AUC(0-τ) on Day 1" will be constructed using the appropriate error term. The point estimate and associated 90% CI will then be exponentially back-transformed to provide point and 90% CI estimates for the ratios "AUC(0-τ) on Day 15: AUC(0-τ) on Day 1." If dose-by-day interaction is not significant, then a single point estimate and 90% CI pooled across all doses for the ratio AUC(0-τ) on Day 15: AUC(0-τ) on Day 1 may be constructed with all estimates for each dose.

Steady State Assessment

To evaluate whether steady state was achieved, statistical analysis of steady-state Cτ will be performed after log-transformation of Cτ on Days 3, 6, 9, 12, 13, and 15. A mixed effect model will be fitted by dose and day (as a continuous covariate) as a fixed effect term and subject as a random effect term. The coefficients for the slope of the day effect on the log-scale will be used to evaluate steady-state for each dose group. Using the pooled estimate of variance, the 90% CIs for the slope will be calculated.

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.

9.4.3. Exploratory Analyses

Exploratory analyses will be performed to correlate PK parameters (AUC[0-t], AUC[0-∞], and Cmax for Parts 1 and 3; AUC[0-t], AUC[0-∞], AUC[0-τ], and Cmax for Part 2) of GSK3342830 with safety findings of GSK3342830 in healthy adult subjects (Parts 1 and 2) and healthy adult Japanese subjects (Part 3), and to evaluate the production of any GSK3342830 metabolites in plasma and urine.

Detailed descriptions of the analyses in this study will be presented in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable.
- Obtaining signed informed consent.
- Investigator reporting requirements (e.g., reporting of AEs/SAEs/protocol deviations to IRB/IEC).
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject before participation in the study.
- The IRB/IEC, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

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

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

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

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

10.4. Quality Assurance

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

10.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK/PPD monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the

investigator or the head of the medical institution, where applicable, of the impending action.

- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

10.6. Records Retention

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

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

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

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

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

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

5-HT	5-hydroxytryptamine, serotonin
ACR	albumin to creatinine ratio
AE	adverse event
Ae	amount excreted in urine
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-∞)	AUC extrapolated from time zero to infinity
AUC(0-τ)	AUC over the dosing interval τ
AUC(0-24)	AUC from time zero to 24 hours after dosing
AUC(0-t)	AUC from time zero to the last quantifiable concentration after dosing
BP	blood pressure
CL	total systemic clearance
CI	confidence interval
CLr	renal clearance
Cmax	maximum plasma concentration
Cτ	trough concentration
dL	deciliter
DMID	Division of Microbiology and Infectious Diseases
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EM	erythema multiforme
FDA	Food and Drug Administration
Feu(t1-t2)	urinary excretion ratio relative to dose
FSH	follicle-stimulating hormone
FTIH	first time in human
g	gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
hCG	human chorionic gonadotropin
Hgb	hemoglobin
Hct	hematocrit
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICH	International Council for Harmonisation

IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous
kg	kilogram
KIM-1	kidney injury molecule 1
L	liter
lb	pound
µg	microgram
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mL	milliliter
mm Hg	millimeters of mercury
msec	millisecond
NGAL	neutrophil gelatinase-associated lipocalin
NOAEL	no observed adverse effect level
NOEL	no observed effect level
OC RDC	Oracle Clinical Remote Data Capture System
PK	pharmacokinetic
QTc	corrected QT; the measure of time between the start of the Q wave and the end of the T wave
QTcB	corrected QT interval using Bazett's formula
QTcF	corrected QT interval using Fridericia's formula
SAE	serious adverse event
SJS	Stevens-Johnson syndrome
SRM	study reference manual
RAP	reporting and analysis plan
RBC	red blood cell
t1/2	terminal elimination half-life
TEN	toxic epidermal necrolysis
TID	3-times daily
Tmax	time to Cmax
ULN	upper limit of normal
Vss	steady-state volume of distribution
WBC	white blood cell

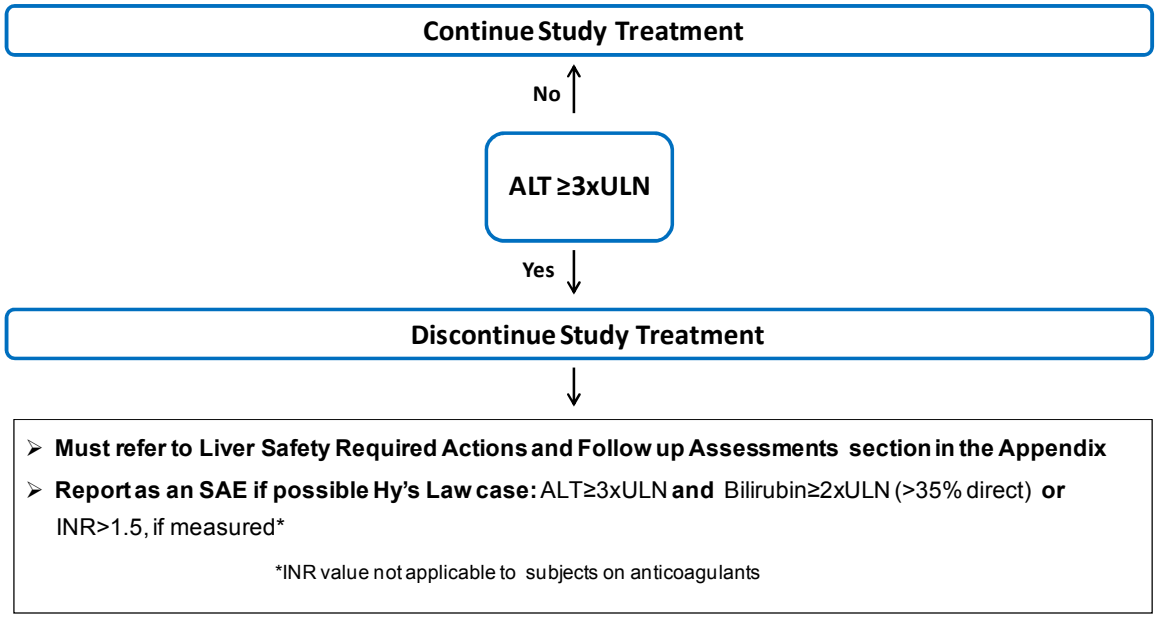
Trademark Information

Trademarks of the GlaxoSmithKline group of companies
GSKDrug

Trademarks not owned by the GlaxoSmithKline group of companies
MedDRA
SAS
WinNonlin

12.2. Appendix 2: Liver Chemistry Stopping Criteria

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver safety required actions and follow-up assessments section can be found in Appendix 3.

12.3. Appendix 3: Liver Safety Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria have been designed to assure subject safety and to evaluate liver event etiology (in alignment with the FDA guidance, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," [DHHS, 2009].

Phase I Liver Chemistry Stopping Criteria and Required Follow-up Assessments

<table>
<tr><th colspan="3">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td colspan="2">ALT ≥3× ULN
If ALT ≥3× ULN AND bilirubin[1,2] ≥2× ULN (>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="3">Required Actions and Follow-Up Assessments after Liver Stopping Event</th></tr>
<tr><th>Actions</th><th colspan="2">Follow-Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event eCRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow-up assessments
• Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
MONITORING:
If ALT ≥3× ULN AND bilirubin ≥2× ULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within 24 hours
• Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT ≥3× ULN AND bilirubin <2× ULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow-up assessments within 24 to 72 hours
• Monitor subjects weekly until liver chemistries resolve, stabilize or return to</td><td colspan="2">• Viral hepatitis serology[3]
• Blood sample for PK analysis, obtained within 1 day of last dose[4]
• Serum creatine phosphokinase and lactate dehydrogenase.
• Fractionate bilirubin, if total bilirubin ≥2× ULN
• 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 ≥3× ULN AND bilirubin ≥2× ULN or INR >1.5:
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins).
• Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the</td></tr>
</table>

Liver Chemistry Stopping Criteria – Liver Stopping Event	
within baseline	preceding week [James, 2009]. **NOTE: not required in China.** • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy eCRF forms.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, eCRF = electronic case report form, HPLC = high pressure liquid chromatography, IgG = Immunoglobulin G, IgM = Immunoglobulin M, INR = international normalized ratio, PK = pharmacokinetic, SAE = serious adverse event, ULN = upper limit of normal.

