TITLE PAGE

Protocol Title: Randomized, Double-blind, Placebo Controlled Dose Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Doses (Intravenous bolus) and constant intravenous infusion over 7 Days of GSK3335065 in Healthy Adult Subjects

Protocol Number: 201570

Short Title: Safety, Tolerability Pharmacokinetics, and Pharmacodynamics investigation of GSK3335065 (IV) in healthy adults

Compound Number: GSK3335065

Sponsor Name and Legal Registered Address:

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Approval Date: 29-Nov-2017

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November-29-2017
Date

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 03	*29-Nov-2017*
Amendment 02	*21-August 2017*
Amendment 01	*11-July-2017*
Original Protocol	*14 June 2017*

Amendment 03 29-November-2017

Overall Rationale for the Amendment: Change in post dose safety observation period, PK and PD assessment time points based on emerging PK data.

Section # and Name	Description of Change	Brief Rationale
Synopsis	Changes described in main sections of the protocol below	As below
Section 2.1 Schedule of Activities	Table updated with cohorts for parts A, B and C with corresponding new timepoints	To ensure consistency following the additional timepoints
	Discharge from clinical unit and brief physical examination has been changed from Day 4 to Day 8 in the remainder of Part A and Part C (Cohort 13)	To increase domiciling period and safety observation period based on emerging PK data
Section 2.2 Schedule of Activities: Part B and C (Cohort 14)	Discharge from clinical unit and brief physical examination has been changed from Day 11 to Day 15	To increase domiciling period and safety observation period based on emerging PK data.
Section 5.1 Overall Design	• Revised Part A study Schematic has been included	Operational feasibility due to the increase in domiciling period.
Section 5.1.1 and Section 10.2.1	Part A will have Cohorts 3 to 8 with changed duration from 19 weeks to 7 weeks and design change from cross-over to parallel.	Operational feasibility due to the increase in domiciling period
Section 5.1.2 Part B, Section 5.4.2, Section 9.5.1, Section 12.3	• Part B will have Cohorts 9 to 12 • Subjects will be admitted in the unit from the day prior to dosing until Day 15	• To ensure consistency following changes to Part A
Section 5.2 Number of Participants, Section 10.2.1	Number of evaluable subjects has been increased from 64 to 112. Also number of subjects for Part A has been increased from 16 to 64.	This is a consequence of the change to the study design in Part A

Section # and Name	Description of Change	Brief Rationale
Section 7.3 Method of Treatment Assignment	Method of treatment assignment has been changed from randomization in sequences in each session to randomization of either active or placebo at the start of each cohort.	Study design in Part A was changed to parallel design for operational feasibility.
Section 9.7 Biomarkers/Pharmacodynamics	Include a short (approximately 12-14 hours) run-in PD sampling period prior to dosing.	To improve the understanding of the variability and to allow better interpretation of the PD markers in relation to study drug

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1. SYNOPSIS

Protocol Title: Randomized, Double-blind, Placebo-controlled Dose Escalation Study to Evaluate Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single Doses (intravenous bolus) and constant intravenous infusion over 7 Days of GSK3335065 in Healthy Adult Subjects

Short Title: Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics investigation of GSK3335065 (IV) in healthy adults

Rationale: GSK3335065 is being developed as a treatment for acute pancreatitis with the intent of reducing 3-hydroxykynurenine (3HK) levels to the normal range (or lower) and maintaining them at this level throughout the 7-day treatment period.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To determine the safety and tolerability of GSK3335065 administered as a single IV bolus (Part A and C), and as a constant IV infusion over 7 days (Part B and C) in healthy volunteers	• Adverse event / Serious Adverse event monitoring • Laboratory parameters (hematology, clinical chemistry,urinalysis) • 12-lead ECG parameters (PR, QRS, QT, QTcF, etc.) • Vital signs (systolic and diastolic blood pressure, heart rate)
Secondary	
• To determine the pharmacokinetic characteristics of GSK3335065 administered as a single IV bolus (Part A and C), and as a constant IV infusion over 7 days (Part B and C) in healthy volunteers	• Pharmacokinetic Parameters: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, t_{last}, C_{max}, C_{avg}, t_{max}, CL, V, $t_{½}$
• Determine dose/exposure effects of GSK3335065 on KMO inhibition (pharmacodynamics) in healthy volunteers (All Parts)	• Evaluate changes in levels of TRP metabolites (3HK and KYN)

Overall Design: This is a phase I**,** first time in human (FTIH), three part, randomized, placebo-controlled dose escalation study that will utilize an adaptive design for combining Single Ascending Dose (SAD) by IV bolus (Part A) with Ascending Doses by intravenous (IV) continuous infusion dosing for 7 days (Part B) in healthy males. Part C will recruit women of non-child bearing potential (WONCBP) only, and a single dose by

IV bolus will be investigated prior to multiple dose (7 day) being investigated. The decision to proceed to the next dose level in Part A will be based on safety and tolerability data obtained up to 8 days post dose from at least 6 subjects at the prior dose level.

Number of Participants: 112 evaluable subjects. Part A will comprise of 64 healthy male subjects (Cohorts 1 to 8). Part B of 32 healthy male subjects (Cohorts 9 to 12). Part C will comprise of 16 women of non child bearing potential (Cohorts 13 to 14).

Treatment Groups and Duration:

Part A will last up to approximately 7 weeks from screening to follow-up. Part A was initiated using an interlocking four period crossover design with two cohorts and the intention that all participants will receive four ascending IV bolus doses of GSK3335065. Subjects in cohorts 1 and 2 received a single dose of 0.1 mg and 0.25 mg GSK3335065, respectively. All subjects from cohorts 1 and 2 will be discontinued from the study.

For operational feasibility, the design of Part A will be changed to a parallel cohort design and dosing will be continued at the third dose level (1.3 mg) (Amendment 3). For each subsequent dose level, a cohort of 8 subjects will receive a single dose of GSK3335065.

Prior to initiation of Parts B and C, a review of all available safety, tolerability, PK and PD data from Part A will be conducted and potential changes to the dosing paradigm, safety observation period and assessments will be communicated in a future amendment to the protocol as appropriate.

Part B will last up to approximately 13 weeks from screening to follow-up. Particpants will receive one IV bolus dose of GSK3335065 immediately follwed by an IV infusion over seven days.

Part C cohort 7 will last approximately 7 weeks and Part C cohort 8 up to 13 weeks from screening to follow-up. Cohort 7 will comprise of a single IV bolus. Cohort 8 will mirror Part B.

2. SCHEDULE OF ACTIVITIES (SOA)

- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic/biomarker or other 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.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The Institutional Review Boards (IRB)/ Independent Ethics Committees (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form (ICF).

2.1. Part A & C – Cohort 1, 2, 3, 4, 5, 6, 7, 8 & 13, single bolus dose, healthy volunteer subjects

Procedure	Screening (within 28 days of Day 1)	Study Period (Days)									Follow-up (7-14 days following discharge)	Notes
		-1	1	2	3	4	5	6	7	8		
Outpatient Visit	X										X	
Admission to Clinical Unit		X										
Inpatient Stay at Clinical Unit		←----------										
Discharge from Clinical Unit										X		Following completion of all assessments
Informed consent	X											
Inclusion and exclusion criteria	X	X										
Demography	X											
Full physical exam incl height and weight	X											
Brief Physical		X								X	X	Brief physical upon discharge from every cohort (Day 8)
Medical history (includes substance usage)	X											Substances: Drugs, Alcohol, tobacco and caffeine
Clinical Safety Laboratory Assessments *(HIV, Hep B and Hep C Screen at screening only[1])*	X	X		X				X		X	X	Screening and day -1 safety labs must be in fasted state. [1]If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required.
LFTs (ALT, AST, AP, direct and indirect Bilirubin)	X	X	X		X			X		X	X	

Procedure	Screening (within 28 days of Day 1)	Study Period (Days)									Follow-up (7-14 days following discharge)	Notes
		-1	1	2	3	4	5	6	7	8		
cTnI & BNP	X	X	X[2]	X		X				X		[2] 6hrs post-dose
FSH	X											Females only, if required
Urine Drug/Alcohol Breath Test	X	X									X[3]	[3] Alcohol breath test only
12-lead ECG	X	X	X	X	X	X		X		X	X	Triplicate ECGs will be obtained at screening and predose. Single measurements at 30min, 6hr, 12hr, 24hr, 72hr, 120hr, 168hrpost-dose. ECG times may be adjusted once initial PK data is available.

Procedure	Screening (within 28 days of Day 1)	Study Period (Days)									Follow-up (7-14 days following discharge)	Notes
		-1	1	2	3	4	5	6	7	8		
Continuous ECG monitoring			X									Continuous monitoring from -1 hour pre-dose to 24hours post dose. Based on preclinical data levels of parent compound and tryptophan metabolites are expected to reach peak levels within a few hours of the start of dosing. A review of telemetry data will therefore be performed after 24 hours for clinically relevant alerts (see Appendix 9 for guidance). In the absence of such a signal, monitoring will revert to regular ECG assessments. In case clinically relevant changes are observed telemetry will be continued as long as deemed appropriate by the investigator. At the investigator's discretion and in consultation with the medical monitor telemetry could be reinitiated at any time during the study should any potential signals in regular ECG assessments emerge.
Transthoracic Echocardiogram	X											Additional echocardiograms may be performed if increases in cTNI or BNP are observed (see Section 8 for details), or at any time at the discretion of the investigator

Procedure	Screening (within 28 days of Day 1)	Study Period (Days)									Follow-up (7-14 days following discharge)	Notes
		-1	1	2	3	4	5	6	7	8		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	VS assessments will be performed in triplicate at screening and at pre-dose. All post dose assessments will beperformed as single measurements at 30 min and 1 hr, 6hr, 24hr, 48hr, 72hr, 96hr, 120hr, 144hr, 168hr post-dose as outlined in Section 9.4.2. VS times may be adjusted based on emerging PK data.
Study Treatment			X									
Assessment of infusion site			←----------→									Up to day 8
Blood (PK)			←-----For sampling time points, see Section 9.5.1----------→								X	Additional blood PK samples may be collected other than those timepoints specified in Section 9.5.1 or on additional days based on emerging data
Urine (metabolism)		X	X									Equivalent to admission on day -1 to pre-dose day 1 and 0-24 hours post-dose as outlined in Section 9.5.2. Part A Cohorts Only.
Blood (PD)		←-----For sampling time points, see Section 9.7----------→									X	Additional 3HK and PD Biomarker samples may be collected other than those timepoints specified in Section 9.7 or on additional days based on emerging data

Procedure	Screening (within 28 days of Day 1)	Study Period (Days)									Follow-up (7-14 days following discharge)	Notes
		-1	1	2	3	4	5	6	7	8		
PGx Sample			X									Pre-dose if possible. Informed consent for optional genetics research must be obtained before collecting a sample
AE/SAE review		←----------===========								----------→	X	
Concomitant medication review	X	←----------								----------→	X	

2.2. Part B & C – Cohorts 9, 10, 11, 12 & cohort 14, single bolus dose plus 7 day infusion, healthy volunteer subjects

Procedure	Screening (within 28 days of Day 0)	Study Period (Days)																Follow-up (Day 32 ± 2 days)	LFT Follow-up (Day 62 ±2 days)	Notes
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			
Outpatient Visit	X																	X	X	
Admission to Clinical Unit		X																		
Inpatient Stay at Clinical Unit		←----------															→----------			
Discharge from Clinical Unit																	X			Following completion of all assessments
Informed consent	X																			
Inclusion and exclusion criteria	X	X																		

Procedure	Screening (within 28 days of Day 0)	Study Period (Days)															Follow-up (Day 32 ± 2 days)	LFT Follow-up (Day 62 ±2 days)	Notes
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			
Demography	X																			
Full physical exam incl height and weight	X																			
Brief Physical		X															X	X		
Medical history (includes substance usage)	X																			Substances: Drugs, Alcohol, tobacco and caffeine
Clinical Safety Laboratory Assessments *(HIV, Hep B and Hep C Screen at screening only[2])*	X	X		X		X		X		X		X		X		X		X		Screening and day -1 safety labs must be in fasted state. [2]If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required
LFTs (ALT, AST, AP, direct and indirect Bilirubin)	X	X	X	X	X	X	X	X	X	X	X	X	X		X		X	X	X	
cTnI / BNP	X	X	X	X		X			X			X			X		X			6hrs, 24hrs and 72hrs post dose. D7 immediately after end of infusion. D10, D13 and D15 anytime.
Urine Drug/Alcohol Breath Test	X	X																X[3]	X[3]	[3]Alcohol Breath test only
FSH	X																			Females only, if required

Procedure	Screening (within 28 days of Day 0)	Study Period (Days)															Follow-up (Day 32 ± 2 days)	LFT Follow-up (Day 62 ±2 days)	Notes
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Triplicate ECGs will be obtained at screening and predose. Single measurements 30min and 6hr, 12hr, 24hr, and on Days 3-15 post-dose (equivalent to 36hr, 48hr, 72hr, 96hr, 120hr, 144hr, 168hr, 192hr, 216hr, 240hr, 264hr, 288hr, 312hr, 336hr, 360hr post-dose). ECG times may be adjusted once initial PK data is available.

Procedure	Screening (within 28 days of Day 0)	Study Period (Days)															Follow-up (Day 32 ± 2 days)	LFT Follow-up (Day 62 ±2 days)	Notes
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			
Continuous ECG Monitoring			X																	Continuous monitoring from -1 hour pre-dose to 24hours post dose. Based on preclinical data levels of parent compound and tryptophan metabolites are expected to reach peak levels within a few hours of the start of dosing. A review of telemetry data will therefore be performed after 24 hours for clinically relevant alerts (see Appendix 9 for guidance). In the absence of such a signal, monitoring will revert to regular ECG assessments. In case clinically relevant changes are observed telemetry will be continued as long as deemed appropriate by the investigator. At the investigator's discretion and in consultation with the medical monitor telemetry could be reinitiated at any time during the study should any potential signals in regular ECG assessments emerge.
Transthoracic Echocardiogram	X																			Additional echocardiograms may be performed if increases in cTN or BNP are observed (see Section 8 for details), or at any time at the discretion of the investigator

Procedure	Screening (within 28 days of Day 0)	Study Period (Days)															Follow-up (Day 32 ± 2 days)	LFT Follow-up (Day 62 ±2 days)	Notes
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		VS assessments will be performed in triplicate at screening and pre-dose. Single measurement at 30 min and 1 hr, 6hr, 24hr, and on Days 3-15 post-dose as outlined in Section 9.4.2. VS times may be adjusted based on initial PK data.
Columbia Suicide Severity Rating Scale (C-SSRS)	X	X			X				X								X			
Cognitive Assessments (6-CIT, fingertapping test and NPI)		X				X			X											
Study Treatment			←---------- →																	
Assessment of infusion site			←----------→																	Up to 36 hrs post-start of infusion
Blood (PK)			←-------For sampling time points, Section 9.5.1----------→																	Additional blood PK samples may be collected other than those timepoints specified in Section 9.5.1 or on additional days based on emerging data
Urine (metabolite)		X			X															Equivalent to admission on day -1 to pre-dose day 1 and 48-72 hours post-dose. PART B Cohorts Only.

