TITLE PAGE

Protocol Title: A Randomized, Placebo Controlled, Double Blind, Single and Repeat Dose Escalation Phase 1 Study to Evaluate Safety, Tolerability, and Pharmacokinetics of GSK3915393 in Healthy Participants and open label assessment of coadministration of GSK3915393 with grapefruit juice and itraconazole on the pharmacokinetics of GSK3915393

Protocol Number: 213585/ Amendment 02

Compound Number or Name: GSK3915393

Brief Title: A Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of GSK3915393 in Healthy Participants and to evaluate the interaction between GSK3915393 and grapefruit juice and itraconazole

Study Phase: Phase 1

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information can be found in the Study Reference Manual.

Regulatory Agency Identifying Number(s) (EudraCT): 2020-003213-36

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SPONSOR SIGNATORY:

Protocol Title: A Randomized, Placebo Controlled, Double Blind, Single and Repeat Dose Escalation Phase 1 Study to Evaluate Safety, Tolerability, and Pharmacokinetics of GSK3915393 in Healthy Participants and open label assessment of coadministration of GSK3915393 with grapefruit juice and itraconazole on the pharmacokinetics of GSK3915393

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Geo Derimanov **Date**

Discovery Medicine Physician Director

GlaxoSmithKline

The signed page is a separate document.

Medical Monitor Name and Contact Information [will be provided separately OR can be found in the Study Reference Manual]

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 2	25-FEB-2021	TMF-11859187
Amendment 1	30-SEP-2020	2020N440921_01
Original Protocol	05-AUG-2020	2020N440921_00

Amendment 2

Overall Rationale for the Amendment:

This amendment is to change Part C of the study from a Gluten Challenge in Celiac patients to a CYP3A4 interaction investigation in healthy participants. Recent *in-vitro* studies have shown that GSK3915393 is a substrate for both intestinal (gut) and hepatic CYP3A4. The CYP3A4 interaction investigation will enable the impact of moderate CYP3A4 inhibitors and CYP3A4 inducers that may be included in future clinical trials to be modelled. Since expression of intestinal CYP3A4 is altered in patients with Celiac Disease (CeD), it is important to understand the predicted pharmacological activity of GSK3915393 in patients. Therefore, this amendment will also determine the impact of intestinal CYP3A4 on the predicted exposure of GSK3915393 in the lamina propria (the site of TG2 activity in CeD).

Owing to the rapid progress of the COVID-19 vaccination programme in the UK, a risk assessment for the concomitant use of a COVID-19 vaccine for subjects in the study has been conducted. There are no contraindications to vaccinating a participant while they are participating in the study as no interaction is expected between COVID-19 vaccinations and GSK3915393. To avoid the risk of side effects from vaccination being captured in the study safety assessment, participants will not be eligible for the study if they have received a COVID-19 vaccination within 1 week of admission or readmission to the clinical unit or are demonstrating signs and symptoms following earlier vaccination.

In addition, the risk management plan at the clinical unit has been updated. Local procedure no longer requires screening COVID-19 tests for studies. Therefore Covid-19 test at screening has been removed from the protocol for all remaining study parts and participants must be negative at admission to the unit and are tested again on discharge.

Section # and Name	Description of Change	Brief Rationale
Protocol Title and Brief Title 1.1 Synopsis 1.2. Schema 1.3.3. Part C SoA 2.1. Study Rationale 2.3.1. Risk Assessment. 2.3.2. Benefit Assessment 2.3.3. Overall Benefit:Risk Conclusion. 3. Objectives and Endpoints 4.1. Overall Design. 4.1.1. Number of Participants 4.1.2. Study Intervention Groups and Duration. 4.2. Scientific Rationale for Study Design 4.2.1 Participant input into Design.	All sections have been updated to amend Part C of the study from a Gluten Challenge in Celiac patients to a CYP3A4 interaction investigation in healthy participants.	Sponsor decision to remove the gluten challenge arm from the study. *In-vitro* data indicates that GSK3915393 is primarily metabolised by CYP3A4 in both hepatic and intestinal microsomes. A new cohort is added to the study to define the extent of metabolism by CYP3A4 in humans by studying the effect of grapefruit juice and itraconazole (ITZ) on the pharmacokinetics of GSK3915393 in healthy volunteers.

Section # and Name	Description of Change	Brief Rationale
4.3.4. Top Dose Selection for Part A 4.3.7. Dose Selection for Part B. 4.3.9 Dose Selection for Part C 5. Study Population. 6.1. Study Intervention(s) Administered 6.3. Measures to Minimize Bias: Randomisation and Blinding. 6.5. Dose Modification 7.1.5. COVID-19 Discontinuation 8.4.4. Itraconazole and Hydroxy Itraconazole PK Plasma collection. 8.6. PD/Biomarkers 9. Statistical Considerations 10.6 Appendix 6: Abbreviations and Trademarks.		

Section # and Name	Description of Change	Brief Rationale
5.2.1. Exclusion criteria.	COVID-19 vaccination exclusion criteria has been added.	To avoid the risk of side effects from vaccination being captured in the study safety assessment, participants will not be eligible for the study if they have received a COVID-19 vaccination within 1 week of admission or readmission to the clinical unit or are demonstrating signs and symptoms following earlier vaccination.
1.3.2. Part B SoA 5.1.1. Inclusion Criteria	COVID-19 test at screening has been removed from the protocol for all remaining study parts.	The risk management plan at the clinical unit has been updated. Local procedure no longer requires screening COVID-19 tests for studies. Participants must be negative at admission.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Randomized, Placebo Controlled, Double Blind, Single and Repeat Dose Escalation Phase 1 Study to Evaluate Safety, Tolerability, and Pharmacokinetics of GSK3915393 in Healthy Participants and open label assessment of coadministration of GSK3915393 with grapefruit juice and itraconazole on the pharmacokinetics of GSK3915393

Brief Title: A Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of GSK3915393 in Healthy Participants and to evaluate the interaction between GSK3915393 and grapefruit juice and itraconazole

Rationale:

Celiac Disease (CeD) is a common T cell-mediated disorder triggered by dietary gluten with a worldwide prevalence estimated at one percent.