NOTES:

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥3× ULN **and** bilirubin ≥2× ULN. 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 ≥3× ULN **and** bilirubin ≥2× ULN (>35% direct bilirubin) or ALT ≥3× ULN **and** INR >1.5, if INR measured, which may indicate severe liver injury (possible "Hy's Law"), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. Pharmacokinetic sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date and time of the PK blood sample draw and the date and time of the last dose of study treatment before blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date or 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 Study Reference Manual.

12.4. Appendix 4: Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration are reported to account for much of the risk for the condition [Gorin, 2012] with certain variants reported to influence treatment response [Chen, 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including GSK3342830 or any concomitant medicines;
- Enterobacteriaceae susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or after completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a RAP before initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

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

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been

identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 6 mL blood sample will be taken for DNA extraction. A blood sample is collected at the baseline visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the SRM. The DNA from the blood sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The blood sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or "coded") with the same study-specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

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

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained before any blood is taken.

Subject Withdrawal from Study

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

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

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

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data have not been analyzed, it will not be analyzed or used for future research.
- Genetic data that have been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

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

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

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

12.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.5.1. Definition of Adverse Events

Adverse Event Definition:
• An AE is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

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

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

convenience admission to a hospital).

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

12.5.2. Definition of Serious Adverse Events

If an event is not an AE per definition in Section 12.5.1, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

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

a. Results in death

b. Is life-threatening

NOTE:

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

c. Requires hospitalization or prolongation of existing hospitalization

NOTE:

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

d. Results in disability/incapacity

NOTE:

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

e. Is a congenital anomaly/birth defect

f. Other situations:

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

g. Is associated with liver injury and impaired liver function defined as:

- ALT ≥3× ULN and total bilirubin* ≥2× ULN (>35% direct), **or**
- ALT ≥3× ULN and international normalized ratio (INR)** >1.5.

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

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

12.5.3. Definition of Cardiovascular Events

Cardiovascular Events Definition:

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

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

12.5.4. Recording of AEs and SAEs

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) relative to the event. • The investigator will then record all relevant information regarding an AE/SAE in the eCRF. • It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.5.5. Evaluating AEs and SAEs

Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study according to the US National Institute of Allergy and Infectious Diseases DMID criteria for toxicity assessment (Appendix 6). An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 12.5.2).

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE. • A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.

- The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event 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, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

12.5.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the medical monitor.
- Site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the “reviewed” box at the bottom of the eCRF page within 72 hours of submission of

the SAE.

- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the medical monitor by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.6. Appendix 6: DMID Adult Toxicity Tables for AE Assessment

ESTIMATING SEVERITY GRADE: For abnormalities NOT found elsewhere in the Toxicity Tables, use the following scale to estimate grade of severity:

GRADE 1	**Mild**	Transient or mild discomfort (<48 hours); no medical intervention/therapy required
GRADE 2	**Moderate**	Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required
GRADE 3	**Severe**	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible
GRADE 4	**Life-threatening**	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable

SERIOUS OR LIFE-THREATENING AEs: ANY clinical event deemed by the investigator to be serious or life-threatening should be considered a Grade 4 event. Clinical events considered to be serious or life-threatening include, but are not limited to: seizures, coma, tetany, diabetic ketoacidosis, disseminated intravascular coagulation, diffuse petechiae, paralysis, acute psychosis, and severe depression.

COMMENTS REGARDING THE USE OF THESE TABLES

- Standardized and commonly used toxicity tables (Division of AIDS, National Cancer Institute's Common Toxicity Criteria, and World Health Organization) have been adapted for use by the Division of Microbiology and Infectious Diseases (DMID) and modified to better meet the needs of participants in DMID trials.
- For parameters not included in the following Toxicity Tables, sites should refer to the "Guide for Estimating Severity Grade" located above.
- Criteria are generally grouped by body system.
- Some protocols may have additional protocol-specific grading criteria, which will supersede the use of these tables for specified criteria.

HEMATOLOGY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin	9.5 to 10.5 g/dL	8.0 to 9.4 g/dL	6.5 to 7.9 g/dL	<6.5 g/dL
Absolute Neutrophil Count	1000 to 1500 /mm^3	750 to 999 /mm^3	500 to 749 /mm^3	<500 /mm^3
Platelets	75,000 to 99,999 /mm^3	50,000 to 74,999 /mm^3	20,000 to 49,999 /mm^3	<20,000 /mm^3
White Blood Cells	11,000 to 13,000 /mm^3	13,000 to 15,000 /mm^3	15,000 to 30,000 /mm^3	>30,000 or <1000 /mm^3
% Polymorphonuclear Leukocytes + Band Cells	>80%	90 to 95%	>95%	N/A
Abnormal Fibrinogen	Low: 100 to 200 mg/dL High: 400 to 600 mg/dL	Low: <100 mg/dL High: >600 mg/dL	Low: <50 mg/dL High: N/A	Fibrinogen associated with gross bleeding or with disseminated coagulation
Fibrin Split Product	20 to 40 mcg/mL	41 to 50 mcg/mL	51 to 60 mcg/mL	>60 mcg/mL
Prothrombin Time (PT)	1.01 to 1.25 × ULN	1.26 to 1.5 × ULN	1.51 to 3.0 × ULN	>3 × ULN
Activated Partial Thromboplastin (APTT)	1.01 to 1.66 × ULN	1.67 to 2.33 × ULN	2.34 to 3 × ULN	>3 × ULN
Methemoglobin	5.0 to 9.9%	10.0 to 14.9%	15.0 to 19.9%	>20.0%
N/A = not applicable, ULN = upper limit of normal.				

CHEMISTRIES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Hyponatremia	130 to 135 mEq/L	123 to 129 mEq/L	116 to 122 mEq/L	<116 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypernatremia	146 to 150 mEq/L	151 to 157 mEq/L	158 to 165 mEq/L	>165 mEq/L or abnormal sodium *with* mental status changes or seizures
Hypokalemia	3.0 to 3.4 mEq/L	2.5 to 2.9 mEq/L	2.0 to 2.4 mEq/L or intensive replacement therapy of hospitalization required	<2.0 mEq/L or abnormal potassium *with* paresis, ileus, or life-threatening arrhythmia
Hyperkalemia	5.6 to 6.0 mEq/L	6.1 to 6.5 mEq/L	6.6 to 7.0 mEq/L	>7.0 mEq/L or abnormal potassium *with* life-threatening arrhythmia
Hypoglycemia	55 to 64 mg/dL	40 to 54 mg/dL	30 to 39 mg/dL	<30 mg/dL or abnormal glucose *with* mental status changes or coma
Hyperglycemia (nonfasting and no prior diabetes)	116 to 160 mg/dL	161 to 250 mg/dL	251 to 500 mg/dL	>500 mg/dL or abnormal glucose *with* ketoacidosis or seizures
Hypocalcemia (corrected for albumin)	8.4 to 7.8 mg/dL	7.7 to 7.0 mg/dL	6.9 to 6.1 mg/dL	<6.1 mg/dL or abnormal calcium *with* life-threatening arrhythmia or tetany
Hypercalcemia (corrected for albumin)	10.6 to 11.5 mg/dL	11.6 to 12.5 mg/dL	12.6 to 13.5 mg/dL	>13.5 mg/dL or abnormal calcium *with* life-threatening arrhythmia
Hypomagnesemia	1.4 to 1.2 mEq/L	1.1 to 0.9 mEq/L	0.8 to 0.6 mEq/L	<0.6 mEq/L or abnormal magnesium *with* life-threatening arrhythmia
Hypophosphatemia	2.0 to 2.4 mg/dL	1.5 to 1.9 mg/dL or replacement Rx required	1.0 to 1.4 mg/dL intensive therapy or hospitalization required	<1.0 mg/dL or abnormal phosphate *with* life-threatening arrhythmia
Hyperbilirubinemia (when accompanied by any increase in other liver function test)	1.1 to <1.25 × ULN	1.25 to <1.5 × ULN	1.5 to 1.75 × ULN	>1.75 × ULN
Hyperbilirubinemia (when other liver function tests are in the normal range)	1.1 to <1.5 × ULN	1.5 to <2.0 × ULN	2.0 to 3.0 × ULN	>3.0 × ULN
Blood urea nitrogen	1.25 to 2.5 × ULN	2.6 to 5 × ULN	5.1 to 10 × ULN	>10 × ULN
Hyperuricemia (uric acid)	7.5 to 10.0 mg/dL	10.1 to 12.0 mg/dL	12.1 to 15.0 mg/dL	>15.0 mg/dL
Creatinine	1.1 to 1.5 × ULN	1.6 to 3.0 × ULN	3.1 to 6.0 × ULN	>6 × ULN or dialysis required
Rx = therapy, ULN = upper limit of normal.				