Procedure	Screening (within 28 days of Day 0)	Study Period (Days)															Follow-up (Day 32 ± 2 days)	LFT Follow-up (Day 62 ±2 days)	Notes
		-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15			
Blood (PD)			←------For sampling time points, Section 9.7----------→																	Additional 3HK and PD Biomarker samples may be collected other than those timepoints specified in Section 9.7 or on additional days based on emerging data
Bile Sampling (enterotest)					X															Only to be performed at highest dose administered. Part B only
PGx Sample			X																	Pre-dose if possible. Informed consent for optional genetics research must be obtained before collecting a sample
AE/SAE/PSRAE review		←----------→																X		
Concomitant medication review	X	←----------→																X		

3. INTRODUCTION

3.1. Study Rationale

GSK3335065 is being developed as a treatment for acute pancreatitis with the intent of reducing 3-hydroxykynurenine (3HK) levels to the normal range (or lower) and maintaining them at this level throughout the treatment period. It is envisaged that it will be given intravenously (IV) as an initial bolus followed by continuous infusion over a 7 day period.

This first time in human trial is primarily designed to determine the safety, tolerability pharmacokinetics, and pharmacodynamics of GSK3335065 in healthy male and female (women of non child bearing potential, WONCBP) volunteers. Additionally, the study will employ a biomarker strategy for establishing proof of mechanism and assist in dose finding for future studies. It has been designed to determine a well tolerated single bolus dose and constant IV infusion dose regimen to achieve a minimum of 85% reduction in 3HK levels in healthy volunteers over 7 days of drug administration.

The study will employ an adaptive design comprised of three Parts:

Part A: Single Ascending Dose (SAD) by IV bolus in males

Part B: Ascending Doses by IV constant infusion for 7 days in males after single IV bolus in males

Part C: Single dose by IV bolus in females of non-child bearing potential (WONCBP), and continuous infusion over 7 days in WONCBP.

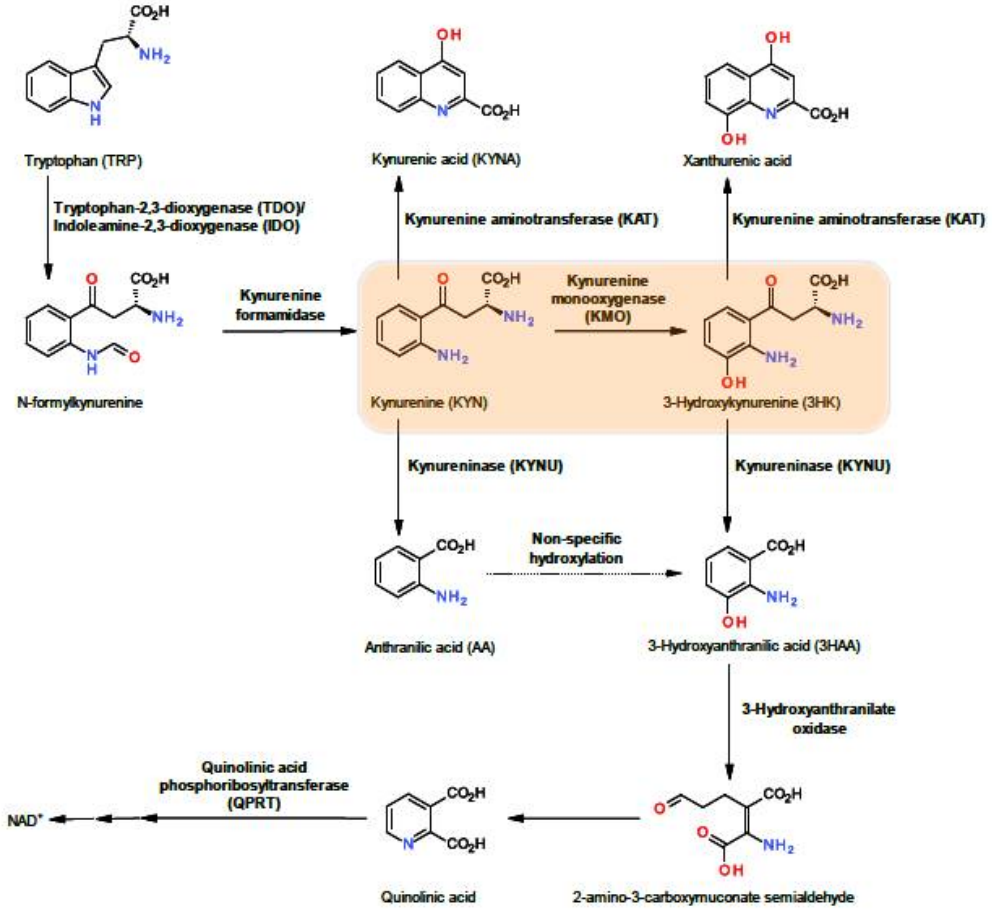
The study population is comprised of healthy male (Parts A and B) and female (WONCBP) (Part C) subjects. Women of child bearing potential are not included in this study due to the limited assessment of GSK3335065 on reproduction. Inclusion of females in the study will serve two main purposes: to generate safety/tolerability data in females prior to inclusion of females in a future Proof Of Concept study, and to rule out potential clinically relevant pharmacokinetics (PK) differences between males and females prior to inclusion of females in the POC study. Gender differences are currently not expected based on preclinical findings.

3.2. Background

The peripheral metabolism of Tryptophan (TRP) occurs preferentially via the kynurenine (KYN) pathway (Figure 1). TRP metabolism is increased in a range of inflammatory conditions following induction of expression of indole dioxygenases (IDO) by cytokines such as interferon-γ. This results in increased production of downstream metabolites including 3-hydroxykynurenine (3HK) which is known to cause oxidative stress and be cytotoxic. A recent prospective study undertaken as a collaboration between GSK and the University of Edinburgh showed a strong association between disease severity and the plasma concentrations of 3-HK in patients diagnosed with acute pancreatitis (Skouras et al, 2016). 3HK is formed exclusively through the action of kynurenine-3-monooxygenase (KMO). There is no evidence of upregulation of KMO in disease, and as depletion of

TRP is also observed, the increase in 3HK probably results directly from the increased flux through the pathway as a result of upregulation of IDO. Genetic or pharmacological inhibition of KMO protects rodents from kidney and lung damage when subjected to a model of pancreatic injury driven secondary organ dysfunction (Mole et al, 2016). GSK3335065 is being developed as an intravenously administered inhibitor of KMO which will reduce the production of 3HK and thereby limit damage to secondary organs during an attack of acute pancreatitis.

Figure 1 Kynurenine Monooxygenase (KMO) is a branchpoint in the Kynurenine Pathway of Tryptophan metabolism



Inhibition of KMO *in vivo* in preclinical species results in an accumulation in both the substrate (kynurenine (KYN) and in the products of the alternative metabolic routes (kynurenic acid (KYNA) and anthranillic acid (AA)). Of these, KYNA is of particular note as it may act on receptors within the central nervous system (CNS). However, to date no adverse effects relating to this metabolic diversion have been observed during the preclinical studies.

Detailed information relating to non-clinical pharmacology, safety pharmacology, PK and metabolism, toxicology and other pre-clinical data can be found in the GSK3335065 Investigators Brochure [GlaxoSmithKline Document Number 2016N273923_01].

3.3. Benefit/Risk Assessment

The current study represents the first administration of GSK3335065 to healthy subjects. Considerations for safety monitoring are derived primarily from non-clinical data. Preliminary data from the first two dose levels (0.1 mg and 0.25 mg) in Part A (SAD) of this study is available (see below for details). The following section (Section 3.3.1) outlines the risk assessment and mitigation strategy for this protocol. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK3335065 may be found in the Investigator's Brochure.

Summary of preliminary clinical data from 0.1 mg and 0.25 mg single doses in Part A (SAD)

No SAEs have been reported.

In cohort 1 period 1 (0.1 mg Single dose), six subjects reported a total of 7 AEs (back pain, epistaxis, contusion, headache, infusion site erythema, tachycardia, upper respiratory tract infection). All events were mild to moderate in intensity and are considered not related to the study medication based on the blinded review of the investigator. In this cohort a total of 5 subjects were withdrawn from the study, of which 1 subject (subject PPD was withdrawn due to an AE. This subject developed a 11-beat run of broad complex tachycardia for 4 seconds approximately 20 hrs post dose. At the time of the event the subject was asleep and remained asymptomatic until discharge from the unit. This event was considered abnormal and clinically significant by the investigator but not related to the study medication. Four subjects PPD and PPD were withdrawn from the study for logistical reasons.

In cohort 2 period 1 (0.25 mg SD), two subjects reported a total of 3 AEs (back pain, contact dermatitis secondary to cannula dressing, vessel puncture bruise). All events were considered mild to moderate in intensity and are considered not related to the study medication based on the blinded review of the investigator.

Except for subject # PPD (see above) no clinically significant safety signals were observed in any of the subjects during physical examinations, 12 lead ECGs, cardiac telemetry, vital signs and laboratory tests at any dose level.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [GSK 3335065]		
Because cardiovascular (CV) changes were observed in rat safety assessments studies, there is a risk of cardiac-related adverse events being observed in man	In a rat preliminary dose range finding study via continuous infusion, increases in cardiac troponin I (cTnI) and N-terminal brain natriuretic peptide (NT-proANP) concentrations and degenerative and/or inflammatory changes in the heart were seen in rats given 300 mg/kg/day. In a rat preliminary dose range finding study via oral gavage, myocardial necrosis and inflammatory cell infiltrate were seen in the hearts of rats given 400 mg/kg/day (with no changes in cardiac biomarkers).	The CV changes observed in rats were only noted at exposures 128-fold higher than the highest exposure predicted in this study and at concentrations 232-fold higher than those predicted in this study and were accompanied by changes in cardiac biomarkers that can be monitored (cTnI and brain natriuretic peptide [BNP]): Subjects with cTN or BNP > ULN will be excluded (Exclusion criterion # 5) Monitoring for cTn and BNP in all parts of the study (Section 2, Time and Events Table) Stopping criteria based on cTn and BNP increases (Section 8.1.4) Continuous ECG minitoring during the first 24hr after initiation of dosing, followed by 12-lead ECG assessments The NOAEL for this effect is 75-fold the highest exposures and 177 times the concentration proposed in this study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Haemodynamic changes	In a screening cardiovascular study in the rat, there were increases in blood pressure (maximum 12 mmHg), pulse pressure (maximum 5 mmHg), heart rate (maximum 63 bpm) and body temperature (0.7°C), and decreases in QA interval (maximum 5 msec).	No effect concentration in the rat (16.8µg/mL) was 4200-fold higher than the targeted concentration at starting dose (0.004µg/mL). Regular Vital Sign (BP and HR) assessments during the study (Section 2 Time and Events Table) Stopping criteria based on Vital Sign changes (Section 8.1.4) Continuous ECG monitoring during initial 24hrs after initiation of dosing, followed by 12-lead ECG assessments.
Liver changes	In rats, there was centrilobular hepatocyte hypertrophy and increased liver weight at ≥140 mg/kg/day; and additional liver pathology changes and increases in aspartate aminotransferase, alanine aminotransferase activity and total bilirubin concentrations at ≥300 mg/kg/day. GSK3335065 is a carboxylic acid and has the potential to form reactive acyl glucuronide metabolites which could contribute to idiosyncratic liver toxicity. An in vitro assay in human liver microsomes showed there was no turnover of GSK3335065 in microsomes and no acyl glucuronides were detected. However, an	Subjects with ALT or bilirubin >1.5xULN prior to dosing will be excluded (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). (Exclusion Criterion #1). Subjects with current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) will be excluded (Exclusion Criterion #2). Monitoring for ALT, AST, alkaline phosphatase and bilirubin at each dose level (Section 2 Time

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	acyl glucuronide with a measured half-life of 2 hrs was detected in rat plasma following 7 days continuous infusion. Therefore there is a risk that this metabolite may be formed in humans. This might be of clinical concern if the total daily dose exceeds 100 mg.	and Events Table) Stopping criteria based on LFT increases (Section 8). The NOAEL for these effects is 75-fold the highest exposures proposed in this study. The highest dose proposed in this study is 73.4 mg total dose on day 1 followed by 50.4 mg total dose/day (Above signals are considered an increased concern if daily dose is ≥100 mg). Selected plasma PK samples generated during Part A will be subjected to additional analysis in order to determine if any acyl glucuronides are present. In addition, plasma, urine and bile samples will be used to generate full metabolic profiles in samples taken during the study.
Haematological changes	Decreases in haemoglobin concentration, packed cell volume, red blood cell count and reticulocyte counts were seen in rats at ≥36 mg/kg/day. In the spleen, increased levels of haemopoiesis were seen in rats at ≥140 mg/kg/day, and vacuolation was seen in rats at 180 mg/kg/day.	The NOAEL for these effects is 75-fold the highest exposures proposed in this study. Haematology parameters will be monitored during the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Inflammatory changes	In rats, inflammatory cell foci were seen in the harderian gland (≥140 mg/kg/day), prostate (≥6 mg/kg/day), urinary bladder (≥15 mg/kg/day) and testes (15 mg/kg/day). Increases in neutrophil, lymphocyte, monocyte and total white blood cell counts in rats at ≥180 mg/kg/day.	The NOAEL for this effect is 75-fold the highest exposures proposed in this study. Haematology parameters will be monitored during the study.
Study Procedures		
Intravenous Dosing – Pain, irritation and inflammation at the injection site	General concern in giving IV medication	In 14-day infusion studies in rats and dogs, no irritancy was seen at the dosing sites. In vitro hemolysis assessment of GSK3335065 showed no evidence of haemolytic potential or incompatibility with plasma in humans. The infusion site will be assessed at various times up to 36 hours post-dose using a 0–3 scale as follows: Grade 0=none; Grade 1=pain or itching or erythema; Grade 2=pain or swelling, with inflammation or phlebitis; Grade 3=ulceration or necrosis

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Entero-Test Streaks of blood on the string due to local irritation have been infrequently noted. Rarely, a patient will be unable to swallow the capsule because of gagging or will vomit after doing so. Gagging upon retrieval of the string can occur. On a few occasions, an entire string has been swallowed without ill effects and passes out from the body in the faeces.		The use of Entero-Test has been approved by the FDA (510(k), Summary of safety and effectiveness). The string will be securely taped in place during the collection time to minimize risk of swallowing the entire string. Any subject incapable of swallowing the capsule will be allowed to participate in the study without duodenal bile collection.
Other		
Central Nervous System effects (off-target) due to metabolic diversion. Inhibition of KMO may result in increased KYNA levels in humans, which theoretically might affect suicidal ideation and behaviour, and cause cognitive and/ or behavioural effects.	GSK3335065 increases KYNA levels in the brain in rats. No behavioural signs were noted during 14 day infusion studies in rats and dogs, and no effects were observed in the bespoke IRWIN test.	Subjects with a history or current evidence of depression, bipolar disorder, suicidal ideation and behaviour, or a lifetime history of suicide attempt will be excluded (Exclusion criterion #4) Subjects will be closely monitored in a domiciled environment. Sentinel dosing approach will be adopted in Parts A and B. In line with FDA guidance, assessment of suicidal ideation and behaviour occurrence will be conducted in subjects who receive continuous infusion of GSK3335065 (Section 2 Time and Events Table)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Assessments of cognitive safety will be performed in subjects with continuous infusion of GSK3335065 (Section 2 Time and Events Table) Stopping criteria based on assessments of suicidal ideation and behaviour, and cognitive safety (Section 8.1.4)
Adverse effects due to reduction of 3 hydroxykynurenine (3HK) levels below the physiological range.	KMO deficient mice have undetectable levels of 3HK and elevation of metabolites, such as kynurenine (KYN), kynurenic acid (KYNA) and anthranilic acid (AA), but are viable and healthy. Robust increases in KYN, KYNA, AA and decreases in xanthurenic acid (XA) and quinolinic (QA) were measured in both rats and dogs in the 7-day dose rang finding studies. Additionally a robust decrease in 3HK was observed in the dog study. 3HK levels could not be determined in the rat study. However the mid dose used in this rat study had previously been shown to reduce 3HK levels on the first day of dosing in a pharmacology study. Any adverse effects of changes in any of the TRP metabolites, including 3HK, would have been noted in these studies. No information on the dynamics of the pathway after KMO inhibition in man is available and specific data on the rate of recovery of tryptophan metabolites, including 3HK, after	General safety monitoring will be conducted throughout the study, dose escalation criteria and stopping criteria (summarized in Appendix 3, Dose Escalation Committee), and a sentinel dosing approached (Section 5.1.1 and Section 5.1.2) have been outlined in the protocol. Based on preliminary PK data from the initial two dose levels in Part A (SAD) a conservative safety observation period of 168 hours after single bolus infusion and after cessation of dosing in the 7-day continuous infusion study in a domiciled setting was chosen; 3HK data from humans is not available yet. The safety observation period will be reassessed based on emerging safety, PK and PD data during the trial. Additional 3HK samples may be collected based on emerging data.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	treatment with GSK3335065 is not available from preclinical studies. Published studies with related KMO inhibitors have shown that recovery of metabolites typically occurs within 24-48hr after a bolus dose in rats (Mole et al 2016; Liddle et al, 2017 although 3HK itself was not measured in these studies.	