The only treatment currently available for CeD is strict adherence to a gluten-free diet (GFD), which improves mucosal villous atrophy and reduces symptoms in most patients. However, gluten cross-contamination has been demonstrated in the majority of patients adhering to a GFD as determined from gliadin immunogenic peptides in urine and feces. A significant number of patients continue to experience symptoms on a GFD and have incomplete mucosal healing.

The enzyme transglutaminase 2 (TG2) is responsible for the generation of deaminated gluten peptides (dGP), the immunodominant antigen that triggers the inflammatory cascade in gastrointestinal tissue which drives mucosal injury. By reducing the generation of dGP, treatment with a TG2 inhibitor should decrease the sensitivity of patients to gluten thereby reducing persistent mucosal damage and symptoms on a GFD and ensuring that inadvertent exposure to gluten will not invoke inflammation or symptoms.

GSK3915393 is being developed as an orally administered inhibitor of TG2 for the treatment of patients with CeD. This study is the first time into human study (FTIH) for GSK3915393. Parts A and B of the study will evaluate the safety, tolerability and pharmacokinetics (PK) of single ascending and repeat oral doses of GSK3915393 in healthy adult participants. In addition, during Part A, the PK following a single intravenous (IV) microdose of GSK3915393 will be evaluated and during Part B, the impact of food on the PK of GSK3915393 will be assessed. Part C will evaluate the impact of co-administration of GSK3915393 with grapefruit juice and itraconazole on the PK of GSK3915393.

The results of this study are intended to identify well tolerated dose(s) of GSK3915393 to be used in further studies. The victim drug interaction potential of GSK3915393 with the CYP3A4 inhibitors, grapefruit juice and itraconazole, will be evaluated. In addition, the results will also inform the anticipated pharmacological effect by enabling prediction of

the concentration of GSK3915393 at the target site of action in patients with Celiac Disease.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
Part A Dose Escalation Single Dose • To evaluate the safety and tolerability of single escalating oral doses of GSK3915393 administered in the fed state in healthy adult participants **Part B Dose Escalation Repeat Dose** • To evaluate the safety and tolerability of repeat escalating oral doses of GSK3915393 twice daily (BID) administered in the fed and fasted state in healthy adult participants **Part C CYP3A4 Victim Interaction** • To characterize the PK profile of IV GSK3915393 administered alone and when co-administered with itraconazole in healthy adult participants • To characterize the PK profile of oral GSK3915393 administered alone and when co-administered with grapefruit juice or with itraconazole in healthy adult participants	**Part A and B** • Occurrence of serious adverse events (SAEs), adverse events (AEs) and treatment related AEs • Occurrence of clinically significant changes in physical examination, vital signs, laboratory parameters, and 12-lead electrocardiogram (ECG) findings. **Part C** • Cmax, Tmax, AUC(0-t), (AUC(0-∞)) and (t1/2) as appropriate
Secondary	
Part A Dose Escalation Single Dose • To characterize the PK profile of single oral doses of GSK3915393 in healthy adult participants • To characterize the PK profile of a single intravenous dose of	**Part A** • Maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (tmax), area under the plasma drug concentration versus time curve from time zero to last quantifiable concentration (AUC(0-t)),

Objectives	Endpoints
GSK3915393 in healthy adult participants • To evaluate the safety and tolerability of single microdose doses of GSK3915393 in healthy adult participants	AUC from time zero to infinity (AUC(0-∞)), and apparent terminal half-life (t1/2) as appropriate. • Clearance (CL) and volume of distribution (Vd) following IV administration and absolute bioavailability (F) of oral administration • Fraction of drug escaping hepatic metabolism (F_H) and product of fraction of drug absorbed (F_A) and fraction of drug escaping gut metabolism (F_G) i.e., (F_A*F_G). • Clinical safety and tolerability data including adverse events (AEs) and serious adverse events (SAEs), clinically significant changes in laboratory values, vital signs and 12 lead electrocardiogram (ECG) readings and physical examinations
Part B Dose Escalation Repeat Dose • To characterize the PK profile of single doses and repeat oral doses of GSK3915393 in healthy adult participants • To assess the impact of food on the PK of GSK3915393 in healthy adult participants • To evaluate time to steady-state	**Part B** • Cmax, Tmax, AUC(0-t), and AUC over the dosing interval AUC(0-τ) • Cmax, Tmax and AUC(0-τ) following 1st dose of day • Pre-dose concentrations on Days 2, 3, 5, 7 and 14
Part C CYP3A4 Victim Interaction • To evaluate the safety and tolerability of a single oral dose of GSK3915393 when administered with grapefruit juice or with itraconazole in healthy adult participants • To evaluate the safety and tolerability of single intravenous dose of GSK3915393 when administered with	**Part C** • Occurrence of serious adverse events (SAEs), adverse events (AEs) and treatment related AEs • Occurrence of clinically significant changes in physical examination, vital signs, laboratory parameters, and 12-lead electrocardiogram (ECG) findings. • F_A F_G and F_H

Objectives	Endpoints
itraconazole in healthy adult participants • To investigate absorption characteristics and first pass clearance of GSK3915393	

Overall Design:

This FTIH study will be a randomized, , single centre trial in three parts. Parts A and B are double blind, placebo controlled and Part C is open label.