ENZYMES				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Aspartate aminotransferase (AST)	1.1 to <2.0 × ULN	2.0 to <3.0 × ULN	3.0 to 8.0 × ULN	>8.0 × ULN
Alanine aminotransferase (ALT)	1.1 to <2.0 × ULN	2.0 to <3.0 × ULN	3.0 to 8.0 × ULN	>8.0 × ULN
Gamma glutamyl transferase (GGT)	1.1 to <2.0 × ULN	2.0 to <3.0 × ULN	3.0 to 8.0 × ULN	>8.0 × ULN
Alkaline Phosphatase	1.1 to <2.0 × ULN	2.0 to <3.0 × ULN	3.0 to 8.0 × ULN	>8.0 × ULN
Amylase	1.1 to 1.5 × ULN	1.6 to 2.0 × ULN	2.1 to 5.0 × ULN	>5.1 × ULN
Lipase	1.1 to 1.5 × ULN	1.6 to 2.0 × ULN	2.1 to 5.0 × ULN	>5.1 × ULN
ULN = upper limit of normal.				

URINALYSIS				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Proteinuria	1+ or 200 mg to 1 g loss/day	2 to 3+ or 1 to 2 g loss/day	4+ or 2 to 3.5 g loss/day	Nephrotic syndrome or >3.5 g loss/day
Hematuria	Microscopic only <10 RBC/hpf	Gross, no clots >10 RBC/hpf	Gross, with or without clots, or red blood cells casts	Obstructive or required transfusion
HPF = high powered field, RBC = red blood cells.				

CARDIOVASCULAR				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cardiac rhythm	N/A	Asymptomatic, transient signs, no Rx required	Recurrent/persistent; symptomatic Rx required	Unstable dysrhythmia; hospitalization and treatment required
Hypertension	Transient increase >20 mm Hg; no treatment	Recurrent, chronic increase >20 mm Hg; treatment required	Acute treatment required; outpatient treatment or hospitalization possible	End organ damage or hospitalization required
Hypotension	Transient orthostatic hypotension with heart rate increased by <20 beats/minute or decreased by <10 mm Hg systolic BP. No treatment required	Symptoms due to orthostatic hypotension or BP decreased by <20 mm Hg systolic; correctable with oral fluid treatment	Requires IV fluids; no hospitalization required	Mean arterial pressure <60 mm Hg or end organ damage or shock; requires hospitalization and vasopressor treatment
Pericarditis	Minimal effusion	Mild/moderate asymptomatic effusion, no treatment	Symptomatic effusion; pain; EKG changes	Tamponade; pericardiocentesis or surgery required
Hemorrhage, Blood Loss	Microscopic/occult	Mild, no transfusion	Gross blood loss; 1 to 2 units transfused	Massive blood loss; >3 units transfused
BP = blood pressure, EKG = electrocardiogram, IV = intravenous, N/A = not applicable, Rx = therapy.				

RESPIRATORY				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Cough	Transient; no treatment	Persistent cough; treatment responsive	Paroxysmal cough; uncontrolled with treatment	N/A
Bronchospasm, Acute	Transient; no treatment; FEV_1 70 to 80% of peak flow	Requires treatment; normalizes with bronchodilator; FEV_1 50 to 70% of peak flow	No normalization with bronchodilator; FEV_1 25 to 50% of peak flow; or retractions present	Cyanosis: FEV_1 <25% of peak flow; or intubation necessary
Dyspnea	Dyspnea on exertion	Dyspnea with normal activity	Dyspnea at rest	Dyspnea requiring oxygen therapy
FEV_1 = forced expiratory volume in 1 second, N/A = not applicable.				

GASTROINTESTINAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Nausea	Mild or transient; maintains reasonable intake	Moderate discomfort; intake decreased significantly; some activity limited	No significant intake; requires IV fluids	Hospitalization required
Vomiting	1 episode in 24 hours	2 to 5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	Physiologic consequences requiring hospitalization or requiring parenteral nutrition
Constipation	Requiring stool softener or dietary modification	Requiring laxatives	Obstipation requiring manual evacuation or enema	Obstruction or toxic megacolon
Diarrhea	Mild or transient; 3 to 4 loose stools/day or mild diarrhea lasting <1 week	Moderate or persistent; 5 to 7 loose stools/day or diarrhea lasting >1 week	>7 loose stools/day or bloody diarrhea; or orthostatic hypotension or electrolyte imbalance or >2 L IV fluids required	Hypotensive shock or physiologic consequences requiring hospitalization
Oral discomfort/ Dysphagia	Mild discomfort; no difficulty swallowing	Some limits on eating/drinking	Eating/talking very limited; unable to swallow solid foods	Unable to drink fluids; requires IV fluids
IV = intravenous.				

NEUROLOGICAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Neuro-Cerebellar	Slight incoordination dysdiadochokinesis	Intention tremor, dysmetria, slurred speech; nystagmus	Locomotor ataxia	Incapacitated
Psychiatric	Mild anxiety or depression	Moderate anxiety or depression; therapy required; change in normal routine	Severe mood changes requiring therapy; or suicidal ideation; or aggressive ideation	Acute psychosis requiring hospitalization; or suicidal gesture/attempt or hallucinations
Muscle strength	Subjective weakness; no objective symptoms/signs	Mild objective signs/symptoms; no decrease in function	Objective weakness; function limited	Paralysis
Paresthesia (burning, tingling, etc.)	Mild discomfort; no treatment required	Moderate discomfort; non- narcotic analgesia required	Severe discomfort; or narcotic analgesia required with symptomatic improvement	Incapacitating; or not responsive to narcotic analgesia
Neurosensory	Mild impairment in sensation (decreased sensation, e.g., vibratory, pinprick, hot/cold in great toes) in focal area or symmetrical distribution; or change in taste, smell, vision, and/or hearing	Moderate impairment (moderately decreased sensation, e.g., vibratory, pinprick, hot/cold to ankles) and/or joint position or mild impairment that is not symmetrical	Severe impairment (decreased or loss of sensation to knees or wrists) or loss of sensation of at least moderate degree in multiple different body areas (i.e., upper and lower extremities)	Sensory loss involves limbs and trunk; paralysis; or seizures

MUSCULOSKELETAL				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Arthralgia (joint pain)	Mild pain not interfering with function	Moderate pain, analgesics and/or pain interfering with function but not with ADL	Severe paid; pain and/or analgesics interfering with ADL	Disabling pain
Arthritis	Mild pain with inflammation, erythema or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema or joint swelling; interfering with function but not with ADL	Severe pain with inflammation, erythema or joint swelling, and interfering with ADL	Permanent and/or disabling joint destruction
Myalgia	Myalgia with no limitation of activity	Muscle tenderness (at other than injection site) or with moderate impairment of activity	Severe muscle tenderness with marked impairment of activity	Frank myonecrosis
ADL = activities of daily living.				