3.3.2. Benefit Assessment

There will be no benefits demonstrated in this study and there will be no clinical benefits to the participants.

3.3.3. Overall Benefit:Risk Conclusion

Taking into account the measures that will be implemented to minimize the risk to subjects participating in the clinical study, the potential risks associated with the administration of GSK3335065 are considered to be justified by the potential benefits that may be afforded to patients with AP if the hypothesis that activation of the KMO pathway is a major driver of the disease is confirmed. This information could provide a breakthrough in the knowledge of the disease pathology which could facilitate the clinical development efforts for future therapies.

4. OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
• To determine the safety and tolerability of GSK3335065 administered as a single IV bolus (Part A and C), and as a constant IV infusion over 7 days (Part B and C) in healthy volunteers	• Adverse event / Serious Adverse event monitoring • Laboratory parameters (hematology, clinical chemistry, urinalysis) • 12-lead ECG parameters (PR, QRS, QT, QTcF, etc.) • Vital signs (systolic and diastolic blood pressure, heart rate)
Secondary	
• To determine the pharmacokinetic characteristics of GSK3335065 administered as a single IV bolus (Part A and C), and as a constant IV infusion over 7 days (Part B and C) in healthy volunteers	• Pharmacokinetic Parameters: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, t_{last}, C_{max}, C_{avg}, t_{max}, CL, V, $t_{½}$
• Determine dose/exposure effect of GSK3335065 on KMO inhibition (pharmacodynamics) in healthy volunteers (All Parts)	• Evaluate changes in levels of TRP metabolites (3HK and KYN)

Objective	Endpoint
Exploratory	
• Determine the effect of KMO inhibition on other components of the KYN pathway of TRP metabolism (All Parts) • To investigate the plasma, urinary) and biliary (Part B) metabolic pathways of GSK3335065 in healthy subjects	• Evaluate changes in TRP, KYNA, AA, 3-HAT, XA, QA and other pathway components. • GSK335065-related material in plasma, urine and bile

5. STUDY DESIGN

5.1. Overall Design

This is a phase 1 first time in human (FTIH), three part, randomized, placebo-controlled dose escalation study that will utilize an adaptive design for combining Single Ascending Dose (SAD) by IV bolus (Part A) with Ascending Doses by IV constant infusion dosing for 7 days (Part B) in males. Part C will recruit WONCBP only, and a single dose by IV bolus will be investigated prior to multiple dose (7 day) being investigated.

Constant infusion dosing in Part B will be initiated after completion of dosing in Part A using an initial dose level that is considered safe and well tolerated and expected not to exceed the highest exposures safely achieved in Part A. Prior to initiation of Parts B and C, a review of all available safety, tolerability, PK and PD data from Part A will be conducted and potential changes to the dosing paradigm, safety observation period and assessments will be communicated in a future amendment to the protocol as appropriate.

The single and repeat doses administered in Part C will be ones that have already been administered to males in Part A and B (respectively) and are considered safe and well-tolerated.

Pharmacologic activity will be determined by assessing levels of product and substrate of KMO activity (3HK, KYN) at each dose level. The impact of compound on the broader components of the TRP metabolic pathway (Figure 1) will also be assessed.

Dose response/escalation will be assessed as outlined in Appendix 3 by:

a) Safety and tolerability as determined by adverse events, clinical laboratory assessment and vital signs (Parts A and B)

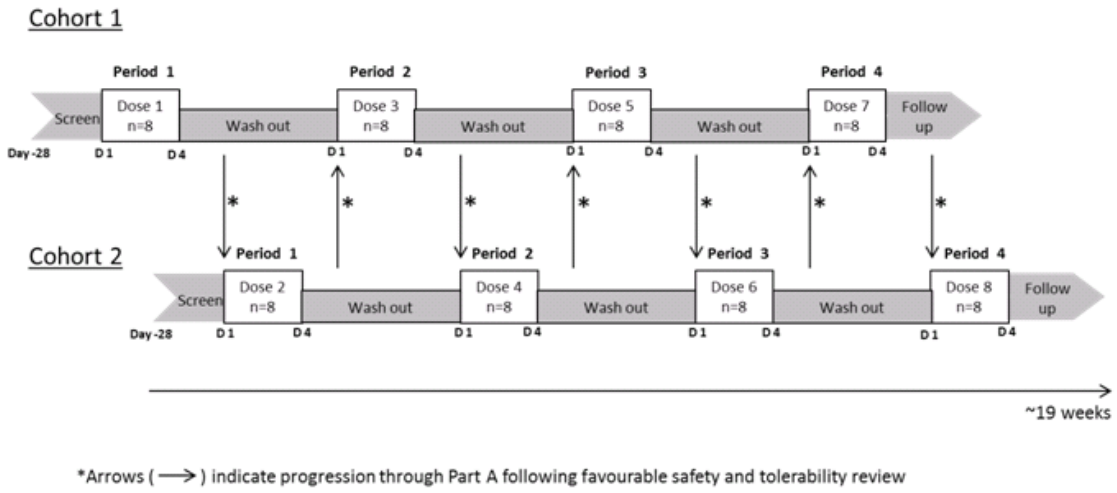
b) Pharmacokinetic data and modelling to remain below NOAEL (Parts A & B),

c) The effect on 3HK and KYN

Bile will be collected *via* the Entero-Test (Guiney et al, 2011) at the time points indicated in Section 9.6 . It is anticipated that only subjects that receive the highest dose in Part B

will also participate in the exploratory study of biliary secretion of GSK3335065 and/or its metabolites.

Figure 2 Part A Study Schematic



*Arrows (⟶) indicate progression through Part A following favourable safety and tolerability review

Figure 2 Revised Part A Study Schematic

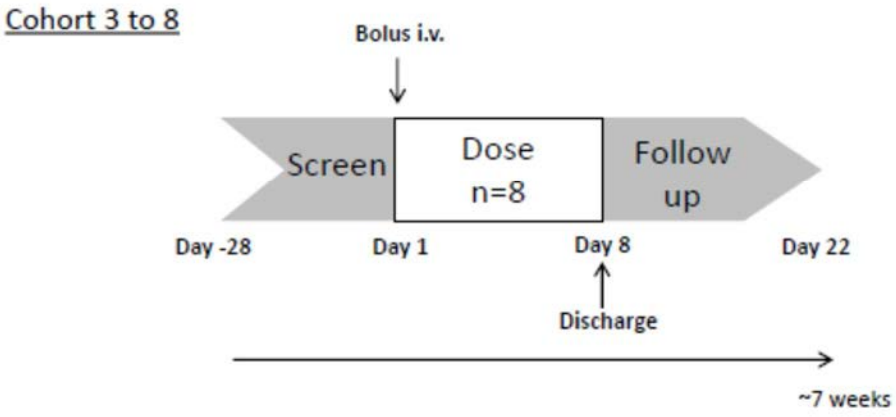


Table 1 Part A Predicted Doses for Single Ascending Dose (NOTE: actual doses may change based on emerging data.

Cohort	Period 1		Period 2		Period 3		Period 4	
1	**0.1 mg (MABEL)**		**1.3 mg**		**5.5 mg**		**35 mg**	
2		**0.25 mg**		**2.6 mg**		**12 mg**		**54 mg**

Table 2 Part A Predicted Doses for Single Ascending Dose (NOTE: actual doses may change based on emerging data).

Cohort	Dose (mg)
3	1.3
4	2.6
5	5.5
6	12
7	35
8	54

The 0.1 mg and 0.25 mg doses have been completed. For operational reasons, dosing in Part A will be continued using a parallel design and dosing will continue at the third dose level (1.3 mg).

Figure 3 Part B Study Schematic

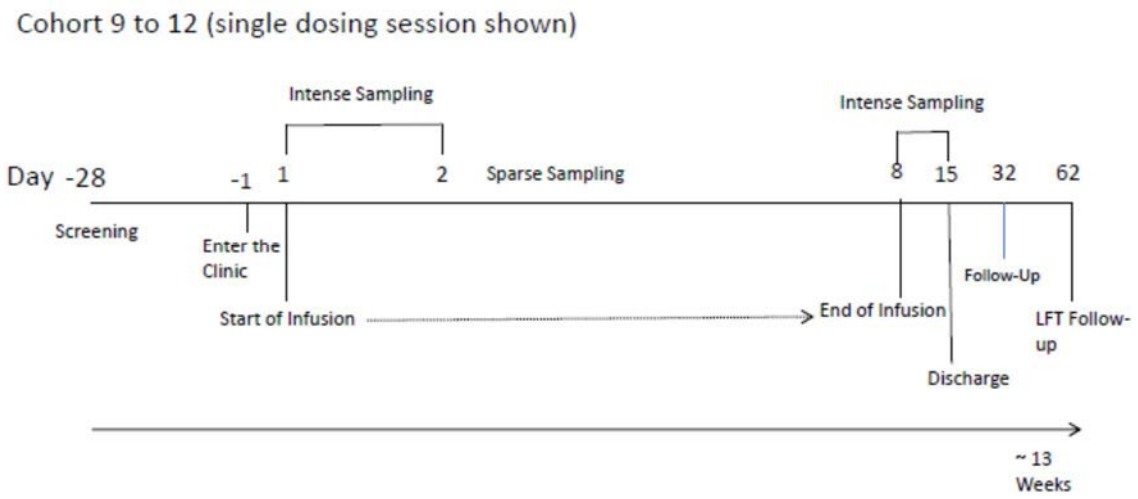
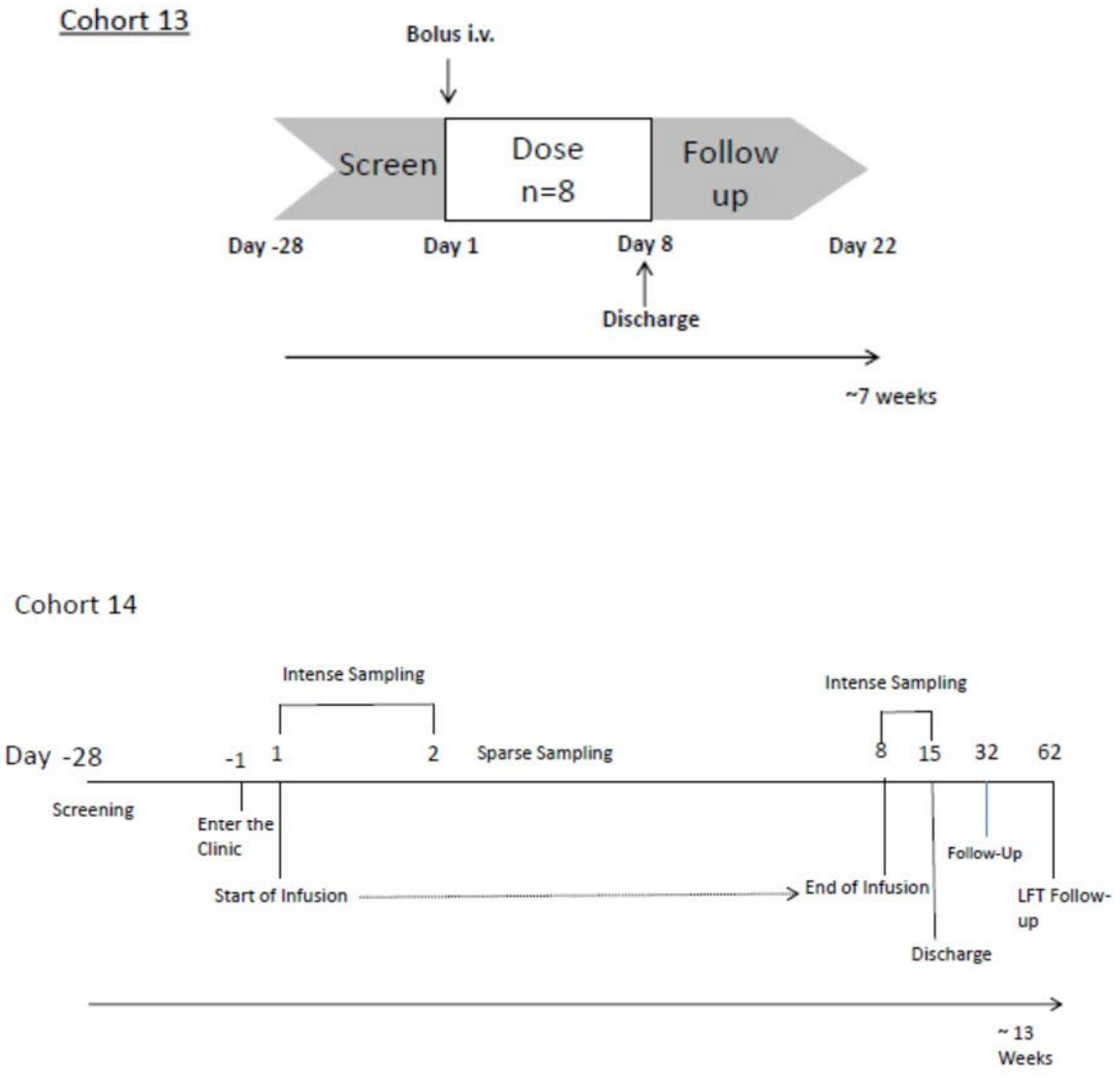


Table 3 Part B Predicted Doses for Multiple Ascending Dose (NOTE: actual doses may change based on emerging data). 4 ascending doses are planned in Part B to characterize the 3HK dose response curve.