1. **Part A** is a crossover design, single-dose (SD), dose escalation study in one cohort of healthy participants. Participants will receive single ascending doses of GSK3915393 or matching placebo as an oral dose in periods 1, 2, 4 and 5 and as a single IV microdose dose of GSK3915393 in period 3. The initial dosing for all periods in which the dose level has been escalated will be staggered so that 2 participants will be dosed as sentinel participants, one with study drug and one with placebo. After approximately 24 hours, and provided the investigator considers the safety and tolerability of the sentinels to be acceptable, the remainder of the participants scheduled for the period may be dosed. Sentinel dosing will not be required in period 3 for the open label IV microdose.

2. **Part B** is a parallel group, 14-day, repeat oral dose, dose escalation study in 3 cohorts of healthy participants. Participants will receive GSK3915393 or matching placebo BID in each of the sequential cohorts. The initial dosing for all periods in which the dose level has been escalated will be staggered so that 2 participants will be dosed as sentinel participants, one with study drug and one with placebo. After at least 4 days, provided the investigator considers the safety and tolerability of the sentinels to be acceptable, the remainder of the participants scheduled for the period may be dosed.

3. **Part C** will be 5 SD periods in healthy adult participants. In period 1 all participants will receive an IV microdose of GSK3915393. In period 2, all participants will receive an IV microdose of GSK3915393 following prior dosing with itraconazole. In periods 3 and 4, participants will receive oral GSK3915393 with or without grapefruit juice in a randomized crossover design. In period 5, all participants will receive oral GSK3915393 following prior dosing with itraconazole.

Brief Summary: The purpose of this study is to assess the safety, tolerability and pharmacokinetics of escalating single and repeat doses of GSK3915393 compared to placebo in healthy participants and to determine the victim drug interaction potential of GSK3915393 with CYP3A4 inhibitors.

Number of Participants:

A sufficient number of participants will be screened to ensure a minimum of 60 participants are eligible to be randomised. Part A will have 12 randomized participants, part B will have 36 randomized participants and part C will have 12 randomized participants. Up to 12 additional participants in part A or part B may be enrolled to allow for evaluation of additional dose levels, up to a maximum 72 randomised participants, excluding replacements.

Intervention Groups and Duration:

Part A

Participants in Part A will participate in 5 dosing periods and will receive 1 oral placebo dose and 4 active doses; 3 as an oral GSK3915393 dose and 1 as a single GSK3915393 IV microdose dose in period 3.

In each dosing period in which the dose level has been escalated and with the exception of period 3 where participants will be receiving the IV microdose, safety data from approximately the first 24 hours of sentinel dosing will be reviewed by the Principal Investigator (PI) prior to commencing dosing of the remainder of the cohort. The starting dose is 15 mg. The decision to proceed to the next dose level will be made by the Dose Escalation Committee based on safety, tolerability and available PK data (at a minimum data up to 24h post dose sample). The IV dose will be 100 µg.

Participants in Part A will be enrolled in the study for at least 14 weeks (up to 28 days screening, 5 in house dose assessment periods of up to 5 days each, 1 washout period between each dose of at least 7 days and up to 14 day follow up period).

Part B

Part B will investigate 3 repeat dose levels in 3 separate cohorts of participants who are not enrolled in part A of the study. Participants will be randomized to receive either GSK3915393 or placebo in each cohort. The starting dose for part B will be selected after review of safety, tolerability and PK data from at least two oral dose levels in part A (IV dosing is not required to make the part B dose decision) and it will be selected such that the predicted maximum daily exposure does not exceed a daily exposure that has been well tolerated in part A. Safety data from at least the first 4 days of sentinel dosing will be reviewed by the PI prior to dosing the remainder of the cohort. Since the half-life of GSK3915393 is predicted to be <2h, PK steady state is expected to be achieved on day 1. The 4 day time frame was selected to provide sufficient duration of dosing to assess safety data, however this duration may be increased based on emerging PK data.

It is planned that participants will be dosed twice daily (approximately 10h and 14h dosing intervals).

Preliminary safety and tolerability from 14 days of dosing and PK data from 7 days of dosing (up to 10h timepoint) for each cohort will be reviewed prior to dose escalation and will be used to determine the dose to be administered in the subsequent cohort. The

decision to proceed to the next dose level will be made by the Dose Escalation Committee based on safety, tolerability and available PK data.

Participants will be enrolled in the study for approximately 8 weeks (up to 28 days screening, approximately 16 days in-house assessment period, and up to 14 day follow up period).

Part C

Participants in Part C will participate in 5 single dosing periods of GSK3915393. In period 1 all participants will receive an IV microdose of GSK3915393. In period 2 all participants will receive oral doses of itraconazole for 6 days and an IV microdose of GSK3915393 on the 4th day of itraconazole dosing. In periods 3 and 4, participants will receive oral GSK3915393 with water or with grapefruit juice in a randomized crossover design. In period 5, all participants will receive oral doses of itraconazole for 6 days and a single oral dose of GSK3915393 on the 4th day of itraconazole dosing. The IV microdose of GSK3915393 will be 100 µg and the oral dose of GSK3915393 will be selected after review of the IV PK data from periods 1 and 2 and will not exceed 20 mg.

Since the half-life of GSK3915393 may be significantly extended upon coadministration with itraconazole, there is increased potential for carryover effects after these regimens compared to the other regimens. For this reason, the itraconazole regimens will be given in fixed periods (2 and 5) rather than in randomized sequence. An extended washout period of at least 7 days is incorporated between periods 2 and 3.