SKIN				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Mucocutaneous	Erythema; pruritus	Diffuse, maculo papular rash, dry desquamation	Vesiculation or moist desquamation or ulceration	Exfoliative dermatitis, mucous membrane involvement or erythema, multiforme or suspected Stevens-Johnson or necrosis requiring surgery
Induration	<15 mm	15 to 30 mm	>30 mm	N/A
Erythema	<15 mm	15 to 30 mm	>30 mm	N/A
Edema	<15 mm	15 to 30 mm	>30 mm	N/A
Rash at injection site	<15 mm	15 to 30 mm	>30 mm	N/A
Pruritus	Slight itching at injection site	Moderate itching at injection extremity	Itching over entire body	N/A
N/A = not applicable.				

SYSTEMIC				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Allergic reaction	Pruritus without rash	Localized urticarial	Generalized urticarial; angioedema	Anaphylaxis
Headache	Mild, no treatment required	Transient, moderate; treatment required	Severe; responds to initial narcotic therapy	Intractable; requires repeated narcotic therapy
Fever: oral	37.7 to 38.5°C or 100.0 to 101.5°F	38.6 to 39.5°C or 101.6 to 102.9°F	39.6 to 40.5°C or 103 105°F	>40°C or >105°F
Fatigue	Normal activity reduced <48 hours	Normal activity decreased 25 to 50%; >48 hours	Normal activity decreased >50%; cannot work	Unable to care for self

12.7. Appendix 7: Allergic Reactions Including Anaphylaxis

ALLERGIC REACTION

Pruritus without rash (Grade 1 allergic reaction):

Subjects with Grade 1 allergic reaction should be evaluated by the investigator immediately. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature >38.5°C
2. Eosinophilia
3. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, subjects with Grade 1 allergic reaction may continue the study drug at the discretion of the investigator. The subject should be advised to contact the investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the subject may be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed. The subject should remain on the study to be followed for safety and pharmacokinetics as outlined in Section 7.1.

Localized urticaria (Grade 2 allergic reaction):

Subjects with Grade 2 allergic reaction should be evaluated by the investigator immediately. The study drug should be permanently discontinued if the following signs or symptoms are noted at any time:

1. Temperature >38.5°C
2. Eosinophilia
3. Respiratory involvement including bronchospasm, laryngospasm, or angioedema
4. Any indication of internal organ involvement (hepatitis, nephritis)

In the absence of the above signs or symptoms, subjects with Grade 2 allergic reaction may continue the study drug at the discretion of the investigator. The subject should be advised to contact the investigator immediately if there is any worsening of the allergic reaction and/or if any systemic signs or symptoms worsen. If the allergic reaction is considered to be most likely due to concomitant illness or non-study medication, standard management, including discontinuation of the likely causative agent, should be undertaken. If no other causative factor is found after clinical evaluation, the subject may

be treated symptomatically until the rash resolves. Antihistamines, topical corticosteroids, or antipruritic agents may be prescribed. The subject should remain on the study to be followed for safety and pharmacokinetics as outlined in Section 7.1.

Generalized urticaria or angioedema (Grade 3 allergic reaction):

Subjects will permanently discontinue the study drug and be withdrawn from the trial. Subjects will be treated as clinically appropriate. Subjects should be followed up until resolution of the AE and standard management should be undertaken.

Anaphylaxis (Grade 4 allergic reaction):

Anaphylaxis is an immediate and potentially life-threatening systemic reaction to an exogenous stimulus e.g., a drug.

Anaphylaxis typically involves 2 or more body systems (cutaneous, respiratory, cardiovascular, neurologic, or gastrointestinal) usually within 60 minutes of exposure but can be delayed up to several hours and can less commonly be biphasic or protracted despite treatment.

The term anaphylaxis typically has been reserved for allergic, Immunoglobulin E-mediated immediate hypersensitivity reactions. Anaphylactoid responses (also included here) are clinically indistinguishable reactions that occur by non-antigen/antibody-mediated mechanisms. Both reactions produce clinical sequelae due to the massive release of mediators from mast cells and basophils but hypotension and associated cardiac AEs are less common in anaphylactoid reactions. In contrast to anaphylactic reactions, anaphylactoid reactions can occur upon initial exposure to exogenous stimulus.

Subjects will permanently discontinue the study drug and be withdrawn from the trial. Subjects will be treated as clinically appropriate. Subjects should be followed up until resolution of the AE and standard management should be undertaken.

Revised ACTG Toxicity Grade	Definitions	Investigator Action
Grade 1	Pruritus without rash	May continue therapy
Grade 2	Localized urticaria	May continue therapy
Grade 3	Generalized urticaria Angioedema	Discontinue therapy
Grade 4	Anaphylaxis	Discontinue therapy

12.8. Appendix 8: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential and Collection of Pregnancy Information

12.8.1. Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential

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

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Oral contraceptive, either combined or progestogen alone [Hatcher, 2007]
- Injectable progestogen [Hatcher, 2007]
- Contraceptive vaginal ring [Hatcher, 2007]
- Percutaneous contraceptive patches [Hatcher, 2007]
- Male partner sterilization with documentation of azoospermia before the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007]. The documentation on male sterility can come from the clinic personnel's review of the subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.
- Male condom plus partner use of one of the previously listed contraceptive options

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

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

12.8.2. Contraceptive Requirements for Male Subjects with Female Partners of Reproductive Potential

Male subjects with female partners of child-bearing potential must agree to use one of the following contraception requirements from the time of first dose of study drug until completion of the Follow-up visit:

a. Vasectomy with documentation of azoospermia

b. Male condom plus partner use of one of the following contraceptive options:

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Oral contraceptive, either combined or progestogen alone [Hatcher, 2007]
- Injectable progestogen [Hatcher, 2007]
- Contraceptive vaginal ring [Hatcher, 2007]
- Percutaneous contraceptive patches [Hatcher, 2007]

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

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

12.8.3. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.
- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy that is considered reasonably related to the study treatment by the investigator will be reported to GSK as described in Appendix 5. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating:

- Will be withdrawn from the study.

Pregnancy information for female partner of male subject

- Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who are randomized to receive study drug.
- After obtaining the necessary signed informed consent from the female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 2 weeks of learning of the partner's pregnancy.
- Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK.
- Generally, follow-up will be no longer than 6 to 8 weeks after 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.

12.9. Appendix 9: Additional Details on the *in vivo* Efficacy Calculations and Animal to Human Scaling

Efficacy studies using an infusion system to reproduce human drug exposures in the rat were conducted to explore the activity of GSK3342830 (based on relevant human exposure profiles for a compound of similar series). The profile was used to evaluate the efficacy of GSK3342830 against a range of challenge strains in a rat pneumonia model. GSK3342830 was highly efficacious against multi-drug resistant *P. aeruginosa* and carbapenemase-producing *K. pneumoniae* using an exposure curve based on a modelled 1-g, 1-hour infusion administered every 8 hours (free AUC[0-8] of 80 h•µg/mL). Studies against *A. baumannii* isolates suggest a higher exposure would likely be needed for efficacy. A 2 g, 3-hour infusion regimen administered every 8 hours was efficacious against most *A. baumannii* strains (free AUC[0-8] of 168 h•µg/mL) but higher doses may be needed for some strains. Using these data, the range for the target therapeutic exposures to be achieved in humans are:

- Free AUC(0-t) of 80 to 336 h•µg/mL after administration of single doses.
  - 336 h•µg/mL was derived from 2 × 168 h•µg/mL, based on the assumption that an additional 2-fold increase in dose may provide an efficacious exposure against certain *A. baumannii* strains.
- Based on a human free fraction of 72%, this would predict single dose total drug AUC(0-t) values of 112 to 467 h•µg/mL.
- This corresponds to a target a total AUC(0-24) exposure range of 336 to 1401 h•µg/mL in humans after administration of repeat TID doses.