Cohort	Minimum Dose	Middle Doses	Maximum Dose
9	IVB 0.14 mg + IV Inf. 0.012 mg/h (0.44 mg cumulative dose on day 1 followed by 0.29 mg/day on days 2-7)		
10		IVB 7.5 mg + IV Inf. 0.63 mg/h (22.6 mg cumulative dose on day 1 followed by 15.1 mg/day on days 2-7)	
11		IVB 12 mg + IV Inf. 1.1 mg/h (38.4 mg cumulative dose on day 1 followed by 26.4 mg/day on days 2-7)	
12			IVB 23 mg + IV Inf. 2.1 mg/h (73.4 mg cumulative dose on day 1 followed by 50.4 mg/day on days 2-7)

Figure 4 Part C Study Schematic



5.1.1. Part A: Single Ascending Dose (IV Bolus) in males

Part A is a randomized, double-blind (Sponsor unblinded), placebo-controlled, single intravenous ascending dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of GSK3335065 in healthy male subjects. Part A was initiated using an interlocking crossover design. 8 Healthy male subjects (6 active, 2 Placebo) were assigned to one of two cohorts (Cohorts 1 and 2). Subjects in cohorts 1 received a single dose of 0.1 mg GSK3335065, and subjects in cohort 2 received a single dose of

0.25 mg GSK3335065. All subjects from cohorts 1 and 2 will be discontinued from the study.

To facilitate subject recruitment, the design of Part A will be changed to a parallel cohort design and dosing will be continued at the third dose level (1.3 mg). For each cohort of 8 subjects at each dose, 6 subjects will receive active drug and 2 subjects will receive placebo using a predefined allocation schedule. Hence, each subject in cohorts 3-8 will receive one active dose strengths or placebo in a parallel study design according to the dose escalation scheme described in a latter section.

Characterization of the GSK3335065 PK relationship will be performed based on emerging data from lower dose levels to ensure that anticipated exposures will not exceed an approximately 75-fold exposure margin in terms of AUC to the rat NOAEL. Characterization of the PD response to GSK3335065 may be performed on an ongoing basis or reviewed at the completion of Part A.

Sentinel dosing: In Part A, the first 2 subjects in each cohort will act as sentinels. One of these subjects will be randomized to active treatment, and the other will receive placebo. At least 24 hours will elapse (relative to the start of dosing) before administration of GSK3335065 to the subsequent subjects at the same dose level to allow for assessment of potential adverse experiences. This assessment will include evaluation of safety parameters including physical examination findings, 12-lead Electrocardiogram (ECGs), clinical laboratory tests and clinical monitoring for adverse events. If there are no clinically relevant safety or tolerability concerns, the remaining 6 subjects in the same dosing session will receive the dose.

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

Screening	All screening assessments to be completed within 28 days prior to the first dose.
Treatment Period	For Cohorts 1 and 2, each subject will take part in four dosing session. During each study period subjects will be in-house from the day prior to dosing until Day 4 post dose when they will be discharged after post dose assessments have been completed. Subjects in Cohorts 1 and 2 will return to the unit approximately 3 weeks later to be dosed again on the following day. Following the completion of period 4, subjects will return as out-patients for any post-dose assessments.
Washout Period	Approximately 10 to 21 days between doses[a].
Follow-up	7-14 days after final study drug administration in the Cohort. If warranted, additional follow-up visits may be scheduled.
Total Duration	Approximately 19 weeks

Table 5 Study Duration of Cohorts 3, 4, 5, 6, 7, 8 (Part A)

Screening	All screening assessments to be completed within 28 days prior to the first dose.
Treatment Period	Each subject will take part in one dosing session. During each study period subjects will be in-house from the day prior to dosing until Day 8 post dose when they will be discharged after post dose assessments have been completed. All subjects may return to the unit approximately 2 weeks after discharge from the unit as out-patients for any post-dose assessments.
Follow-up	Approximately 7-14 days after discharge from the unit. If warranted, additional follow-up visits may be scheduled.
Total Duration	Approximately 7 weeks

5.1.2. Part B: Multiple Ascending Dose (IV Bolus followed by an IV Infusion over 7 days) in Males

Prior to initiation of Part B, a review of all available safety, tolerability, PK and PD data from Part A will be conducted and potential changes to the dosing paradigm, safety observation period and assessments will be communicated in a future amendment to the protocol as appropriate.

Part B is a randomized, placebo-controlled, sequential panel, multiple ascending dose (IV bolus followed by continuous IV infusion over 7 days), double-blind (Sponsor unblinded) trial to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of GSK3335065 in healthy male subjects. Subjects will be assigned to one of four Cohorts (9, 10, 11 or 12), and subjects will only participate in one single cohort. In each cohort subjects will be randomized to receive an IV bolus on day 1 subsequently followed by a continuous IV infusion for seven days.aof either the active study drug (n=6) or placebo (n=2).

Sentinel Dosing: We will stagger each new ascending dose in Part B so that 2 leading subjects will be dosed first. One of these subjects will be randomized to receive active treatment, and the second will receive placebo. Once these subjects have completed the 7-day dosing period, the safety and tolerability data will be reviewed. If there are no clinically relevant safety or tolerability concerns, the remaining 6 subjects will be dosed.

During the course of the 7 day infusion period the participants will be given two approximately 30 minute windows on Day 3 and Day 6 after completion of PK and PD collection in order to perform activities (i.e. shower) without having the canula inserted. The window may be modified based on emerging safety and PK data.

Table 6 Study Duration of Cohorts 9, 10, 11, 12 (Part B)

Screening	All screening assessments to be completed within 28 days prior to the first dose.
Treatment Period	During each study period subjects will be in-house from the day prior to dosing until Day 15 when they will be discharged after post-dose assessments have been completed. Subjects will return to the unit as out-patients for any post-dose assessments.
Follow-up	Approximately 14 days after discharge following termination of study drug administration. If warranted, additional follow-up visits may be scheduled. Additional Liver Function Tests (51 days after discharge)
Total Duration	Each cohort is approximately 13 weeks

5.1.3. Part C: IV Bolus followed by an IV Infusion over 7 days in WONCBP

Prior to initiation of Part C, a review of all available safety, tolerability, PK and PD data from Part A will be conducted and potential changes to the dosing paradigm, safety observation period and assessments will be communicated in a future amendment to the protocol as appropriate.

Part C will be a randomized, placebo-controlled and double-blind trial to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of GSK3335065 conducted in WONCBP only, and will consist of two cohorts (13 and 14). Cohort 13 will investigate a single intravenous dose, and Cohort 14 will investigate a multiple dose (continuous IV infusion over 7 days). In each cohort subjects will be randomized to receive repeat doses of either active (n=6) or placebo (n=2).Cohort 13 and 14 can commence upon safety, tolerability and PK data from the equivalent dose group is available from the male cohort. Cohort 13 will complete prior to cohort 14 initiation.

In cohort 14 participants will be given two 30 minute windows on Day 3 and Day 6 after completion of PK and PD collection in order to perform activities (i.e. shower) without having the canula inserted. These windows may be modified based on emerging safety and PK data.

Table 7 Study Duration of Cohort 13 (Part C)

Screening	All screening assessments to be completed within 28 days prior to the first dose.
Treatment Period	Each subject will take part in a single dosing session. Subjects will be in-house from the day prior to dosing until Day 8 post dose when they will be discharged after post dose assessments have been completed. Subjects will return as out-patients for any post-dose assessments.
Follow-up	Approximately 7-14 days after discharge from the unit. If warranted, additional follow-up visits may be scheduled.
Total Duration	Approximately 7 weeks

Table 8 Study Duration of Cohort 14 (Part C)

Screening	All screening assessments to be completed within 28 days prior to the first dose.
Treatment Period	During the study period subjects will be in-house from the day prior to dosing until Day 11 when they will be discharged after post-dose assessments have been completed. Subjects will return to the unit as out-patients for any post-dose assessments.
Follow-up	14 days after discharge following termination of study drug administration. If warranted, additional follow-up visits may be scheduled. Additional Liver Function Tests- 51 days after discharge
Total Duration	Approximately 13 weeks

5.2. Number of Participants

Sufficient subjects will be randomised to achieve 112 evaluable subjects (Part A: 64 healthy male subjects, Part B: 32 healthy male subjects, Part C; 16 WONCBP (8 subjects for Cohort 13, 8 subjects for Cohort 14). If subjects drop out early or lost to follow up, additional subjects may be enrolled as replacement subjects and assigned to the same treatment sequence following Sponsor approval, in order to ensure an adequate number of subjects are evaluable..

5.3. Participant and Study Completion

A participant is considered to have completed the study if he/she has completed all phases of the study including last scheduled procedure shown in the Schedule of Activities.

A subject who receives an active dose of study medication and for whom a pharmacokinetic specimens have been collected will be considered an evaluable subject for assessing the pharmacokinetics.

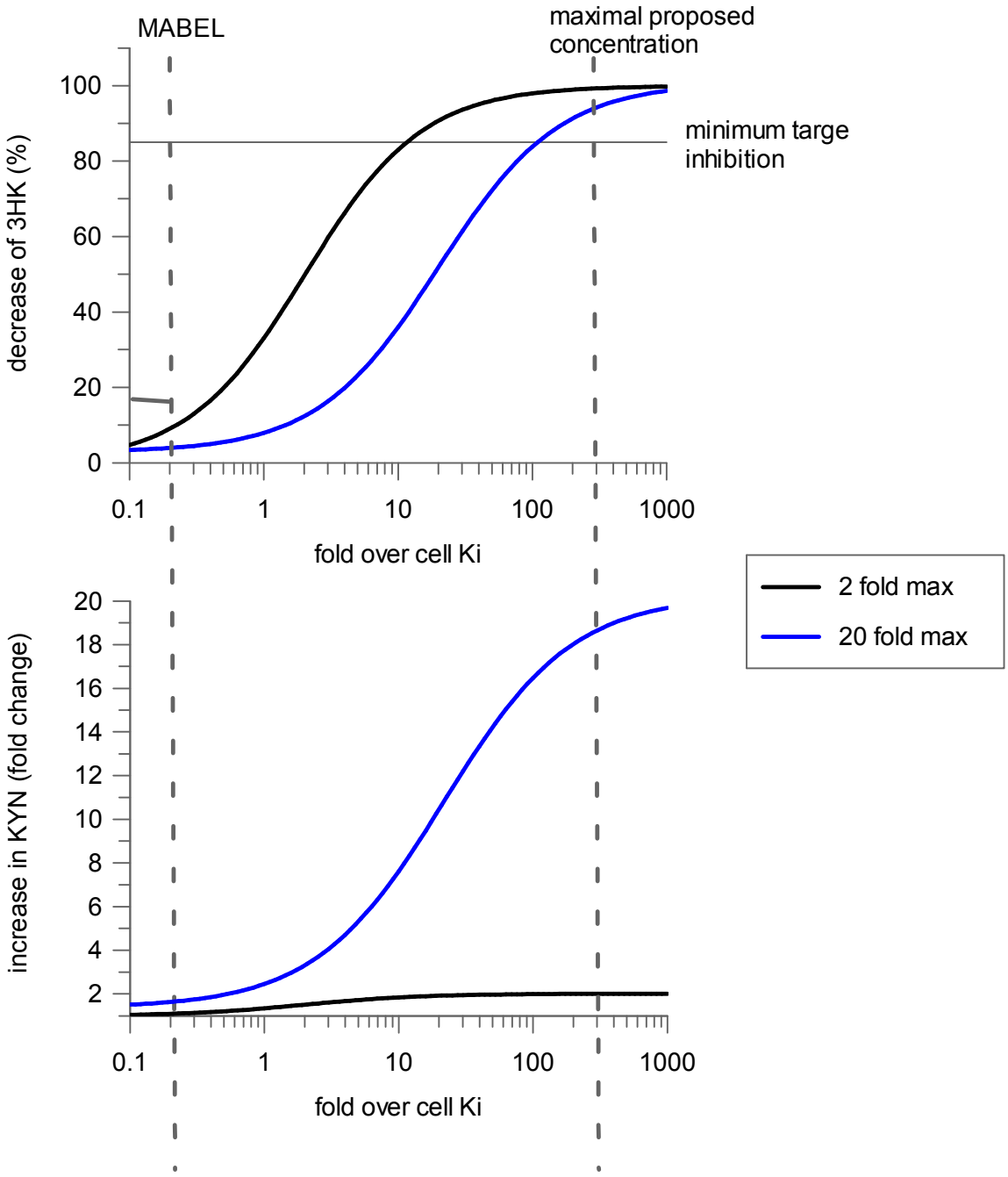
The end of the study is defined as the date of the last visit of the last participant in the study.

5.4. Dose Justification

5.4.1. Starting dose for Part A

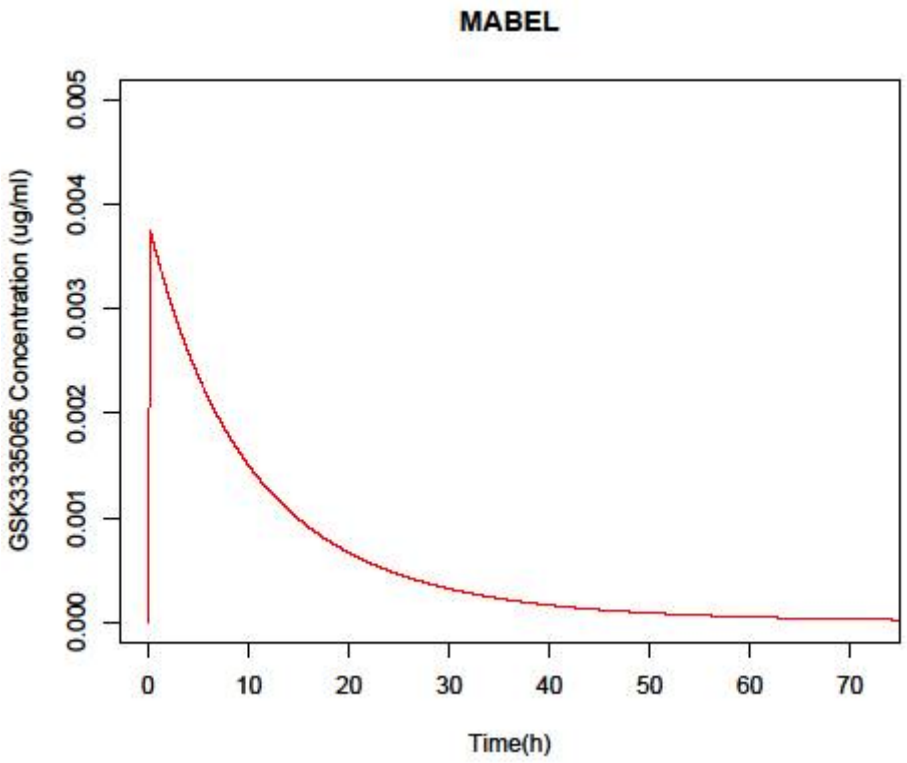
Inhibition of KMO in pre-clinical species results not only in a decrease in the rate of formation of 3HK, but also in an accumulation of KYN. This increase in KYN works to oppose the inhibition of KMO by increasing flux through the pathway. In rats, the maximal steady state change in KYN observed following KMO inhibition was between 6 and 10-fold, while in mice deficient in KMO the baseline KYN level was 19 times higher than in wild type animals (Mole et al, 2016). The magnitude of increase in KYN that will be observed in humans is not known so it is not possible to predict exactly what level of 3HK reduction will be observed at any given drug level. Instead modelling has been used to establish an appropriate dose range to cover a range of potential human scenarios (2 fold to 20-fold increase in KYN).