Participants in part C will be enrolled in the study for at least 10 weeks (up to 28 days screening, 5 in house dose assessment periods of between 3 and 6 days each, 1 washout period between each dose and up to 14 day follow up period).

Data Monitoring/ Other Committee: The decision to proceed to the next dose level of GSK3915393 in each Cohort and the oral dose to be used in Part C will be made by the Dose Escalation Committee.

1.2. Schema

Figure 1 Part A – Single Dose

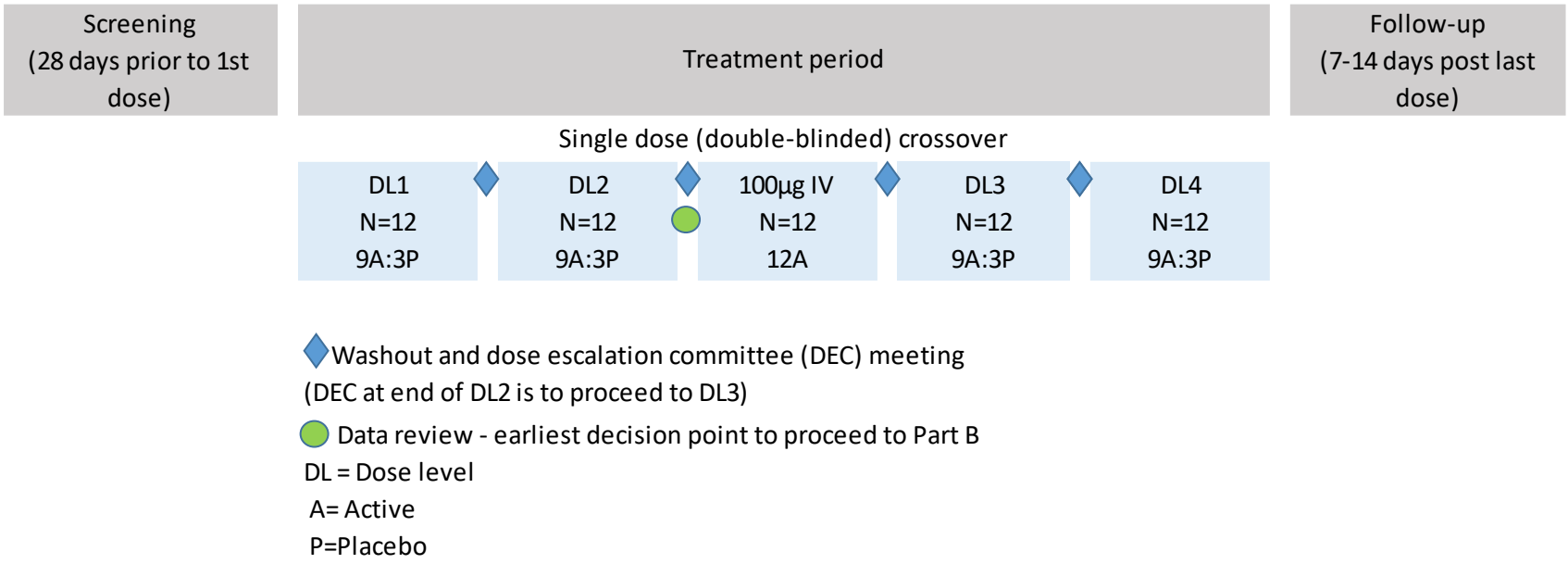
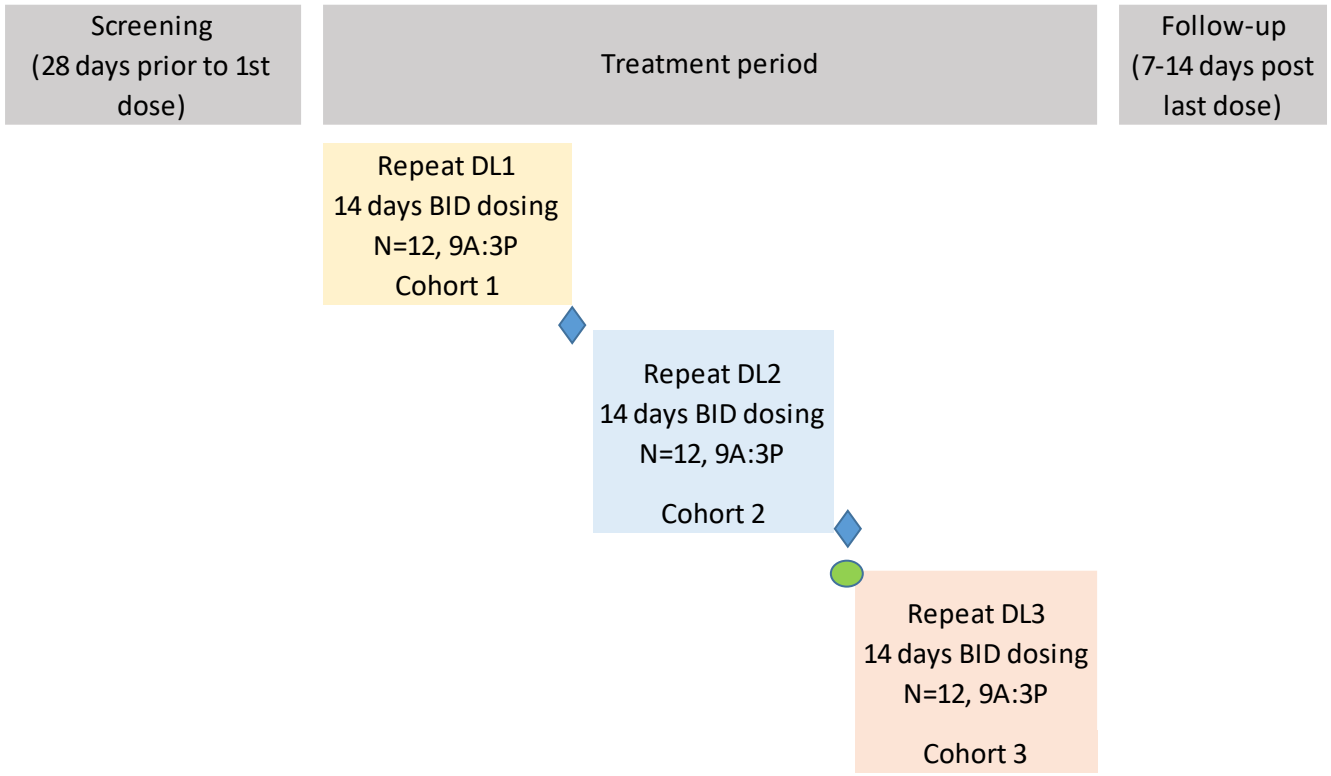
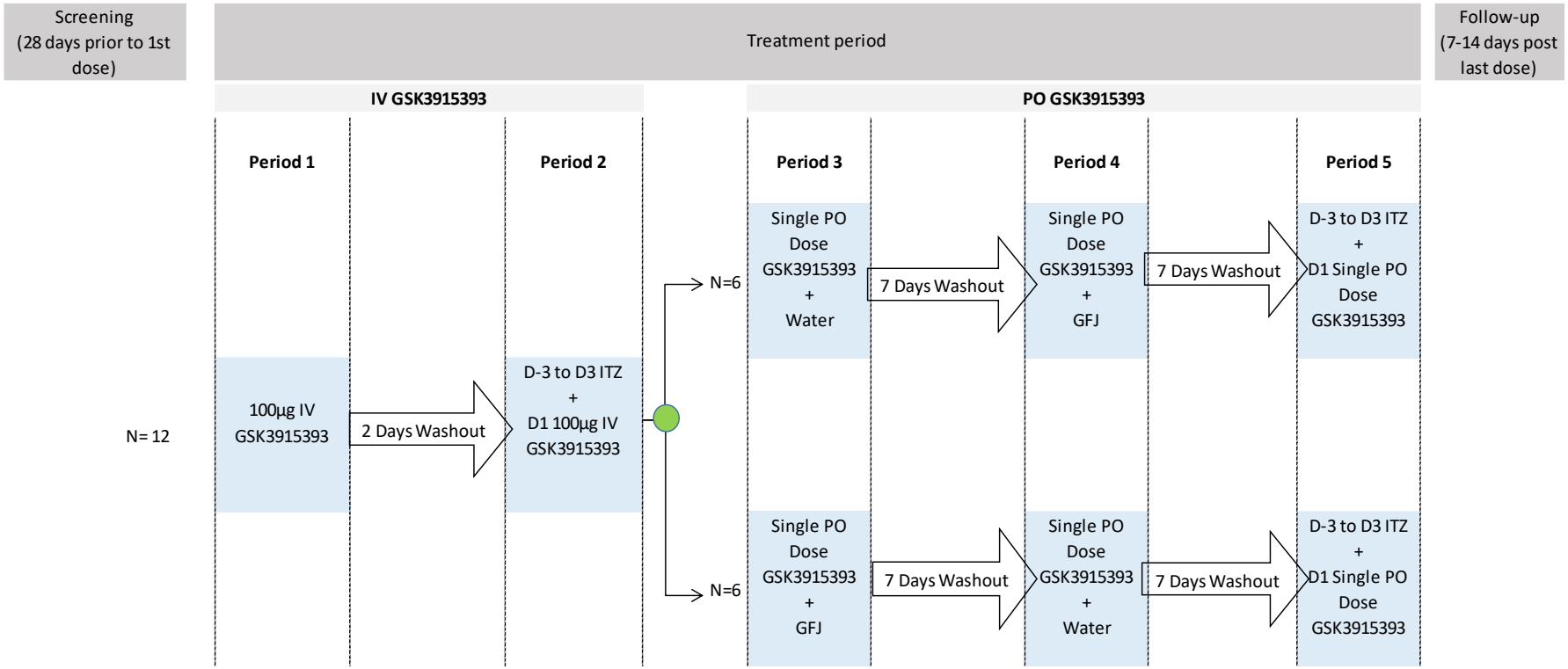