Simulations were conducted to predict AUC and Cmax values for the nominal doses proposed for this protocol. A 3-compartment model developed for a similar siderophore β-lactam with healthy volunteer data was adapted for GSK3342830 by using the predicted clearance and volume of distribution values obtained from scaling with the dedrick monkey method. A total of 3000 subjects were simulated for each dose level and predicted AUC and Cmax values after administration of single doses and administration of repeat doses are shown in Table 8 and Table 9, respectively.

Table 8 Predicted Exposure Values After Administration of Single Doses

Dose (mg)	AUC(0-∞) h•µg/mL			Cmax µg/mL		
	5th percentile	50th percentile	95th percentile	5th percentile	50th percentile	95th percentile
250	51.6	64.3	80.6	20.9	27.5	35.4
500	103	128	161	42.2	54.4	71.1
1000	206	259	320	84.8	110	143
2000	409	512	640	168	218	286
4000	820	1026	1282	334	437	569
6000	1236	1545	1933	509	657	849

NOTES:
Systemic NOAEL exposures: AUC(0-24) = 2875 h•µg/mL and Cmax = 2270 µg/mL.
Target therapeutic exposure range for AUC(0-∞) is 112 to 467 h•µg/mL.
Data given as median and percentile range (range for 90% of the simulated individual data values).

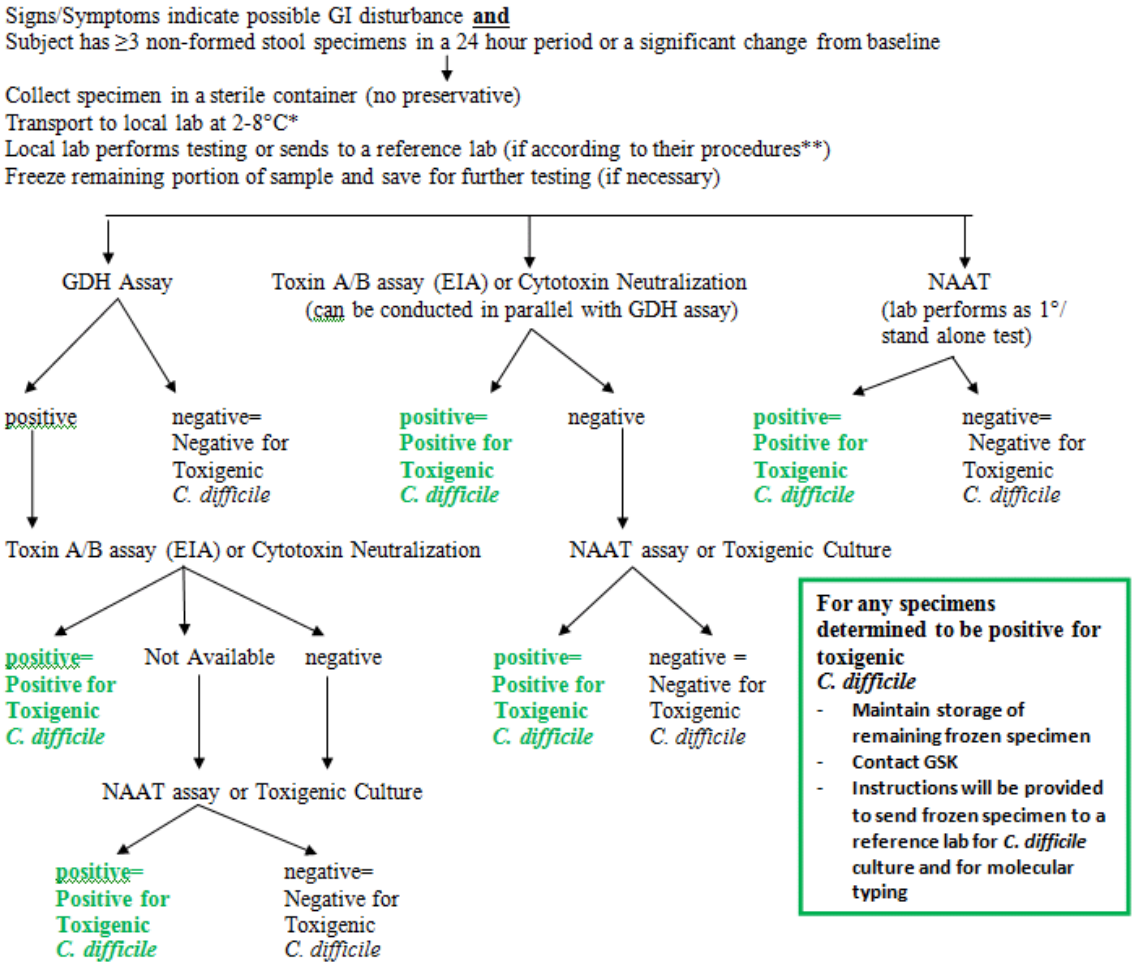
Table 9 Predicted Exposure Values After Administration of Repeat Doses

Dose (mg) TID	AUC(0-24) h•µg/mL			Cmax µg/mL		
	5th percentile	50th percentile	95th percentile	5th percentile	50th percentile	95th percentile
500	309	385	483	42.2	54.4	71.1
1000	618	777	960	84.8	110	143
2000	1227	1536	1920	168	218	286
4000	2460	3078	3846	334	437	569

NOTES:
Systemic NOAEL exposures: AUC(0-24) = 2875 h•µg/mL and Cmax = 2270 µg/mL.
Target therapeutic exposure range for AUC(0-24) is 336 to 1401 h•µg/mL.
Data given as median and percentile range (range for 90% of the simulated individual data values).
Repeat dose data were not simulated but are based on the single dose simulation.

12.10. Appendix 10: *Clostridium difficile* Testing Procedure and Algorithm

The most critical aspect of *Clostridium difficile* (*C. difficile*) testing is specimen handling and storage. It is imperative that the site and/or laboratory freezes ALL stool samples for possible future testing as quickly as possible after sample collection and testing, but no later than 24 hours after collection. If *C. difficile* laboratory tests cannot be performed within 24 hours of collection, the specimen should be frozen immediately.



*If processing and testing cannot be performed within 24 hours, the specimen should be frozen immediately after collection.
**If specimen is sent to a reference laboratory, the procedures to be ordered should follow the same algorithm above.
GDH = glutamate dehydrogenase; NAAT = nucleic acid amplification test

12.11. Appendix 11: Chronic Kidney Disease Epidemiology Collaboration Formula

The glomerular filtration rate will be calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [Levey, 2009] as follows:

$GFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times$ 1.159 [if black]

Where:

- Scr is serum creatinine (mg/dL)
- κ is 0.7 for females and 0.9 for males
- α is –0.329 for females and –0.411 for males
- min indicates the minimum of Scr/κ or 1
- max indicates the maximum of Scr/κ or 1

12.12. Appendix 12: Country-Specific Requirements

No country-specific requirements exist.

12.13. Appendix 13: Protocol Changes

Protocol Amendment 1

Where the Amendment Applies

To all sites participating in 204847

Summary of Amendment Changes with Rationale

An additional cohort will be added to the study. This cohort will consist of Japanese subjects and this component of the study will be designated Part 3. Subjects in Part 3 will receive a single IV dose of GSK3342830. The dose to be administered in Part 3 is planned to be based on preliminary safety and tolerability results of doses determined to be safe and well tolerated in subjects of non-Japanese heritage after completion of the single escalation dose cohorts (Part 1). Parts 2 and 3 are planned to be conducted in parallel.