A model was developed to simulate the clinical doses according to the range increase in KYN previously mentioned and for different degrees of 3HK inhibition. The model utilised the PK preclinical parameters that were scaled to the human counterparts. More specifically, the volume of distribution (V) was predicted from the mean of rat and dog volumes, giving a value of 0.39 L/kg (27 L). Prediction of human clearance (CL) was undertaken using scaling from rat and dog with the method of exponents. Similar values were obtained using methods either restricted (2.9 L/hr) or non restricted (1.9 L/hr) by plasma protein binding so subsequent dose estimates use the mean of these values (2.4 L/hr). Finally, the half-life is predicted to be 7.8 h.



To set the starting dose minimum anticipated biological effect level (MABEL), it was first assumed that the magnitude of the maximal KYN change observed in man following KMO inhibition will be substantially smaller than in the rat (2 fold compared to 6-10 fold), thus making the pathway more sensitive to inhibition. Under these circumstances, a dose targeting 0.2 times the cellular Ki would decrease 3HK levels by no more than 10-20 % while having no measurable impact on KYN levels. In contrast, if the magnitude of the maximal change in KYN in man is assumed to be substantially higher than in the rat (20 fold compared 6-10 fold), then a dose targeting 0.2 times the cellular Ki would be predicted to have no measurable effect on either 3HK or KYN levels. This has therefore

been selected as the MABEL dose. The figure below depicts the predicted PK profile for the MABEL dose.



In accordance with FDA guidance, the maximum recommended starting dose (MRSD) is $1/10^{th}$ (applying the default safety factor) the NOAEL human equivalent dose (HED) in the more sensitive or more relevant preclinical species, correcting for body surface area between species. For GSK3335065 the more sensitive species is the rat as in the rat the lowest HED can be identified. The safety factor may be adjusted depending on the expected pharmacology, toxicology, and preclinical pharmacokinetics of the drug candidate, or previous experience with compounds in the same pharmacologic/structural class. As this is a novel mechanism a more conservative safety factor of 100 to calculate the MRSD was used.

Using the data from the 2 week Good labroratory practices (GLP) toxicity studies in rat, the MRSD was estimated to be 16 mg based on the following calculations:

140 mg/kg/day / 6.2 = 22.6 mg/kg / 100 = 0.226 mg/kg; for a 70 kg human the MRSD is ~ 16mg. Hence, the proposed 0.1 mg MABEL starting dose is approximately 160-fold below the MRSD of 16 mg.

The planned doses and predicted exposures compared to the 2 week GLP study in rats are shown in Table 9 below.

Table 9 Part A Planned doses, predicted exposures, and anticipated margins to rat NOAELs

	Dose	Predicted Cmax (fold Ki) (µg/ml)	Margin to NOAEL (Cmax)	Predicted AUC (0-24h) (µg.hr.mL^{-1})	Margin to NOAEL (AUC 0-24h)
Cohort 1, Period 1	0.1 mg IV bolus	0.004 (0.2xKi)	39750	0.036	46667
Cohort 2, Period 1	0.25 mg IV bolus	0.01 (1xKi)	15900	0.091	18462
To facilitate subject recruitment, the study design will be changed to a parallel cohort design (Amendment 3).					
Cohort 3	1.3 mg IV bolus	0.05 (5xKi)	3180	0.481	3493
Cohort 4	2.6 mg IV bolus	0.1 (10xKi)	1590	0.944	1780
Cohort 5	5.5 mg IV bolus	0.2 (20xKi)	795	2.020	832
Cohort 6	12 mg IV bolus	0.46 (50xKi)	346	4.398	382
Cohort 7	35 mg IV bolus	1.37 (150xKi)	116	12.753	132
Cohort 8	54 mg IV bolus	2.0 (220xKi)	80	22.4	75

Dose Escalation Approach in Part A

The decision to proceed to the next dose level will be based on safety and tolerability data obtained up to 8 days post dose (at discharge from clinical unit) from at least 6 subjects at the prior dose level. The review data set will at a minimum consist of the listings of any adverse events, flagged vital signs, flagged findings during the cardiac monitoring (telemetry) ECG, flagged findings in 12-lead ECGs and laboratory findings (including LFTs, cardiac troponin [cTN], BNP). Available PK data from the prior dose level, together with any available PD data will also be reviewed.

Preliminary PK Data

Estimates of the systemic exposure over 24 hours post-dose, from Part A, Cohorts 1 and 2, were generally consistent with predictions. However, the apparent half-life was significantly longer than the 7.8 hours that had been predicted. Consequently, the PK sampling regimen has been extended to capture the longer terminal phase of elimination.

Preliminary PD Data

Preliminary PD data from Part A to measure the effects of KMO enzyme inhibition showed wide variability in biomarker plasma concentrations both at baseline and during treatment, and included the following biomarkers of the tryptophan pathway: Kynurenine (Kyn), 3-hydroxykynurenine (3-HK)), tryptophan, kynurenic acid, anthranilic acid, 3-hydroxyanthranilic acid, quinolic acid and xanthurenic acid. To enable a reliable assessment of baseline levels and their underlying variability, as well as to ensure all

subjects are in a similar physiological state upon receiving the dose allowing time for any uncontrolled external influences on biomarker levels (food intake, meal time, sleep cycle) to dissipate, subjects will be enrolled at least 12 hours prior to dosing, eg. the afternoon of the day prior to the dose. Blood samples for the measurement of tryptophan pathway biomarkers will be taken regularly. Sleep disruption will be avoided, as it may perturb biomarker levels from their natural levels. On the day prior to dosing (day -1), the proposed sample times are times are as follows: -16hrs, -14hrs, -12hrs and 10hrs followed by -2hrs and approximately 0.5hrs predose on the day of dosing. (day 1). Flexibility around these nominal times will be permitted.

Highest Dose in Part A

The highest dose planned in Part A is a 54 mg dose with an expected exposure margin in terms of AUC to the rat NOAEL of 75-fold. Higher doses may be administered if exposures are lower than predicted but the maximum exposure will not exceed the 75-fold exposure margin in terms of AUC to the rat NOAEL.

5.4.2. Starting dose for Part B

Prior to initiation of Part B a review of all available safety, tolerability, PK and PD data from Part A will be conducted and potential changes to the dosing paradigm, safety observation period and assessments will be communicated in a future amendment to the protocol as appropriate.

In addition to safety/tolerability and PK, the goal of Part B is to characterize the dose-response relationship on KMO inhibition using 4 ascending doses.

Dosing in Part A will be completed prior to initiation of dosing in Part B. The first dose level in Part B will be set to ensure that the highest exposures safely achieved in Part A are not expected to be exceeded. The final decision on the starting dose in Part B will be made after review of preliminary Part A safety, tolerability, PK and PD data. A potential starting dose in Part B could be 0.14 mg IVB + 0.012 mg/h continuous infusion (predicted AUC(0-168) 0.9 ug.hr.ml-1 correlating with an anticipated KMO inhibition of approximately 25%). Based on current predictions a 5.5 mg single dose (Panel 5) is expected to result in an exposure of ~2 $ug.hr.ml^{-1}$ (AUC 0-24h) providing sufficient PK coverage for a 0.14mg IVB + 0.012 mg/h continuous infusion dose over 7 days.

Dose Escalation Approach in Part B

In Part B, a decision to proceed to the next dose level will be based on data obtained up to 15 days post dose (discharge from clinical unit) from at least 6 subjects at the prior dose level. The review data set will at a minimum consist of the listings of any adverse events, flagged vital signs, flagged findings during the neuropsychiatric testing, flagged findings during the cardiac monitoring (telemetry) ECG, 12-lead ECGs, laboratory findings (including LFTs, cTN, BNP), and available PK and PD (3HK levels as PD BMx) data. Doses will be selected to ensure as complete a coverage of the range of pharmacological effects based on data observed in Part A as is possible based on acceptable safety and tolerability. As a guide the doses (i.v. bolus and infusion rates) to achieve the clinical

concentrations within the minimal and maximal targeted concentrations were estimated to be per as Table 10 below.

Anticipated Clinically Efficacious Dose

The PK/PD study conducted in rats suggests that a concentration around 20 times the cellular Ki would be required to achieve an 85% decrease in 3HK levels. GSK3335065 has cellular half maximal potency around 3 nM giving an apparent cellular Ki of 0.85 nM. It is largely excluded from erythrocytes, giving a blood:plasma ratio in human blood of 0.62, and is moderately bound by human plasma proteins, with a free fraction of 2.0% at 10 μM. Thus the minimal level required to achieve 85% inhibition would be a free drug level of 17 nM, requiring total plasma drug level of 850 nM or total blood drug levels of 525 nM (0.18 ug/mL).

5.4.3. Maximum dose/exposure in Part B

The highest dose planned to be explored will target a concentration just over 100 times the Ki in PART B. Modelling suggests that the highest anticipated dose (73.4 mg total dose on day 1 followed by 50.4 mg/day on days 2-7) should achieve reductions of 3HK in excess of 90% even if the increase in KYN observed is substantially larger than that seen in the rat (20 fold compared to 6-10 fold). This value remains below (177-fold for Cmax and 75-fold for AUC(0-24h)) the plasma concentration at the NOAEL in the toxicity studies in rats and dogs. The highest dose also remains below the threshold for increased drug induced liver injury (DILI) risk (100 mg). Higher doses may be administered if exposures are lower than predicted but the maximum exposure will not exceed the 75-fold exposure margin in terms of AUC to the NOAEL.

This dose is anticipated to reduce 3HK levels by >90%. Preclinical data support that lowering 3HK levels through KMO inhibition >90% in humans is anticipated to be safe as KMO deficient mice have undetectable levels of 3HK and elevation of metabolites, such as kynurenine (KYN), kynurenic acid (KYNA) and anthranilic acid (AA), but appear viable and healthy. A robust decrease in 3HK of >90% was observed in the dog 7-day dose range finding study. 3HK levels could not be determined in the rat study. However the mid dose used in this rat study had previously been shown to reduce 3HK levels by ~85% on the first day of dosing in a pharmacology study. Any adverse effects of changes in 3HK would have been noted in these studies.

Table 10 Part B planned doses, predicted exposures, and anticipated margins to rat NOAEL. 4 ascending doses are planned in Part B.

	Dose range IVB & IV infusion	Expected (%) KMO inhibition	Targeted Concentration (Cmax) (ug/ml)	Margin to NOAEL (Cmax)	AUC(0-168h) ($ug.hr.mL^{-1}$)	Margin to NOAEL (AUC 0-24h)
Anticipated starting dose	IVB 0.14 mg + IV Inf. 0.012 mg/h	25%	0.005 (0.6xKi)	31800	0.9	13067
Anticipated pharmacologically active dose	IVB 7.5 mg + IV Inf. 0.63 mg/h	>60%	0.27 (30xKi)	589	47	250
Anticipated pharmacologically active dose	IVB 12 mg + IV Inf. 1.1 mg/h	>85%	0.45 (50*x*Ki)	353	85	138
Highest anticipated dose	IVB 23 mg + IV Inf. 2.1 mg/h	>90%	0.9 (100*x*Ki)	177	156	75

5.4.4. Part C:

Doses selected for Part C (single or repeated administration) will be based on doses shown to be safe and tolerable in Parts A and B respectively and is expected to sit in the pharmacologically relevant range.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be 18 to 50 years of age inclusive, at the time of signing the informed consent. In Part C (WONCBP) participants must be between 18 and 60 years of age.

Type of Participant and Disease Characteristics

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

Weight

4. Body weight >50kg and body mass index (BMI) within the range 18.5 – 32 kg/m^2 (inclusive).

Sex

5. Abstinence/contraceptives: Length of time required for abstinence or use of contraceptives should take into account the reproductive toxicity profile including genotoxicity and teratogenicity, the size of the molecule, and the number of doses.

   a. Male participants:

   A male participant must agree to use contraception as detailed in Appendix 5 of this protocol during the treatment period and for at least 2 days after the last dose of study treatment and refrain from donating sperm during this period.

   b. Female participants:

   Only female participants of non childbearing potential (WONCBP) as defined in Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information are eligible to participate.

Informed Consent

6. Capable of giving signed informed consent as described in Appendix 3 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Alanine transaminase (ALT) and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
2. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)

3. QTcF >450 msec from a mean of triplicate readings taken no more than 2 minutes apart
4. Clinically significant abnormal echocardiogram
5. The participant has a history or current evidence of depression, bipolar disorder, suicidal ideation and behaviour, or a lifetime history of suicide attempt.
6. cTn or BNP >ULN

Prior/Concomitant Therapy

7. Use of prohibited medication (Section 7.7 & Section 7.8)

Prior/Concurrent Clinical Study Experience

8. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
9. Exposure to more than four new chemical entities within 12 months prior to the first dosing day

Diagnostic assessments

10. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. For potent immunosuppressive agents, subjects with presence of hepatitis B core antibody (HBcAb) should also be excluded.
11. A positive pre-study drug/alcohol screen.
12. A positive test for human immunodeficiency virus (HIV) antibody.
13. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within 84 days.

Other Exclusions

14. Poor or unsuitable venous access
15. History of regular alcohol consumption within 6 months of the study defined as:

    An average weekly intake of >14 units. One unit is equivalent to 8 g of alcohol: a half-pint (~240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
16. History of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or Medical Monitor, contraindicates their participation.
17. History of smoking within 6 months of the study.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, and/or pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of study treatment until after collection of the final PK or PD sample.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for at least 24 hours before the start of dosing until after collection of the final pharmacokinetic (PK) and/or pharmacodynamic sample.
- During each dosing session, participants will abstain from alcohol for 72 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample. Participants will also abstain from alcohol 72 hours before the 14 ±2 days follow up procedures have been completed, and 72 hours before the 32 ±2 days follow-up procedure as well as the 62 ± 2 days LFT follow up procedures have been completed.
- Use of tobacco products will not be allowed from screening until after the final follow-up visit.

6.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (eg, watching television, reading).