Figure 2 Part B- Repeat Dose



DL=Dose level
A= Active
P=Placebo
BID=Twice daily dosing

Figure 3 Part C –CYP3A4 Victim Interaction



D = Day
GFJ = Grapefruit Juice
ITZ = Itraconazole
N = Number of participants
washout of at least 7 days and IV data review to select PO dose.
NOTE: Washout periods represent the minimum duration required between each period and may be longer for operational purposes.

1.3. Schedule of Activities (SoA)

The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamic and other biomarkers, may be altered during the course of the study based on emerging data or in-stream analyses (e.g., to obtain data closer to the time of peak plasma concentrations) to better characterize safety, PK, PD or efficacy.

Any changes in the timing or addition of time points for any planned study assessments will 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 IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF).

Allowed time windows will be specified in the Study Reference Manual (SRM).

- The Competent Authority (CA) and Ethics Committee (EC) will be informed of any safety issues that constitute a substantial amendment according to individual obligations including alteration of the safety monitoring scheme or amendment of the ICF. The changes will be approved by the CA and/or the EC before implementation as required.

1.3.1. Part A: Single Dose Administration in Healthy Participants

Procedure (Part A)	**Screening (up to 28 days before Day 1)**	**Sessions 1-5**				**Follow-up**	**Early Withdrawal**	**Notes**
		Day -1	**Day 1**	**Day 2**	**Day 3**			
Outpatient visit	X					X	X	
Admission to clinical unit		X						
Inpatient Stay at clinical unit		<---------->						
Discharge from clinical unit					X			
Informed consent	X							
Inclusion and exclusion criteria	X	X						
Demography	X							
Physical examination	X	X			X	X	X	• Full Physical at screening with height and weight. • Brief physical on all other occasions.
Medical/medication/drug/alcohol history	X	X						
Vital signs (BP, HR, temperature, respiratory rate)	X		X			X	X	• Oral dosing - Pre-dose then 30mins, 1, 2, 4,12, 24, 36h post dose • IV dosing – Pre-dose then 30mins, 1, 2, 4,12, 24, 36h from the start of infusion • BP measurements in triplicate and average recorded in CRF.

Procedure (Part A)	**Screening (up to 28 days before Day 1)**	**Sessions 1-5**				**Follow-up**	**Early Withdrawal**	**Notes**
		Day -1	**Day 1**	**Day 2**	**Day 3**			
12-lead ECG	X		X			X	X	• Oral dosing - Pre-dose then 30mins, 1, 2, 4,12, 24, 36h post dose • IV dosing – Pre-dose then 30mins, 1, 2, 4,12, 24, 36h from the start of infusion. • Triplicate ECGs will be obtained no more than 2 minutes apart at screening and pre-dose. • Single measurements will be obtained at all other timepoints.
Telemetry			<---------->					• From 1h pre-dose to 24h.
24h Holter ECG			<--------->					• Oral dosing - From 1h pre-dose to 24h. • IV dosing - 24h Holter ECG will not be recorded in IV dosing period. • ECG extractions at 3 time points prior to dosing and all post-dose PK time points up to and including the 24h timepoint. • Participants will be resting in a semi-recumbent position for at least 15 min at each PK time point for ECG extractions. • When ECG extractions and/or safety ECGs coincide with vital signs assessment and blood draws, procedures should occur in the following order; ECGs vital signs blood draws.
Clinical laboratory (Chemistry, Hematology & UA)	X	X		X		X	X	• Day 2 clinical laboratory is at 24h post Day 1 dosing. • Sample collected following a fast of at least 8 hours.
Serum Pregnancy test	X	X				X		• In women of childbearing potential (WOCBP) only
Estradiol/FSH test	X							• If indicated

Procedure (Part A)	**Screening (up to 28 days before Day 1)**	**Sessions 1-5**				**Follow-up**	**Early Withdrawal**	**Notes**
		Day -1	**Day 1**	**Day 2**	**Day 3**			
Covid-19 test	X							• Covid-19 testing to be performed according to local site procedures. • Minimum testing; screening (not required if subject had a negative SARS-CoV-2 test within 48 hours prior to date of informed consent signature), prior to admission to the unit and prior to discharge from the unit.
Urine Cotinine, Drug & Alcohol test	X	X						
HIV, Hepatitis B and C screening	X							
Study Treatment			X					Oral dosing – Capsules to be swallowed with 240ml of water IV dose to be infused over a 1h period.
Local tolerability at the site of injection			X					IV dose only 5 mins, 20 mins, 1h (end of infusion), 2, 4, and 24h post start of infusion.
Meals		X	X	X	X			• Oral dosing - On Day 1 Participants will fast 8hr and a standard breakfast will be served approximately 30 minutes prior to dosing. • All other meals on Days -1, 1, and 2 will be served as per the site schedule. • IV dosing - All meals will be served as per the site schedule. • Water permitted on an ad lib basis. • Other decaffeinated drinks allowed by the protocol will be permitted except during fasting periods

Procedure (Part A)	**Screening (up to 28 days before Day 1)**	**Sessions 1-5**				**Follow-up**	**Early Withdrawal**	**Notes**
		Day -1	**Day 1**	**Day 2**	**Day 3**			
Blood sample for PK			X					• Oral dosing - Pre-dose within 30 minutes prior to dose then at 20mins, 40mins, 1, 1.5, 2, 3, 4, 6, 10, 12, 14, 24, 36h post dose. • IV dosing - Pre-dose within 30 minutes prior to dose then at the following timepoints post the infusion start time; 20mins, 40mins, 1h (immediately before end of infusion), 1h 5mins, 1h 10mins, 1h 20mins, 1h 40 mins, 2, 2.5, 3, 3.5, 4, 5, 6 h.
Blood sample for Metabolites			X					• Oral dosing - Pre-dose within 30 minutes prior to dose then at 20mins, 40mins, 1, 1.5, 2, 3, 4, 6, 10, 12, 14, 24, 36h post dose. • IV – No samples collected.
Urine collection for Metabolites			<---------->					• Oral dosing - Urine samples will be collected pre-dose and over 0-24 hours for all cohorts. • IV – No samples collected
AE review			<----------					
SAE review	<----------							
Concomitant medication review		<----------						

1.3.2. Part B: Repeat Dose Administration in Healthy Participants

FU= Follow up

EW = Early withdrawal

Procedure (Part B)	Screening (up to 28 days before Day 1)	Day -1	Day 1	Day 2-6	Day 7	Day 8-13	Day 14	Day 15	Day 18-20	FU	EW	Notes
Outpatient Visit	X								X	X	X	
Admission to Clinical Unit		X										
Inpatient stay at Clinical Unit		<----------										
Discharge from unit								X				
Informed Consent	X											
Inclusion and exclusion criteria	X	X										
Demography	X											
Medical/medication/drug/alcohol history	X	X										
Physical Exam	X	X			X			X		X	X	• Full Physical at screening with height and weight. • Brief physical on all other occasions.