List of Specific Changes

The changes to the protocol and their location within the protocol are noted below; the rationale for the changes is also provided. Added text is underlined, while removed text is shown in ~~strikethrough~~. Minor stylistic or formatting changes that do not alter the conduct of the study are not summarized in this appendix.

Protocol synopsis

Updated to reflect overall changes in the protocol

Section 2.1 Study Rationale

This study represents the first administration of GSK3342830 in humans. It will be conducted to define the safety, tolerability, and pharmacokinetics of GSK3342830 after administration of single and repeat IV doses in healthy adult subjects, and after administration of a single IV dose in healthy adult Japanese subjects.

Rationale: The addition of a cohort consisting of a specific population, Japanese subjects, will provide PK data and enable future pivotal Phase III studies in the respective country.

Section 3 Objectives and Endpoints: Part 2 Exploratory Objectives and Part 3

Exploratory	
• To correlate PK parameters (AUC[0-t], AUC[0-∞], AUC[0-τ], and Cmax) of GSK3342830 with safety findings ~~in healthy adult subjects~~ and evaluate urine discoloration after administration of repeat IV doses in healthy adult subjects	• Exposure-response analyses, as data permit
• To evaluate the production of any GSK3342830 metabolites in plasma and urine and determine the need to perform a more detailed analysis of any metabolites	• Metabolite characterization in plasma and urine and estimation of observed drug-related material in plasma to determine the presence of any metabolite >10%, and estimate the percentage dose eliminated via urine

Part 3	
Primary	
• To investigate the safety and tolerability of GSK3342830 after administration of a single IV dose in healthy adult Japanese subjects	• Clinical safety data from AEs, clinical laboratory tests, vital signs (blood pressure, heart rate, temperature, and respiration rate), and 12-lead ECG readings
Secondary	
• To determine the pharmacokinetics of GSK3342830 after administration of a single IV dose in healthy adult Japanese subjects	• Plasma and urine concentrations and PK endpoints include AUC(0 t), AUC(0-∞), Cmax, Tmax, CL, Vss, t1/2, Feu(t1-t2), Ae, and CLr of GSK3342830, as data permit
Exploratory	
• To correlate PK parameters (AUC[0-t], AUC[0-∞], and Cmax) of GSK3342830 with safety findings after administration of a single IV dose in healthy adult Japanese subjects	• Exposure-response analyses, as data permit
• To evaluate the production of any GSK3342830 metabolites in plasma and urine and determine the need to perform a more detailed analysis of any metabolites	• Metabolite characterization in plasma and urine and estimation of observed drug-related material in plasma to determine the presence of any metabolite >10%, and estimate the percentage dose eliminated via urine

Rationale: The objectives and endpoints were updated to include the exploratory objective of urine discoloration after repeat IV doses (Part 2) and to include the additional cohort (Part 3). The drug may cause urine to appear red or reddish brown (this was seen in animal studies). The inclusion of this exploratory objective will allow an evaluation to determine if this effect is seen in the clinic in order to inform conduct of clinical trials. The additional cohort will consist of Japanese subjects who will receive a single IV dose of GSK3342830. The dose in Part 3 will be selected based on preliminary safety and tolerability results from Part 1. The addition of this cohort will provide PK data and enable future pivotal Phase III studies in the respective country.

Section 4.1 Overall Study Design: Paragraph 1

This is a Phase I, first-time-in-human (FTIH), randomized, double-blind (sponsor unblinded), single-center, placebo-controlled, dose-escalation study to determine the safety, tolerability, and pharmacokinetic (PK) profile of GSK3342830 after administration of single (Part 1) and repeat (Part 2) IV doses in healthy adult subjects~~.~~, and after administration of a single IV dose in healthy adult Japanese subjects (Part 3). Part 1 will investigate escalating single IV doses of GSK3342830. Part 2 will investigate escalating repeat IV doses of GSK3342830 with repeat dosing for 14 days and multiple dosing per day for 13 days as follows: a single IV infusion on Day 1, TID IV infusions on Days 2 through 14 (approximately every 8 hours), and a single IV infusion on Day 15. Part 3 will investigate a single IV dose of GSK3342830 in Japanese subjects.

~~On~~ For Parts 1 and 2, on Day 1, before study drug administration, subjects who meet the criteria for study entry will be assigned to the current dose level cohort and randomized to receive GSK3342830 or placebo. For Part 3, on Day 1, before study drug administration, subjects who meet the criteria for study entry will be randomized to receive GSK3342830 or placebo. All doses of GSK3342830 or placebo are planned to be administered as a 1-hour infusion.

Rationale: The overall study design text was updated to include the additional cohort (Part 3). The updated text clarifies that the Part 3 component will investigate the safety, tolerability, and PK of GSK3342830 after a single IV dose of GSK3342830 administered to healthy adult Japanese subjects. Consistent with Parts 1 and 2, eligible subjects in Part 3 will be randomized to receive either GSK3342830 or placebo.

Section 4.1 Overall Study Design: Paragraph 8

The single dose administration in Japanese subjects component (Part 3) of this study is planned to be conducted in parallel with Part 2. The dose for the Part 3 cohort will be based on preliminary safety and tolerability results of doses determined to be safe and well tolerated in subjects of non-Japanese heritage after completion of the single escalation dose cohorts (Part 1).

Rationale: Part 3 was added to accommodate an additional cohort. It is planned to be conducted in parallel with Part 2. A one-time single dose is planned for Part 3. The updated text clarifies how the dose for Part 3 will be determined and includes planned conduction timing and dose selection for Part 3.

Section 4.2 Treatment Arms and Duration: Part 1 Paragraph 1

Part 1 is planned to include 6 dose level cohorts. ~~Up to 2 a~~ Additional doses (1 per cohort) may be evaluated to further understand the study drug. The planned starting GSK3342830 dose in Part 1 is 250 mg administered as a single IV infusion. The dose is planned to increase in subsequent cohorts to 500, 1000, 2000, 4000, and ≤6000 mg IV as shown in Figure 1. Doses >6000 mg may be administered if the predicted Cmax exposures will not exceed the NOAEL.

Rationale: The maximum planned dose in Part 1 is 6000 mg. However, if the predicted Cmax will not exceed the NOAEL, the addition of this text will allow doses beyond 6000 mg to be administered.

Section 4.2 Treatment Arms and Duration: Part 3

Part 3: Single Dose in Healthy Adult Japanese Subjects

Part 3 is planned to include 1 cohort (Cohort J). The planned GSK3342830 dose in Part 3 will be either 250, 500, 1000, 2000, 4000, or ≤6000 mg based on preliminary safety and tolerability results of doses determined to be safe and well tolerated in subjects of non-Japanese heritage after completion of the single escalation dose cohorts (Part 1). The dose in Part 3 will be administered as a single IV infusion on Day 1.

On Day 1, before study drug administration, subjects will be randomized to treatment with either GSK3342830 or placebo in a 4:1 ratio. Study assessments will be performed as indicated in the Time and Events Tables (Section 7.1).

In Part 3, subjects will remain confined to the clinical unit from admission on Day –1 until all scheduled safety and PK assessments have been completed on Day 3. The duration of study (from Screening to the Follow-up visit) for each subject will be up to approximately 43 days.

Rationale: Part 3 was added to accommodate an additional cohort planned to be conducted in parallel with the repeat dosing component. The additional text clarifies how the dose for Part 3 will be determined, when the subjects will be randomized, and the duration for each subject.

Section 4.3 Type and Number of Subjects: Paragraph 1

For Part 1, approximately 48 healthy adult subjects will be enrolled with approximately 8 subjects in each of the 6 planned cohorts. In each Part 1 cohort, approximately 6 subjects will be assigned to active treatment and approximately 2 subjects will be assigned to placebo. For Part 2, approximately 30 healthy adult subjects will be enrolled with approximately 10 subjects in each of the 3 planned cohorts. ~~In each~~ For Part 3, approximately 10 healthy adult Japanese subjects will be enrolled. In each Part 2 cohort and the Part 3 cohort, approximately 8 subjects will be randomized to receive active treatment and approximately 2 subjects will be randomized to receive placebo.