6.3.4. Exposure to UV

Initial photochemical data suggest that a potential photoreactive risk may exist. As a precaution, until this risk is further assessed via experimental evaluation, patients receiving GSK3335065 should avoid being in strong direct sunlight and/or UV exposure or use protective clothing, sunscreen and sun glasses from dosing till the follow-up visit.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) are allowed to be rescreened once after consultation with the Sponsor.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

7.1. Treatments Administered

Study Treatment Name:	GSK3335065	Placebo
Dosage formulation:	GSK3335065 Solution for injection	Placebo to match GSK3335065 Solution for injection
Unit dose strength(s)/Dosage level(s):	Unit dose strength : 5 mg/mL stock that may be diluted Dosage levels : variable	N/A
Route of Administration	Intravenous injection and infusion	Intravenous injection and infusion
Dosing instructions:	Study medication may be diluted in 0.9% w/v Sodium Chloride and will be administered by intravenous infusion by study personnel following specified regimens	Study medication will be administered by intravenous infusion by study personnel following specified regimens
Packaging and Labeling	Study Treatment will be provided in a carton containing 1x GSK3335065 5mg/ml, 5mL vial. Each carton will be labeled as required per country requirement.	Study Treatment will be provided in a carton containing 1x Placebo to match GSK3335065, 5mL Vial. Each carton and vial will be labeled as required per country requirement.
Manufacturer	GlaxoSmithKline Manufacturing SpA, Parma	GlaxoSmithKline Manufacturing SpA, Parma

7.2. Dose Modification

In case a dose reduction is necessary, the study treatment will be administered as follows:

- This protocol allows some alteration from the currently outlined dosing schedule, but the maximum predicted exposures will not exceed the 75-fold exposure margin in terms of AUC to the rat NOAEL as defined in the 14-day preclinical GLP tox studies.
- The decision to proceed to the next dose level of GSK3335065, will be made by the GSK Study Team based on safety, tolerability and available pharmacokinetic and/or pharmacodynamic data obtained in at least 6 subjects on GSK3335065 at the prior dose level. The actual doses to be administered may be adjusted based on safety, tolerability and preliminary pharmacokinetic and/or pharmacodynamic data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose.
- The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety, tolerability, pharmacokinetic and/or pharmacodynamic findings at a given dose level, or to add cohorts to evaluate additional dose levels. The study procedures for these additional subject(s) or cohort(s) will be the same as that described for other study subjects.
- If the same Serious Adverse Event (SAE) occurs in more than one subject, the dose escalation will be temporarily halted and no further subject will be dosed until a full safety review of the data has taken place. Relevant reporting and discussion with the Medical Monitor, relevant GSK personnel, and with the Ethics Committee will then take place prior to any resumption of dosing.
- The above criteria will apply even if measured pharmacokinetic parameters are below the above mentioned PK stopping criteria, and every effort will be made to take a blood sample at the time of the event for pharmacokinetic analysis in the presence of any of the above events.

7.3. Method of Treatment Assignment

Subjects will be randomized to either active or placebo at the start of each cohort in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software.

A description of each regimen in Part A, Part B and Part C is provided respectively in Table 11, Table 12 , Table 13, Table 14 below.

Table 11 Part A Single Ascending Dose (IV Bolus) in Males:

Cohort 1-8

Subject	Period 1 (sentinels)	Period 1 (remainder)						
X	Placebo							
X	Dose 1							
X		Dose 1						
X		Dose 1						
X		Dose 1						
X		Dose 1						
X		Dose 1						
X		Placebo						

Table 12 Part B Multiple Ascending Dose (i.v. bolus followed by an i.v. infusion) in Males:

Cohort	No. of Subjects							
		Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Cohort 9 (sentinel)	1 1	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo
Cohort 9 (remaining)	5 1	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo
Cohort 10 (sentinel)	1	Dose 2 Placebo	Dose 2	Dose 2	Dose 2	Dose 2	Dose 2	Dose 2
Cohort 10 (remaining)	1	Dose 2	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Cohort 11 (sentinel)	5 1	Placebo	Dose 2 Placebo	Dose 2 Placebo	Dose 2 Placebo	Dose 2 Placebo	Dose 2 Placebo	Dose 2 Placebo
Cohort 11 (remaining)	1 1	Dose 3 Placebo	Dose 3 Placebo	Dose 3 Placebo	Dose 3 Placebo	Dose 3 Placebo	Dose 3 Placebo	Dose 3 Placebo
Cohort 12 (sentinel)	5 1	Dose 3 Placebo	Dose 3 Placebo	Dose 3 Placebo	Dose 3 Placebo	Dose 3 Placebo	Dose 3 Placebo	Dose 3 Placebo
Cohort 12 (remaining)	1 1 5 1	Dose 4 Placebo Dose 4 Placebo	Dose 4 Placebo Dose 4 Placebo	Dose 4 Placebo Dose 4 Placebo	Dose 4 Placebo Dose 4 Placebo	Dose 4 Placebo Dose 4 Placebo	Dose 4 Placebo Dose 4 Placebo	Dose 4 Placebo Dose 4 Placebo

Part C: Single (i.v. bolus) or Multiple Dose (i.v. bolus followed by an i.v. infusion) in WONCBP:

Table 13 Cohort 13: Single (i.v. bolus) Dose

Subject	Period 1 (remainder)
X	Placebo
X	Dose 1
X	Dose 1
X	Dose 1
X	Dose 1
X	Dose 1
X	Dose 1
X	Placebo

Table 14 Cohort 14: Multiple Dose (i.v. bolus followed by an i.v. infusion)

Cohort	No. of Subjects							
		Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Cohort 14	6 2	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo	Dose 1 Placebo

7.4. Blinding

This will be a double-blind (Sponsor unblinded) study in which the subjects and site staff (Pharmacist unblinded to prepare study drug) will be blinded for the duration of the study, and the following will apply.

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

A subject may continue in the study if that subject's treatment assignment is unblinded.

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

7.5. Preparation/Handling/Storage/Accountability

A description of the methods and materials required for the preparation of GSK3335065 solution for injection will be detailed in a Study Specific Technical Agreement/Memo (SSTA) or Pharmacy Manual which will be accompanied by a Quality Agreement.

No special preparation of study treatment is required.

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

Precaution will be taken to avoid direct contact with the study treatment. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

7.6. Treatment Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The

dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

- GSK3335065 will be intravenously administered to subjects at the site. Administration will be documented in the source documents and reported in the CRF. The date and time of each bolus dose administered in the clinic, and the start / stop date and time of each infusion 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.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Ibuprofen, at doses of ≤800 mg/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the Medical Monitor.

7.8. Prohibited Medications and Non-Drug Therapies

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

The use of paracetamol is not allowed in his study.

7.9. Treatment after the End of the Study

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

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Discontinuation from treatment is "permanent". Once a subject is discontinued, she/he shall not be allowed to restart treatment.

8.1.1. Liver Chemistry Stopping Criteria

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

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

8.1.2. QTc Stopping Criteria

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
    - For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
    - Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *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 electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

In addition a healthy volunteer that meets either bulleted criterion below will be withdrawn from the study:

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

8.1.3. Rechallenge

8.1.3.1. Study Treatment Restart or Rechallenge

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

8.1.4. Additional Stopping Criteria

This section provides vital sign (blood pressure, heart rate), respiratory, oral temperature, and neuropsychiatric criteria for discontinuation of GSK 3335065 infusion. If criteria specified for action here are met, actions must be followed. Study investigators may also decide to discontinue dosing based on their clinical judgement for observations that are not specifically meet these thresholds, if they feel this is appropriate for best ensuring the safety of study subjects.

Blood Pressure:

- Resting semi-recumbent systolic blood pressure (SBP) of ≤80 mmHg that is confirmed (median of 3 measurements, and at least 20% decrease from baseline) and sustained for ≥20min with or without symptoms of hypotension. Sustained is defined as persistent (threshold is met or exceeded on all rechecks over a 20 min period; minimum of 3 consecutive measurements over a 20 min interval)
- Resting semi-recumbent SBP ≥80 mmHg but ≤100 mHg that is confirmed (median of 3 measurements) and sustained if associated with symptoms of hypotension (e.g. fainting, lightheadedness, dizziness, anxiety)
- Hypotension requiring intervention such as Trendelenburg position w/wo fluid rescucitation
- Resting semi-recumbent SBP ≥180 mmHg that is confirmed (median of 3 measurements, and at least 20% increase from baseline with or without symptoms of hypertension (e.g. headaches, lightheadedness, anxiety)

Heart Rate:

- Tachycardia (resting semi-recumbent heart rate >100bpm) of any duration associated with symptoms that the study investigator considers potentially associated with cardiac ischemia and/or hemodynamic compromise. Concerning symptoms might include chest pain, shortness of breath or lightheadedness.
- Resting semi-recumbent heart rate of ≥130 bpm that is confirmed (median of 3 measurements) and sustained. Sustained is defined as persistent (threshold is met or exceeded on all rechecks over a 20 min period; minimum of 3 consecutive measurements over a 10 min interval).
- Increase in resting semin-recumbent heart rate ≥60 bpm from the predose baseline (median of 3 measurements and sustained).

If a vital sign threshold is exceeded which may result in discontinuation as defined above, the vital sign should immediately be repeated twice (i.e 3 measurements within approximately 5 minutes) and the median value will be used at that time point. If the median value exceeds the threshold, it will be considered confirmed that the value exceeded the potential discontinuation threshold and the subject must be discontinued.

Cardiac Troponin/ B-type Natriuretic Peptide (BNP):

If the local cardiac troponin (cTn) is >ULN or B-type Natriuretic Peptide (BNP) is >2x ULN for the assay, that subject will undergo repeat cTN or BNP testing and urgent evaluation if symptoms suggestive of cardiac ischemia or heart failure are present, and a transthoracic echocardiogram will be performed.
Asymptomatic volunteers: If the repeat value is within the normal range, the subject may continue in the study with close follow-up of symptoms. If the repeat value for cTn is >ULN or BNP is >2x ULN the subject must be discontinued from the study.
Symptomatic volunteers: Cardiology consultation will be obtained immediately for any subject with new signs or symptoms suggestive of cardiac ischemia or heart failure and the subject must be discontinued from the study. Concerning symptoms may include:

- chest pain,
- increased shortness of breath
- rapid or irregular heartbeat
- diaphoresis
- anxiety
- fatigue, tiredness
- confusion

Tympanic Temperature:

- Confirmed (median of 3 measurements) ≥38.5ºC at any time point between bolus/infusion initiation and 1 hour after completion of the dosing.

Respiratory Issues:

- In case the subject complains of dyspnea or shortness of breath, or if there is objective evidence of bronchospams or other respiratory difficulty, the subject will be immediately evaluated and if confirmed the subject must be discontinued from the study.

Neuropsychiatric Issues:

Suicidal Ideation and Behaviour:
If Columbia Suicide Severity Rating Scale (C-SSRS) and/or PSRAE assessments indicate a clinically relevant increase in suicidal ideation or behavior or a subject shows new signs or symptoms during the infusion period suggestive of an increase in suicidal ideation and behavior psychiatric consultation will be obtained and the Sponsor's Medical Monitor should be contacted. Discontinuation is mandated in case the patient scores "yes" on item four or item five of the Suicidal Ideation Section of the Columbia Suicide Severity Rating Scale (C-SSRS) or "yes" on any item of the Suicidal Behaviour Section. In addition, study investigators may also decide to discontinue dosing based on their clinical judgment for observations that do not specifically meet these thresholds, if they feel this is appropriate for best ensuring the safety of study subjects.

Cognitive Safety:

- If cognitive test results (i.e. fingertapping test [FTT], 6-item cognitive impairment test [6-CIT], Neuropsychiatric Inventory [NPI]) indicate a clinically significant

effect of GSK3335065 on cognitive safety or the subject shows new signs or symptoms during the infusion period suggestive of an effect on cognitive safety, psychiatric consultation should be obtained and the Sponsor's Medical Monitor should be contacted. If the increased risk can be confirmed the subject must be discontinued from the study.

In case there is objective evidence that a subject is in psychological distress, the subject will be immediately evaluated and the subject must be discontinued from the study if the investigators based on their clinical evaluation feel this is appropriate for best ensuring the safety of study subjects. Concerning symptoms might include:

- Nervousness,
- Anxiety, irritability
- Sudden worsening of mood
- Sudden outbursts of anger ("anger attacks")
- Sudden panic or anxiety attacks
- Agitation
- Feeling unreal or detached
- Confusion or trouble concentrating
- Forgetfulness or problems with memory
- Mood swings
- Trouble sleeping, insomnia
- Fatigue, tiredness

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the Schedule of Activities ((SOA) Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.
- 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 (PK then PD)

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Efficacy Assessments

There is no efficacy assessment in this study.

9.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (refer to Section 8).

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

- All SAEs will be collected from admissions at the time points specified in the SoA (Section 2).
- All AEs will be collected from admission until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non serious AEs of special interest (as defined in Section 12.4 will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4.

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.3. Treatment of Overdose

For this study, any dose of GSK3335065 greater than the agreed dose for a particular cohort, dosing session or study part will be considered as an overdose.

GSK does not recommend specific treatment for an overdose

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

1. Contact the Medical Monitor immediately
2. Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until GSK3335065 can no longer be detected systemically (at least 8 days which is equivalent to 5 times the observed preliminary half life of ~35 hours for GSK3335065).
3. Obtain a plasma sample for pharmacokinetic (PK) analysis within 1 days 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 CRF.

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.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities ((SOA) Section 2).

9.4.1. Physical Examinations

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

9.4.2. Vital Signs

- Tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in semi-recumbent with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 3 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute) at screening and pre-dose. The average of the 3 blood pressure readings will be recorded on the CRF.

9.4.3. Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (Section 2.2 and Section 2.1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and [QTc] intervals. Refer to Section 8.1.2 for [QTc] withdrawal criteria and additional [QTc] readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.

- ECG measurement should be preceded by at least 5 minutes rest semi-recumbent

9.4.4. Continuous ECG monitoring

- Continuous ECG monitoring (using telemetry or a bedside ECG monitor) will be performed as described in the Schedule of Activities. Any abnormal findings on continuous ECG monitoring should be confirmed by a 12-lead ECG.

9.4.5. Echocardiogram

- A transthoracic echocardiogram will be performed as specified in the Time and Events table. Images will be obtained in standard views, the time to acquire images should not exceed approximately 45 min.

9.4.6. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

9.4.7. Suicidal Risk and Cognitive Safety Monitoring

GSK3335065 is essentially excluded from the CNS but several of the metabolites in the KYN pathway cross the blood brain barrier and therefore peripheral inhibition of KMO would be expected to alter central levels. Indeed, at a dose that generated systemic concentrations equivalent to a high dose used in rat exploratory dose escalation studies

(10x cellular Ki), kynurenic acid (KYNA) levels increased >10-fold above baseline in rats. No observations indicative of an effect on behaviour have been seen in the rat or dog following repeat dosing with GSK3335065. An Irwin study has been conducted as part of the standard safety pharmacology package to support FTIH, and there were no effects on peripheral or central nervous system activity, body temperature or locomotor activity. However, KYNA is known to be neurologically active with increased levels leading to a decrease in excitatory neurotransmitters such as glutamate, dopamine and acetylcholine in humans, and KYNA is increased in cerebrospinal fluid (CSF) of patients with schizophrenia or bipolar disorder type 1 with psychotic features.

9.4.7.1. Columbia Suicide Severity Rating Scale (C-SSRS)

There has been some concern that elevated central KYNA levels may be associated with an increased risk of suicidal thinking or behaviour when given to human subjects. GSK considers it important to monitor for such events before or during clinical studies with compounds such as this. Subjects being treated with GSK3335065 should be assessed and monitored appropriately for suicidality and unusual changes in behaviour.

Baseline assessment of suicidal ideation and behaviour and treatment emergent suicidal ideation and behaviour will be assessed during this study using the Columbia Suicide Severity Rating Scale (C-SSRS). C-SSRS is a brief questionnaire designed to assess severity and change in suicidality by integrating both behaviour and ideation. The C-SSRS was designed to address the need for a summary measure to track changes in the severity/intensity of suicidality across both clinical settings and treatment trials. It assesses intensity of ideation (a potentially important marker of severity), specifically asking about frequency, duration, intrusiveness, controllability and deterrents. In addition, both the modal and most severe forms of ideation are captured. This procedure should be performed in subjects receiving continuous infusion of GSK3335065 over 7 days (Part B and Part C cohort 8) at times outlined in the Schedule of Activities (Section 2.2). The questionnaires should be completed, by a health professional trained in this procedure following discussions with the subject at each visit. If additional information is provided by a caregiver, relative, friend etc then this information should also be taken into account when completing the questionnaire. Any suicide attempts or Investigator concerns about issues raised during the completion of this questionnaire should be discussed immediately (with 24 h) with the GlaxoSmithKline Medical Monitor.