Procedure (Part B)	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Day 2-6**	**Day 7**	**Day 8-13**	**Day 14**	**Day 15**	**Day 18-20**	**FU**	**EW**	**Notes**
Vital Signs (BP, HR, Temperature, respiratory rate)	X	X	X	X	X	X	X	X		X	X	• Days 1, 7 and 14; within 1 hour before the start of AM dose (pre-dose) and at 1, 2, 4, 12, and 24 hours after AM dose. • Days, 3, 4, 5, 6, 9, 10, 11, 12, and 13; within 1 hour before the start of AM dose (pre-dose). • BP measurements in triplicate and average recorded in CRF.
12-Lead ECG	X		X	X		X	X			X	X	• Triplicate 12-lead safety ECGs will be obtained no more than 2 minutes apart at screening and within 1 hour before the start of AM dose (pre-dose) on Days 1, 6, 10 and 14 • Single measurements will be obtained at follow up/ EW and Days 1 & 14 at, 30min, 1hr, 2hr, 4hr, 12hr, and 24hr post AM dose.
Telemetry			X				X					• Telemetry from -1h (i.e., 1h pre-dose) to 24h on Day 1 and Day 14
24h Holter ECG			X									• From 1h pre-dose to 24h. • ECG extractions at 3 time points prior to dosing and all post-dose PK time points up to and including the 24 h timepoint. • Participants will be resting in a semi-recumbent position for at least 15 min at each PK time point for ECG extractions. • When ECG extractions and/or safety ECGs coincide with vital signs assessment and blood draws, procedures should occur in the following order; ECGs vital signs blood draws.

Procedure (Part B)	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Day 2-6**	**Day 7**	**Day 8-13**	**Day 14**	**Day 15**	**Day 18-20**	**FU**	**EW**	**Notes**
Clinical Labs (Chemistry, Hematology, and Urinalysis)	X	X		X*	X	X*		X	X*	X	X	• *Day 3, Day 11 and 1 visit only on any day between Day 18-20 • Sample collected following a fast of at least 8 hours.
Serum Pregnancy test	X	X						X		X	X	• In WOCBP only • Day 14 test to be taken after PM dose.
Estradiol/FSH	X											• If indicated
Covid 19 test	X											• Covid-19 testing to be performed according to local site procedures. • Minimum testing; prior to admission to the unit and prior to discharge from the unit.
Urine Cotinine, Drug & Alcohol Test	X	X										
HIV, Hep B, Hep C	X											

Procedure (Part B)	Screening (up to 28 days before Day 1)	Day -1	Day 1	Day 2-6	Day 7	Day 8-13	Day 14	Day 15	Day 18-20	FU	EW	Notes
Meals		X	X	X	X	X	X	X				Breakfast • Participants will fast 8hr and a standard breakfast will be given approximately 30 min pre dose (except on Day 3 and Day 5 (see below)). On day 7 breakfast will be eaten within 20 minutes. • Day 3 - Participants will fast 8hr and will be dosed fasted, a low-fat breakfast will be served approximately 2hr after dosing. • Day 5 - Participants will fast 8hr a high fat breakfast meal will be given approximately 30 min. pre dose & eaten within 20 minutes. Lunch • Day 12 in the cohort undergoing bile sampling - A high fat small lunch meal will be served at approximately 5 hours post dose. • On all other day's lunch and snacks will be served according to the sites schedule. Dinner • On D1 dinner will be served approximately 1 h before PM dose. On all other days the dinner meal will be given approximately 40 mins prior to the PM dose. Fluids • Water permitted on an ad lib basis • Other decaffeinated drinks allowed by the protocol will be permitted except during fasting periods and while the EnteroTracker is in place.

Procedure (Part B)	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Day 2-6**	**Day 7**	**Day 8-13**	**Day 14**	**Day 15**	**Day 18-20**	**FU**	**EW**	**Notes**
Bile sampling						X						• Day 12 • For the highest dose cohort only: EnteroTracker swallowed 2 h post-AM dose. • 5 h post dose a food stimulus will be administered. • After 6 hr post dose the string will be removed.
Dosing			X	X	X	X	X					• BID dosing PM dose to be administered 10 hours after AM dose.
Blood sample for PK			X	X	X		X					• Days 1 and 14 - blood samples will be obtained predose within 30 minutes prior to AM dose and then post AM dose at the following timepoints: 20mins, 40mins, 1h, 1.5h, 2h, 3h, 4h, 6h, 10h (10 mins prior to PM dose), 10h 20 min, 10h 40min, 12h, 12.5h, 13h, 14h, 16h, and 24 h (within 10 minutes or less prior to next AM dose). • Days 3, 5, and 7 - blood samples will be obtained predose within 30 minutes prior to AM dose and then postdose at the following timepoints: 20mins, 40mins, 1h, 1.5h, 2h, 3h, 4h, 6h, 10 (approximately 10 mins prior to PM dose).
Blood sample for Metabolites			X				X					• Blood samples for metabolite profiling will be collected at all PK timepoints up to 24h.
Urine collection for Metabolites			X				X					• Urine samples will be collected pre-dose and over 0-24 hours.