Rationale: Part 3 was added to accommodate an additional cohort. The type and number of subjects text was updated to clarify the number of subjects in each part of the study and the number of subjects in each cohort within each part.

Section 4.6.1 Risk Assessment: Mitigation Strategy Column, Telemetry Monitoring in Rows 1 and 2

• Conduct study in inpatient clinical unit for first time in human (FTIH) • Normal vital signs on study entry • Frequent vital signs over the dosing interval • QTc <450 msec • 12-lead electrocardiograms (ECGs) across the initial exposure • Telemetry monitoring for Parts 1 and 3 and initial doses in Part 2

• Conduct study in inpatient clinical unit for FTIH
• Starting dose free Cmax margin: approximately 26×
• Cmax at highest planned dose (6000 mg) similar to (1.1×) Cmax of the no observed effect level (NOEL) dose (250 mg/kg)
• Normal vital signs on study entry
• Frequent vital signs over the dosing interval
• 12-lead ECGs across the exposures
• Telemetry monitoring for Parts 1 and 3 and initial doses in Part 2
• Blood pressure and heart rate stopping criteria:
  • Systolic BP >160 mm Hg for >1 hour
  • Diastolic BP >100 mm Hg for >1 hour
  • Heart rate >120 beats per minute for >1 hour

Rationale: Part 3 was added to accommodate an additional cohort. The text in the mitigation strategy for the of death in preliminary monkey cardiovascular study (row 1) and blood pressure, heart rate, and body temperature changes in monkey cardiovascular study (row 2) potential risks of clinical significance was updated to include telemetry monitoring in Part 3.

Section 5.1 Inclusion Criteria: Type of Subject and Diagnosis Including Disease Severity

3. Additional inclusion criteria for Japanese subjects (Part 3 only):
   - The subject is a non-naturalized Japanese citizen and holds a Japanese passport.
   - The subject has 2 Japanese parents and 4 Japanese grandparents who are non-naturalized Japanese citizens, as confirmed by interview.
   - The subject has been living outside of Japan for less than 10 years, as confirmed by interview.

Rationale: The additional cohort (Part 3) will consist of Japanese subjects. An inclusion criterion specific for a Japanese population was added.

Section 6.1 Investigational Product and Other Study Treatment: Unit Dose strengths/Dosage levels and Dosing Instructions

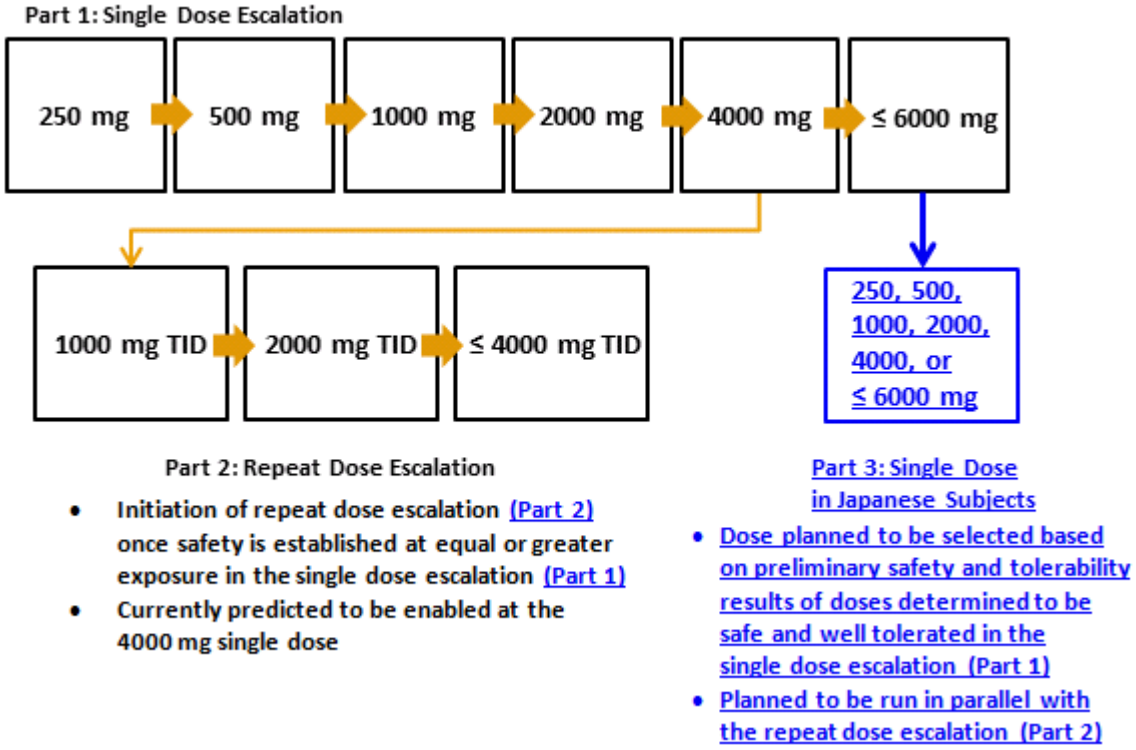
	Study Treatment	
Product name:	GSK3342830	Placebo
Unit dose strengths/Dosage levels:	Unit dose strength:1000 mg/vial as free base equivalent Dosage levels: Part 1: 250, 500, 1000, 2000, 4000, and ≤6000 mg Part 2: 1000, 2000, and ≤4000 mg Part 3: 250, 500, 1000, 2000, 4000, or ≤6000 mg	Not applicable
Dosing instructions:	Parts 1 and 3: Single IV infusion. Part 2: Single IV infusion on Day 1, TID IV infusions (approximately every 8 hours) on Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14, and a single IV infusion on Day 15. Instructions for the preparation of the IV drug are included in the Pharmacy Manual.	Parts 1 and 3: Single IV infusion. Part 2: Single IV infusion on Day 1, TID IV infusions (approximately every 8 hours) on Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14, and a single IV infusion on Day 15. Instructions for the preparation of the IV drug are included in the Pharmacy Manual.

Rationale: Part 3 was added to accommodate an additional cohort. Information in the treatment table was updated to allow for the dose for Part 3 to be determined during the course of the study and to reflect that it will be administered as a one-time single IV infusion.

Section 6.3 Planned Dose Adjustments: Bullet Point 1 and Figure 3

- This protocol allows some alteration from the currently outlined dosing schedule. The maximum daily dose is planned to not exceed 6000 mg in Parts 1 and 3, and 4000 mg in Part 2.

Figure 3 Planned Study Schematic



Rationale: The dose for administration in Part 3 will be selected based on safety and tolerability findings in Part 1. In bullet 1, the text was updated to clarify the planned maximum dose in Part 3 will not exceed the planned maximum dose in Part 1. The planned study schematic (Figure 3) was updated to include the additional cohort (Part 3).

Section 6.10.1 Meals and Dietary Restrictions: Paragraph 4

Subjects will fast from food and drink (except water) for at least 10 hours before dosing on Day 1 (Parts 1, 2, and ~~Part~~ 3) and Day 15 (Part 2 only). Meals at all other times will be provided at times that will not interfere with fasting required for clinical laboratory testing.

Rationale: Part 3 was added to accommodate an additional cohort. The text in the meals and dietary restrictions section was updated to clarify the timing of the required fast for each part of the study.