Families and caregivers of participants being treated with GSK3335065 should be alerted about the need to monitor participants for the emergence of unusual changes in behaviour, as well as the emergence of suicidal ideation and behaviour and to report such symptoms immediately to the study investigator.

9.4.7.2. Possible Suicide Related Adverse Event(s) (PSRAE)

The possibly suicide related adverse event(s) (PSRAE) eCRF page should be completed if there is an occurrence of an AE which in the Investigators judgment is possibly suicide related. This may occur but is not limited to an event that involved suicidal ideation, a preparatory act towards imminent suicidal behavior a suicide attempt, or a completed suicide. Events identified via the C-SSRS should be reported in the PSRAE eCRF page. The Investigator will record information on the eCRF PSRAE form (and AE or SAE

form as appropriate) and submit to the Sponsor as soon as possible after learning of an event.

9.4.7.3. Neuropsychiatric Inventory (NPI)

As described above, tryptophan metabolites can act as neurotransmitters that potentially could also lead to impairment in cognitive function. However this effect is likely to be limited to the duration of treatment and, even if observed, this is not seen as a major liability in the target patient population.

The NPI is an assessment of the frequency and severity of behavioral disturbances. The inventory comprises 10 dimensions: delusions, hallucinations, dysphoria, apathy, euphoria, disinhibition, aggressiveness and agitation, irritability, anxiety, aberrant motor activity (Cummings et al, 1994). Each dimension has a screening question with between 7 and 9 follow-up questions relating to symptoms, asked if the answer to the screening question is 'yes'. The NPI takes approximately 10 minutes for the investigator to administer by talking to the caregiver.

9.4.7.4. Six-Item Cognitive Impairment Test (6-CIT)

The 6-CIT is a brief neuropsychological screening test for cognitive impairment taking less than 5 minutes (three orientation items, count backwards from 20, months of the year in reverse order, and learn an address).

9.4.7.5. Finger Tapping Test (FTT)

The FTT is a quick neuropsychological test that examines motor functioning, specifically, motor speed and lateralized coordination are assessed through this test

9.4.8. Assessment at infusion site

The infusion site will be assessed at various times up to 36 hours post-dose using a 0–3 scale as follows: Grade 0=none; Grade 1=pain or itching or erythema; Grade 2=pain or swelling, with inflammation or phlebitis; Grade 3=ulceration or necrosis.

9.5. Pharmacokinetics

9.5.1. Blood Sample Collection

Blood samples for pharmacokinetic (PK) analysis of GSK3335065 in plasma will be collected at the time points indicated below. 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.

Processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

Part A (cohort 1 &2) and Part C (cohort 7):

1 mL of blood will be collected into Ethylenediaminetetraacetic acid (EDTA) tubes and processed to plasma for pharmacokinetic analysis, at the following time-points:

1 hr pre-dose, then 6 mins, 12 mins, 15 mins, 20 mins, 30 mins 1 hr, 2 hr, 3 hr, 6 hr, 9 hr, 12 hr, 15 hr, 18 hr, 24 hr, 30 hr, 36 hr, 42 hr, 48 hr, 60 hr and 72 hr post-dose.

Part A (cohort 3 - 8) and Part C (cohort 13):

1 mL of blood will be collected into EDTA tubes and processed to plasma for pharmacokinetic analysis, at the following time-points:

1 hr pre-dose, then 6 mins, 12 mins, 15 mins, 20 mins, 30 mins 1 hr, 2 hr, 3 hr, 6 hr, 9 hr, 12 hr, 15 hr, 18 hr, 24 hr, 30 hr, 36 hr, 42 hr, 48 hr, 60 hr,72 hr, 84 hr, 96 hr, 108 hr, 120 hr, 132 hr, 144 hr, 156 hr, 168 hr post-dose.

Blood samples for PK analysis may also be taken during the follow up visit: approximately 7 to 14 days after subjects have left the unit.

Part B (cohort 9-12) & C (cohort 14):

2 mL of blood will be collected into EDTA tubes and processed to plasma for pharmacokinetic analysis, at all time-points specified below, except the ones in **bold**. These time-points will collects **4 mL** in EDTA tubes.

Study Day	PK sampling timepoint(s)
1	-1 hr, -30 mins, 6 mins, 15 mins, 30 mins, 1 hr, 2 hr, 3 hr, 4.5 hr, 6 hr, **9 hr, 12 hr, 18 hr.**
2	**Morning sample** (around 08:00am) taken before first meal of the day
3-7	Morning sample (around 08:00am) taken before first meal of the day
8	Immediately after end of infusion, 6 hrs and 12 hrs following infusion termination
9	18 hrs, 24 hrs and 36 hrs following infusion termination
10	42 hrs, 48 hrs and 60 hrs following infusion termination
11	72 hrs, 84 hrs following infusion termination
12	96 hrs, 108 hrs following infusion termination
13	120 hrs, 132 hrs following infusion termination
14	144 hrs, 156 hrs following infusion termination
15	168hrs following infusion termination

Details of PK blood sample processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

9.5.2. Urine Sample Collection

In this study, urine samples for analysis of GSK3335065 and its metabolites will be collected at the time points listed below. The timing of urine samples may be altered and/or samples may be obtained at additional time points to ensure thorough PK monitoring.

Immediately prior to dosing on Day 1, each subject will be instructed to void their bladder; this first void will be discarded. Urine in this void samples can be used as the 'pre-dose sample'

Study Part	Sample Required	Collection Details
A	Pre-dose, 20 mL	Collected at anytime between D-1 and D1 (prior to dosing)
A	400 mL	Urine collection for all time points listed in the Time and Events Tables will begin immediately following dose administration for each dosing session. The total volume and collection duration will be recorded for each subject. Samples within the time period **0-24 hours** post dose will be pooled per subject and a 400 mL aliquot taken from the bulk collection once the total volume of the 0-24 hr collection has been recorded.
B	Pre-Dose, 20 mL	Collected at anytime between D-1 and D1 (prior to dosing)
B	400 mL	Urine collection for all time points listed in the Time and Events Tables will begin immediately following dose administration. The volume and time will be recorded for each urine sample collected and for each subject. Samples within the time period **48-72** hours will be pooled and a 400 mL aliquot taken.

Details of urine sample processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

9.6. Enterotest – Bile Sample Collection

Bile samples will be collected on Day 3 for the analysis of GSK3335065 and any metabolites for volunteers in the cohort expected to receive the highest dose level (predicted to be cohort 12 [dose level 4]) of Part B only.

Bile fluid is recovered on a highly absorbent nylon line which is contained within a weighted gelatin capsule. The 140 cm line unwinds after capsule swallowing, the capsule dissolves in the stomach and the line then passes into the duodenum. During withdrawal, the weighted section of the capsule separates from the line and passes in the stool. Additional details of bile Entero-test sample collection, processing, storage, and shipping procedures will be provided in the SRM.

9.6.1. Sample Analysis

Plasma PK analysis will be performed under the control of PTS-Bioanalysis, Immunogenicity & Biomarkers (BIB), GlaxoSmithKline, the details of which will be included in the Study Reference Manual (SRM). Concentrations of GSK3335065 will be determined in plasma samples using the currently approved bioanalytical methodology. Once the plasma has been analyzed for GSK3335065 any remaining plasma may be analyzed for other compound-related metabolites under a separate PTS, GSK protocol.

Urine and bile samples will similarly be analysed under a separate PTS-GSK protocol. The results of these analyses will be reported separately.

9.7. Biomarker(s)/Pharmacodynamics Markers

Blood samples for pharmacodynamic (PD) analysis will be collected at the time points indicated below. The actual date and time of each blood sample collection will be recorded. The timing of PD samples may be altered and/or PD samples may be obtained at additional time points to ensure thorough PD monitoring.

2 mL of blood will be collected into EDTA tubes and processed to plasma for pharmacodynamic analysis.

Part A

Day -1, biomarker sampling on the day before dosing: , which correspond approximately to -16 hr, -14 hr, -12 hr and -10 hr prior to dosing.

Day 1, biomarker sampling on the day of dosing: which correspond approximately to -2 hr and within 30 minutes of dosing.

Day 1, biomarker sampling post dose: 6 mins, 15 mins, 30 mins, 1 hr, 1.5 hr, 2 hr, 3 hr, 4.5 hr, 6 hr, 9 hr, 12 hr, 15 hr, 18 hr, 24 hr, 30 hr, 36 hr, 42 hr, 48 hr, 60 hr,72 hr, 84 hr, 96 hr, 108 hr, 120 hr, 132 hr, 144 hr, 156 hr, 168 hr post-dose.

Blood samples for PD analysis may also be taken during the follow up visit: approximately 7 to 14 days after subjects have left the unit.

Part B & C

Study Day	PD sampling timepoint(s)
1	-1 hr, - 30 mins, 6 mins, 15 mins, 30 mins, 1 hr, 2 hr, 3 hr, 4.5 hr, 6 hr, 9 hr, 12 hr, 18 hr.
2-7	Morning sample (08:00am) prior provision of meal
8	6 hrs and 12 hrs following infusion termination
9	18 hrs, 24 hrs and 36 hrs following infusion termination
10	42 hrs, 48 hrs and 60 hrs following infusion termination
11	72 hrs, 84hrs following infusion termination
12	96 hrs, 108 hrs following infusion termination
13	120 hrs, 132 hrs following infusion termination
14	144 hrs, 156 hrs following infusion termination
15	168hrs, 180 hrs following infusion termination

Additional 3HK samples may be withdrawn based on emerging data.

9.7.1. Sample Analysis

Plasma analysis for biomarker concentrations will be performed under the control of PTS-BIB GlaxoSmithKline, the details of which will be included in the Study Reference Manual (SRM). Blood samples will be collected to measure KMO enzyme inhibition by looking at levels of the biomarkers Kynurenine (Kyn) and 3-hydroxykynurenine (3-HK) as secondary endpoints.

In addition, plasma concentrations of the other tryptophan pathway biomarkers may also be determined which may include (but not be limited to): tryptophan, kynurenic acid, anthranilic acid, 3- hydroxyanthranilic acid, quinolic acid and xanthurenic acid. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma has been analyzed for some or all of the tryptophan pathway metabolites/biomarkers as listed above, any remaining plasma may be analyzed for other relevant analytes and the results reported under a separate GlaxoSmithKline protocol.

9.8. Genetics

A 6 mL sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 6 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Study Reference Manual.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

The main purpose of this study is to assess the safety and tolerability of single and repeated intravenous doses of GSK3335065 in healthy volunteers. No formal hypotheses are being tested and no statistical testing will be performed on the safety data.

10.2. Sample Size Considerations

10.2.1. Sample Size Assumptions

Sufficient subjects will be randomised to achieve a total of 112 evaluable subjects (Part A: 64 subjects, part B: 32 subjects and part C: 16 subjects). Part A began comprised of 2 cohorts each with 8 healthy male subjects (6 active, 2 placebo) in a single ascending dose escalation cross-over design. Following preliminary PK data, Part A will be in a parallel design with 6 additional cohorts and 8 healthy male subjects in each cohort (6 active, 2 placebo). Part B will comprise of 4 cohorts each with 8 healthy male subjects (6 active, 2 placebo) in a multiple ascending dose escalation. Part C will be comprised of 2 cohorts each with 8 subjects that are WONCBP (6 active, 2 placebo) in a single dose and multiple dose. Additional subjects or cohorts may be enrolled to allow for evaluation of additional dose levels.

If a subject prematurely discontinues the study in Part B or Part C Cohort 8 of the study, additional replacement subjects may be randomised and assigned to the same treatment sequence at the discretion of the Sponsor in order to achieve 112 evaluable subjects.

No statistical techniques were used to determine the sample size. The sample size is based upon practical considerations for an FTIH study.

10.2.2. Sample Size Sensitivity

No sample size sensitivity was performed.

10.2.3. Sample Size Re-estimation or Adjustment

A sample size re-estimation is not planned.

10.3. Data Analysis Considerations

10.3.1. Analysis Populations

The 'All Subjects' population will be defined as all subjects randomised to treatment who receive at least one dose of study treatment. This population will be used for all tables, figures, listings and analyses unless otherwise stated.

The 'PK Concentration' population will be defined as all subjects for whom a pharmacokinetic sample was obtained and analysed. This population will be used for all summaries of PK concentration data.

The 'PK Parameter' population will be defined as all subjects in the 'PK Concentration' population who provide pharmacokinetic parameters. This population will be used for all summaries and analyses of pharmacokinetic parameters.

All analyses will be based on the actual treatment each subject received. Any departures from the planned treatment according to the randomization schedule will be documented in the CSR.

10.3.2. Treatment Comparisons

10.3.2.1. Primary Comparisons of Interest

There will be no direct comparisons between treatment groups for the safety data.

10.3.2.2. Other Comparisons of Interest

To assess the effect of GSK3335065 on the pharmacodynamic biomarkers and exploratory biomarkers, all active treatment groups will be compared to placebo.

10.3.3. Interim Analysis

Informal data review will be performed between dose escalation of each cohort in part A and between dose escalation in part B (multiple dose ascending phase) to support (i) whether the dose should be escalated and (ii) the next dose level. PK and safety data (including any available PD data) will be reviewed. The GSK pharmacokineticist will extract PK data (including treatment information) from SMS2000 via PKHARP. Standard concentration-time graphs will be derived for each subject by the GSK pharmacokineticist. These parameters will be summarised by each dose level and will be overlaid with initial model's predictions for a comparison. The safety data will be listed and presented for each individual subject by treatment group.

A formal interim analysis are also planned to occur after the completion of Part A. All available data including PK, safety and, if available, selected PD data will be included in this interim analysis. Interim analysis will allow a preliminary assessment of all available data. As this study is double-blind (Sponsor unblinded), the review team will be unblinded with respect to the treatment each subject received. Final data base lock and final analysis will occur when all data are cleaned and entered to database.

10.3.4. Key Elements of Analysis Plan

Final analysis will be performed after the completion of the study and final database lock. Data will be listed and summarized according to GlaxoSmithKline reporting standards, where applicable.

Unless stated otherwise, descriptive summaries will include n, mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum, 95% confidence interval (CI) for non-transformed data with continuous variables. For log-transformed data this will be geometric means with associated 95% confidence interval (CI), and the between-subject CV (%CVb) for continuous variables, whereas n and percent will be used as summary statistics for categorical variables.

Complete details of the planned statistical analysis will be given in the Reporting and Analysis Plan (RAP). Any deviation from the planned analysis will be documented in the final study report.

Placebo data from all doses will be pooled by Part for the summary tables.

10.3.5. Safety Analyses

Safety data will be presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. No formal statistical analysis of the safety data will be conducted.

10.3.5.1. Extent of Exposure

The dates and times, the infusion rate, infusion volume of treatment dosing will be listed to indicate exposure to study drug.

10.3.5.2. Adverse Events

Adverse events will be coded using the MedDRA coding dictionary, to give a preferred term and a system organ class, which will then be used when summarising the data. The verbatim term will be used in the listings.

The incidence of all adverse events (regardless of causality) will be summarised for each treatment group and sorted by system organ class and then by descending total incidence (i.e. across all treatment groups). System organ classes will not be presented when the overall incidence for any adverse event within the particular system is zero. If the total incidence for any two or more adverse events is equal, the events will be presented in alphabetical order. In addition, adverse events considered possibly drug-related by the investigator will be summarised separately.

Separate summaries of serious adverse events and adverse events leading to permanent discontinuation of study treatment or withdrawal from the study will be produced.

10.3.5.3. Clinical Laboratory Evaluation

All haematology, urinalysis and clinical chemistry laboratory values will be flagged high or low relative to their reported normal ranges. Separate listings describing subjects with haematology and clinical chemistry laboratory values with values of potential clinical concern will be produced.

10.3.5.4. Other Safety Measures

The ECG interval data (PR, QRS, QT, QTc and ventricular rate) and vital signs data (systolic blood pressure, diastolic blood pressure and heart rate) will be listed and summarised by treatment group and planned relative time. ECG findings will also be listed. Any vital signs with values of potential clinical concern will be listed.

10.3.6. Pharmacokinetic Analyses

Individual, mean and median plasma GSK3335065 concentration-time profiles will be plotted by treatment (linear and semi-linear profiles). Blood sampling times will be related to the start of the infusion procedure. Actual sampling times will be used to calculate all of the non-compartmental pharmacokinetic parameters. Individual concentrations of GSK3335065 in plasma will be listed and summarised by treatment and nominal time.

Where data permit, the following pharmacokinetic parameters will be determined from the plasma concentration-time data for GSK3335065.

Part A and Cohort 7 (Part C):

- Area under the plasma concentration-time curve from time 0 to last quantifiable concentration (AUC_{0-t}) and extrapolated to infinity ($AUC_{0-\infty}$)
- Time to last observation (t_{last}).
- First observed peak concentrations (C_{max})
- Time to C_{max} (t_{max}).
- Clearance (CL).
- Volume of distribution (V).
- The associated apparent terminal elimination half life ($t_{½}$) will be calculated

Part B and Cohort 8 (Part C):

- Area under the plasma concentration-time curve from time 0 to last quantifiable concentration (AUC_{0-t}) and extrapolated to infinity ($AUC_{0-\infty}$)
- Time to last observation (t_{last}).
- Average concentration (C_{avg})
- Clearance (CL).
- Volume of distribution (V).

The number of data points used to determine the terminal phase will also be listed. Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to standard operating procedure SOP-CPK-001 v01 and using WinNonlin v6.3 by Clinical Pharmacokinetics M&S, Qsci. All derived parameters described above will be listed and summarised according to SOP-BMD-4002 (Standard Statistical Methods for the analysis of Pharmacokinetic Data).

10.3.7. Pharmacodynamic Analyses

The planned PD biomarkers (3HK and KYN) and other secondary/exploratory such as generic inflammatory biomarkers and various metabolites such as: tryptophan, Kynurenic acid, anthranilic acid, 3- hydroxyanthranilic acid, quinolic acid and xanthurenic acid will be listed and summarised by treatment group and planned relative time. An exploratory statistical analysis may be performed on the biomarker data if deemed appropriate. More details will be given in the RAP.

10.3.8. Pharmacokinetics/Pharmacodynamics Analyses

PK/PD analysis of the biomarkers will be conducted between PD biomarkers and PK, other exploratory PK/PD analysis of the biomarkers may be conducted should changes in biomarkers be detected. More details will be provided in the RAP.

10.3.9. Exploratory Analyses

Details of exploratory analysis will be discussed in Report and Analysis Plan (RAP).

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

3-HK	3-hydroxykynurenine
WONCBP	women of non child bearing potential
SAD	Single Ascending Dose
POC	Proof of concept
PK	pharmacokinetics
PD	pharmacodynamics
TRP	Tryptophan
KYN	kynurenine
IDO	indole dioxygenases
KMO	kynurenine-3-monooxygenase
KYNA	kynurenic acid
AA	anthranillic acid
CNS	central nervous system
CV	Cardiovascular
cTnI	cardiac troponin I
BNP	brain natriuretic peptide
ULN	Upper Limit Normal
ECG	Electrocardiogram
BP	Blood Pressure
HR	Heart rate
NOAEL	No Observed Adverse effect level
FTIH	first time in human
Mg	milligram
LFT	Liver Function test
Kg	Kilogram
L	Liter
Hr	Hour
MRSD	maximum recommended starting dose
FDA	Food & Drug Administration
HED	human equivalent dose
MABEL	Minimum Anticipated Biological Effect Level
GLP	Good Laboratory Practice
µg	Microgram
Cmax	Maximum observed plasma concentration
AUC (0-24)	Area under concentration time curve from zero to time 24 h
cTN	Cardiac troponin
nM	Nanomolar
µM	Micromolar
DILI	Drug induced liver injury
BMI	Body Mass Index
ICF	informed consent form
ALT	Alanine transaminase

HBsAg	hepatitis B surface antigen
HBcAb	hepatitis B core antibody
HIV	human immunodeficiency virus
CRF	Case report form
GCSP	Global Clinical Safety and Pharmacovigilance
SSTA	Study Specific Technical Agreement
SRM	Study Reference Manual
MSDS	Material Safety Data Sheet
SBP	systolic blood pressure
mmHg	Millimetres of mercury
C-SSRS	Columbia Suicide Severity Rating Scale
PSRAE	Possibly suicide related Adverse event
FTT	fingertapping test
6-CIT	6-item cognitive impairment tes
NPI	Neuropsychiatric Inventory
IRB	Institutional Review Boards
IEC	Independent Ethics Committees
SUSAR	suspected unexpected serious adverse reactions
CSF	cerebrospinal fluid
SRM	Study Reference Manual
BIB	Bioanalysis, Immunogenicity & Biomarkers
IDSL	Integrated Data Standards Library
MAD	multiple ascending dose
CI	confidence interval
SD	standard deviation
CV	coefficient of variation
RAP	Reporting and Analysis Plan
IDSL	Integrated Data Standards Library
MedRA	Medical Dictionary of Regulatory activities
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 to extrapolated to infinity
T_{last}	Time to last observation
T max	Time to C_{max}
CL	Clearance
V	Volume of distribution
$T_{1/2}$	terminal elimination half life
C_{avg}	Average concentration
mg	Milligrams
EDTA	Ethylenediaminetetraacetic acid

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
MedRA
WinNonlin

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 15 will be performed by the Doctors Laboratory
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 15 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit Reticulocytes	RBC Indices: MCV MCH	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose fasting[2]	Calcium	Alkaline phosphatase	Albumin
	cTnI	BNP		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• HIV • Hepatitis B (HBsAg) • Hepatitis C (Hep C antibody) • FSH and estradiol (as needed in women of non-child bearing potential only)[3] • Alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) The results of each test must be entered into the CRF.			

NOTES :

1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7 and Study Treatment Rechallenge Guidelines All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (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).
2. Glucose fasting at screening and admission.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

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

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.]

Data Protection

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

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

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.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

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

Study and Site Closure

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

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

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

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

Committees Structure

Dose Escalation Committee

The decision to proceed to the next dose level within the study part will be made by a Dose Escalation Committee (DEC) consisting of the Principal Investigator (or appropriate designee), Medical Monitor, GSK Study Team Leader, GSK Pharmacokineticist, a GSK GCSP representative and GSK Statistician. All GSK

personnel including the GSK Statistician and the GSK Pharmacokineticist will remain unblinded throughout the course of the study. The decision to progress to Part B and Part C will also be made by the DEC.

Dose escalation criteria for Part A

In Part A, the decision to proceed to the next dose level will be based on safety and tolerability data obtained up to 8 days post dose (discharge from clinical unit) from at least 6 subjects at the prior dose level. The review data set will at a minimum consist of the listings of any adverse events, flagged vital signs, flagged findings during the cardiac monitoring (telemetry) ECG, flagged findings in 12-lead ECGs and laboratory findings (including LFTs, cTN, BNP). Available PK data from the prior dose level, together with any available PD data will also be reviewed. The highest dose planned in Part A is a 54 mg dose with an expected exposure margin in terms of AUC to the rat NOAEL of 75-fold. Higher doses may be administered if exposures are lower than predicted but the maximum exposure will not exceed the 75-fold exposure margin in terms of AUC to the NOAEL.

Decision to proceed to Part B

Prior to initiation of Part B a review of all available safety, tolerability, PK and PD data from Part A will be conducted and potential changes to the dosing paradigm, safety observation period and assessments will be communicated in a future amendment to the protocol as appropriate.

The first dose level in Part B will be set to ensure that the highest exposures safely achieved in Part A are not expected to be exceeded. The review data set will at a minimum consist of the listings of any adverse events, flagged vital signs, flagged findings during the cardiac monitoring (telemetry) ECG, flagged findings in 12-lead ECGs and laboratory findings (including LFTs, cTN, BNP).

Dose escalation criteria for Part B

In Part B, the decision to proceed to the next dose level will be based on data obtained up to 15 days post dose (discharge from clinical unit) from at least 6 subjects at the prior dose level. The review data set will at a minimum consist of the listings of any adverse events, flagged vital signs, flagged findings during the neuropsychiatric testing, flagged findings during the cardiac monitoring (telemetry) ECG, 12-lead ECGs, laboratory findings (including LFTs, cTN, BNP), available PK, and PD (3HK levels as PD BMx) data. Higher doses may be administered if exposures are lower than predicted but the maximum exposure will not exceed the 75-fold exposure margin in terms of AUC to the NOAEL.

In Part C, doses that have been demonstrated to be safe and well tolearated in Part A and B, respectively will be dosed.

Dose escalation stopping rules

Dose escalation stopping criteria will include the following:

- a serious adverse event (SAE) occurs in one or more subjects receiving GSK3335065 that is considered at least possibly related to the study drug;
- Severe non-serious AEs in two or more subjects in the same cohort receiving GSK3335065 that are considered at least possibly related to the study drug

If any of the above dose escalation stopping rules are met the dose escalation will be temporarily halted and no further subject will be dosed until a full safety review of the data has taken place. Relevant reporting and discussion with the Medical Monitor, relevant GSK personnel, with the Ethics Committee and approval of a substantial amendment will then take place prior to any resumption of dosing.

The trial may be paused during review of newly available preclinical/clinical safety, PK or PD data or other items of interest at any time during trial conduct and no further subject will be dosed until a full safety review of the data has taken place. Relevant reporting and discussion with the Medical Monitor, relevant GSK personnel, with the Ethics Committee, and approval of a substantial amendment will then take place prior to any resumption of dosing.

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. •

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that

leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may

not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

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

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **medical monitor or the SAE coordinator**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in Study Reference Manual.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- Documented tubal ligation

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

2. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will not be allowed in the study.

Contraception Guidance

Male participants

- Male participants with female partners of child-bearing potential are eligible to participate if they agree to ONE of the following during the duration of the study and for at least 2 days from last dose:
    - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
    - Agree to use a male condom plus an additional method of contraception with a failure rate of <1% per year when having penile-vaginal intercourse with a woman of childbearing potential
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of

penile penetration during the duration of the study and for at least 2 days from last dose.

- Refrain from donating sperm for duration of study and for at least 2 days from last dose

Collection of Pregnancy Information

Male participants with partners who become pregnant

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

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to acute pancreatitis and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to acute pancreatitis. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to acute pancreatitis or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on acute pancreatitis (or study treatments of this class) continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

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

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

Phase I liver chemistry stopping criteria and required follow up assessments

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

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

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. 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

12.8. Appendix 8: Cognitive Assessments

12.8.1. Columbia Severity Suicide Rating scale

Please refer to Study Reference Manual.

12.8.2. Neuropsychiatric Inventory (NPI)

Please refer to Study Reference Manual

12.8.3. Six-item Cognitive Impairment Test (6-CIT)

Please refer to Study Reference Manual

12.8.4. Finger Tapping Test (FTT

Please refer to Study Reference Manual.

12.9. Appendix 9: Telemetry Assessments

The following arrhythmias should be considered as alerts on a telemetry monitoring system:

- Sinus bradycardia: HR <40 bpm for > 30 sec in length
- Sinus tachycardia HR > 120 bpm for > 30 sec in length
- Supraventricular Tachycardia (SVT) > 30 seconds (at Rates> 150 bpm)
- Atrial fibrillation (1st documentation, HR <40 or > 150bpm and/or >30sec in length)
- Atrial flutter (1st documentation, HR <40 or > 150bpm and/or >30 sec in length)
- Non- sustained Ventricular Tachycardia ≥ 3 consecutive ectopic beats
- Sustained Ventricular Tachycardia ≥ 30 consecutive ectopic beats
- Torsade de points
- Ventricular fibrillation/flutter
- Wide QRS Tachycardia
- Asystole (>3 seconds)
- 2 °AV Block – mobitz Type I & II (check the wakefulness of the subject)
- Complete AV Block
- Idioventricular Rhythm

12.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

DOCUMENT HISTORY	
Document	**Date**
Amendment 03	*DD-MMM-YYYY*
Amendment 02	*21-August 2017*
Amendment 01	*11-July-2017*
Original Protocol	*14 June 2017*

Amendment 01 11-July-2017

Overall Rationale for the Amendment: Correction of Inconsistency in text between Appendix 5 and protocol body

Section # and Name	Description of Change	Brief Rationale
Section 12.5 Appendix 5	Edits to male contraception and sperm donation restriction timelines to align with the protocol body from 3 months in the appendix to 2 days as in the protocol body	Edits requested by MHRA following review of the protocol

Amendment 02 21-August-2017

Overall Rationale for the Amendment: Change in washout period window in Part A and minor administrative changes.

Section # and Name	Description of Change	Brief Rationale
2.1 Schedule of Assessments	Day 1 LFT needs to be performed	LFT on Day 1 originally not ticked in error.
2.2 Schedule of Assessments	• Urine Drug/Alcohol Breath Test • Clarifcation of 12-Lead ECG timepoints between Day 3 and Day 11.	• Superscript reference incorrect. • Need to specify what timepoints ECGs are collected
5.1.1 Part A: Single Ascending Dose (IV Bolus) in males (Table 3)	Projected washout period: between approximately 10 to 21 days between doses	Washout period between doses in Part A (SAD) projected to be approximately 10-21 days, which is supported by the predicted half life of GSK3335065 (approximately 8 hours) and preclinical safety data. While the washout period between single ascending doses may exceed 21 days it must not fall below 5x predicted half life of the parent (5x8hours = 40hours; half life will be updated based on newly generated PK data). These changes are not expected to affect the safety of the study participants. Until actual $t_{1/2}$ data from humans is available, in order to be conservative, the washout period will be at least 10 days, which is approximately 30X predicted $t_{1/2}$.
6.2 Exlusion Criteria 3 & Section 9.4.3 Electrocardiograms	The two sections are not in alignment as to correct procedure for triplicate ECGs at screening	Triplicate ECGs at screening will be taken no more than 2 mins apart, within 4 minutes
9.5.1 (PK) Blood Sample Collection Part B	Clarification as to which samples need to have 4 or 2 ml collected.	Omitted from protocol in error
9.5.2 Urine Sample Collection	Removed urine collections for Part C	Urinary metabolism data needs only to be generated for Part A & B.