Section 7.1 Time and Events Tables: Table 3, Table 4, and Table 6 Titles

Table 3	Time and Events Table: Screening and Day –1; Single and Repeat Dose Escalation (Part 1 and Part 2) and Single Dose (Part 3)
Table 4	Time and Events Table: Part 1 - Single Dose Escalation and Part 3 - Single Dose

Table 6 Time and Events Table: Follow-up Visit; Single and Repeat Dose Escalation (Part 1 and Part 2) and Single Dose (Part 3)

Rationale: Part 3 was added to accommodate an additional cohort planned to be conducted in parallel with the repeat dosing component. GSK3342830 will be administered as a single dose in Parts 1 and 3; therefore the procedures and timing of procedures is the same these parts of the study. The titles of the time and events tables were updated to clarify which the part of the study is applicable in each table.

Section 7.1 Time and Events Table 3

Procedure	Screening (up to 30 days before Day 1)	Day –1	Notes
Blood collection for additional iron tests		X	In Part 2 only. Samples will be collected for potential analysis of some or all of the additional iron tests at the end of the study if a clinical signal is detected.

Rationale: Row was added for blood collection on Day –1 (Part 2 only) for possible analysis of iron biomarkers at the end of the study if a clinical signal is detected.

Section 7.1 Time and Events Table 5

Procedure	Study Day															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Blood collection for additional iron tests[4]	X				X										X	

Rationale: Row was added for blood collection at predose on Days 1, 5 and 15 for possible analysis of iron biomarkers at the end of the study if a clinical signal is detected.

Section 7.1 Time and Events Table 5, Notes 3 and 4

3. An aliquot of the urine sample will be collected for neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1). These samples may be analyzed after the end of the study if a clinical signal is detected. Instructions for collection and storage of these urine samples are included in the Study Reference Manual. Hematology assessments on Days 5 and 15 will also include total iron, total iron binding capacity, ferritin, and reticulocytes. The albumin to creatinine ratio will be determined using the first morning void urine on Days 5 and 15. Urinalysis assessments before dosing on Day 15 will also include urine color.
4. Blood samples will be collected on Day –1, and predose (at least 1 hour before dosing) on Days 1, 5, and 15, and at Follow up visit for potential analysis for some or all of the additional iron tests at the end of the study if a clinical signal is detected.

Rationale: A urine color assessment was added to Day 15 of Part 2. The drug may cause urine to appear red or reddish brown (this was seen in animal studies). Therefore, this assessment was added to determine if this effect is seen in the clinic in order to inform conduct of clinical trials. The note pertaining to the urinalysis assessments in the Time and Events Table for Part 2 was updated to include the urine color assessment.

Blood samples will be collected for possible analysis of iron biomarkers at the end of the study if a clinical signal is detected. This note in the Time and Events Table for Part 2 was added to clarify when the samples will be collected.

Section 7.3.7 Clinical Safety Laboratory Assessments: Table 7 Additional Iron Tests, Urinalysis Parameters, and Notes 1, 2, 4 and 6

Laboratory Assessments	Parameters
Additional Iron Tests[2]	Transferring (apotransferrin) · Ceruloplasmin · Haptoglobin/Hemopexin · Lactoferrin · Hepcidin
Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • ACR[3] • Microscopic examination (if blood or protein is abnormal) • NGAL[4] • KIM-1[45] • Urine color[6]

NOTES:

1. In Parts 1 and 3, analyzed on Day –1 and at Follow-up visit. In Part 2, analyzed on Day –1, Day 5, Day 15, and at Follow-up visit.
2. In Part 2 only, blood samples will be collected on Day –1, and predose (at least 1 hour before dosing) on Days 1, 5, and 15, and at Follow up visit, for potential analysis of some or all of the additional iron tests at the end of the study if a clinical signal is detected.
~~3~~4. The ACR on urine albumin and creatinine will be determined using the first morning void urine at Screening and Follow-up visit for all subjects in both parts of the study. In addition, the ACR will be determined on Day 2 in Parts 1 and 3 and Days 5 and 15 in Part 2. Screening ACR may be performed on urine during the screening visit. Subjects should be provided a sterile urine transport container and instructions on how to collect a first void urine at home for screening. In the event a subject fails by ACR, the subject should be contacted to bring back first void urine for recheck. For the Follow-up visit, subjects must be provided a sterile urine transport container on discharge from the clinical unit and instructed to bring back the first morning void urine on the day of their return Follow-up visit.
6. Assessed before dosing on Day 15 (Part 2 only).

Rationale: Blood samples will be collected for possible analysis of iron biomarkers at the end of the study if a clinical signal is detected. The iron tests are specified in this table. Note 2 was added to clarify when the blood samples for these tests will be collected.

GSK3342830 will be administered as a single dose in Parts 1 and 3; therefore the timing of the total iron and TIBC assessments (note 1) and ACR determination (note 4) will be the same for these parts of the study. A urine color assessment was added to Day 15 of Part 2. The drug may cause urine to appear red or reddish brown (this was seen in animal studies). Therefore, this assessment was added to determine if this effect is seen in the clinic in order to inform conduct of clinical trials. The text in notes 1, 4, and 6 was updated to include the urine color assessment and to clarify when the total iron, TIBC, and urine color assessments and ACR determination will be performed in each part of the study.

Section 9.3.1 Analysis Populations: PK Population and PK Parameter Population

The **PK Population** will consist of all subjects who receive at least 1 dose of GSK3342830 and ~~have evaluable PK data for GSK3342830~~ for whom a PK sample is collected and analyzed.

The **PK Parameter Population** will consist of all subjects in the PK population for whom valid and evaluable PK parameters were derived.

Rationale: A PK parameter population that will be used in the assessment and characterization of PK parameters was added. The text in the analysis populations section was updated to include this population.

Section 9.3.2 Interim Analysis: Paragraph 1

No formal interim analysis is planned for this study. However, one may be conducted in the event of clinically significant safety or PK findings. All preliminary safety, tolerability, and available PK data will be reviewed internally at GSK and with the clinical study site before each dose escalation in Part 1, before initiation of Part 2, and before each dose escalation in Part 2. All preliminary safety and tolerability data from Part 1 will be reviewed internally at GSK and with the clinical study site before dose selection for and initiation of Part 3. Section 6.4 provides further detail on data access and the handling of treatment blinding.

Rationale: Part 3 was added to accommodate an additional cohort. The text in the interim analysis section was updated to clarify when interim analysis will occur in relation to each part of the study.

Section 9.4.2 Secondary Analyses: Pharmacokinetic Analyses, Plasma, AUC(0-∞) and Dose Proportionality, Paragraph 1

Pharmacokinetic Analyses, Plasma, AUC(0-∞)

AUC(0-∞) AUC extrapolated from time zero to infinity (estimated for single dose in Parts 1 and 3, and on Day 1 for repeat dose in Part 2)

Dose Proportionality, Paragraph 1

Dose proportionality of AUC(0-∞) and Cmax on Day 1 in Part 1 and for repeat dose groups AUC(0-τ) and Cmax of GSK3342830 on Day 15 in Part 2 will be assessed separately by day using the following power model:

$$y = \alpha * dose^{\beta}.$$

Rationale: Part 3 was added to accommodate an additional cohort. Single dose administration is planned for Parts 1 and 3, and repeat dose administration is planned for Part 2. The text in the appropriate secondary analysis sections was updated to clarify which data will be used for AUC (0-∞) and dose proportionality for each part of the study.

Section 9.4.3 Exploratory Analyses: Paragraph 1

Exploratory analyses will be performed to correlate PK parameters (AUC[0-t], AUC[0-∞] and Cmax for Parts 1 and 3; AUC[0-t], AUC[0-∞], AUC[0-τ] and Cmax for Part 2) of GSK3342830 with safety findings of GSK3342830 in healthy adult subjects (Parts 1 and 2) and healthy adult Japanese subjects (Part 3), and to evaluate the production of any GSK3342830 metabolites in plasma and urine.

Rationale: Part 3 was added to accommodate an additional cohort, which will consist of healthy adult Japanese subjects. Single dose administration is planned for Parts 1 and 3,

and repeat dose administration is planned for Part 2. The text in the exploratory analyses section was updated to clarify which PK parameters will be correlated with safety findings in each part of the study.