Procedure (Part B)	**Screening (up to 28 days before Day 1)**	**Day -1**	**Day 1**	**Day 2-6**	**Day 7**	**Day 8-13**	**Day 14**	**Day 15**	**Day 18-20**	**FU**	**EW**	**Notes**
4β-hydroxycholesterol sampling			X					X				• Sample to be taken pre-dose on Day 1 in a fasted state. • Sample to be taken at 24hr post AM dose on Day 14. Sample should be in a fasted state.
AE Assessment			<----------								X	
SAE Assessment	<----------										X	
Concomitant Medication Review		<----------									X	

1.3.3. Part C: CYP3A4 Victim Interaction.

FU= Follow up

EW = Early withdrawal

Procedure (Part C)	**Screening (up to 28 days before Day 1)**	**On admission to unit (Day -4 for periods 2 and 5. Day -1 for periods 1, 3 and 4)**	**Periods 2 and 5 only**			**Periods 1 – 5**			**Early Withdrawal**	**FU**	**Notes**
			Day -3	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**			
Outpatient visit	X								X	X	
Inpatient Stay at clinical unit		X	X	X	X	X	X	X			
Informed consent	X										
Inclusion and exclusion criteria	X	X									
Demography	X										
Physical examination	X	X						X	X	X	• Full Physical at screening with height and weight. • Brief physical on all other occasions.
Medical/medication/drug/alcohol history	X	X									

Procedure (Part C)	**Screening (up to 28 days before Day 1)**	**On admission to unit (Day -4 for periods 2 and 5. Day -1 for periods 1, 3 and 4)**	**Periods 2 and 5 only**			**Periods 1 – 5**			**Early Withdrawal**	**FU**	**Notes**
			Day -3	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**			
Vital signs (BP, HR, temperature, respiratory rate)	X	X	X	X	X	X	X	X	X	X	• Periods 2 and 5 days -3 to -1 assessment performed pre itraconazole dosing. • Day 1 IV GSK3915393 dosing – Pre-dose then 30mins, 1, 2, 4,12, 24h from the start of GSK3915393 infusion. • Day 1 oral GSK 3915393 dosing - Pre-dose then 30mins, 1, 2, 4,12, 24h, post dose (timepoints relative to GSK 3915393 dosing) • Period 2 and 5 only 48h post oral GSK 3915393 dose or start of infusion. • BP measurements in triplicate and average recorded in CRF.

Procedure (Part C)	**Screening (up to 28 days before Day 1)**	**On admission to unit (Day -4 for periods 2 and 5. Day -1 for periods 1, 3 and 4)**	**Periods 2 and 5 only**			**Periods 1 – 5**			**Early Withdrawal**	**FU**	**Notes**
			Day -3	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**			
12-lead ECG	X		X			X	X		X	X	• Day -3 ECG performed pre-ITZ dosing • Oral GSK 3915393 dosing - Pre-dose then 30mins, 1, 2, 4,12, 24h, post dose • IV dosing – Pre-dose then 30mins, 1, 2, 4,12, 24h from the start of infusion. • Triplicate ECGs will be obtained no more than 2 minutes apart at screening and pre-dose. • Single measurements will be obtained at all other timepoints.
Clinical laboratory (Chemistry, Hematology & UA)	X	X			X		X	X	X	X	• Periods 1,3,4: D-1 and D2 (24h post D1 oral GSK 3915393 dose or start of infusion) • Periods 2 and 5: D-4, D-1(pre itraconazole dose), and D3 (48h post D1 oral GSK 3915393 dose) • Sample collected following a fast of at least 8 hours.
Serum Pregnancy test	X	X							X	X	• In women of childbearing potential (WOCBP) only
Estradiol/FSH test	X										• If indicated

Procedure (Part C)	**Screening (up to 28 days before Day 1)**	**On admission to unit (Day -4 for periods 2 and 5. Day -1 for periods 1, 3 and 4)**	**Periods 2 and 5 only**			**Periods 1 – 5**			**Early Withdrawal**	**FU**	**Notes**
			Day -3	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**			
Covid-19 test		X					X				• Covid-19 testing to be performed according to local site procedures. • Minimum testing; prior to admission to the unit and prior to discharge from the unit.
Urine Cotinine, Drug & Alcohol test	X	X									
HIV, Hepatitis B and C screening	X										
GSK3915393 dosing						X					Periods 1 and 2: IV GSK 3915393 dose to be infused over a 1h period. Period 2: IV GSK 3915393 dose to start 1 hour after Itraconazole dosing. Period 3 and 4: Capsules of GSK 3915393 to be swallowed with water or with GFJ (volume to be defined in SRM) depending on randomisation. Period 5; Capsules of GSK 3915393 to be swallowed with water 1 hour after Itraconazole dosing.
Local tolerability at site of injection.						X	X				IV dose only 5 mins, 20 mins, 1h (end of infusion), 2, 4, and 24h post start of infusion.

Procedure (Part C)	**Screening (up to 28 days before Day 1)**	**On admission to unit (Day -4 for periods 2 and 5. Day -1 for periods 1, 3 and 4)**	**Periods 2 and 5 only**			**Periods 1 – 5**			**Early Withdrawal**	**FU**	**Notes**
			Day -3	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**			
Itraconazole dosing			X	X	X	X	X	X			Periods 2 and 5 only: Itraconazole to be dosed 1 hr before oral GSK3915393 dosing or start of GSK3915393 IV infusion on Day 1.

Procedure (Part C)	**Screening (up to 28 days before Day 1)**	**On admission to unit (Day -4 for periods 2 and 5. Day -1 for periods 1, 3 and 4)**	**Periods 2 and 5 only**			**Periods 1 – 5**			**Early Withdrawal**	**FU**	**Notes**
			Day -3	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**			
Meals		X	X	X	X	X	X	X			• On day 1 participants will fast 8hr prior to dosing (with Itraconazole or GSK3915393 depending on period) and a standard breakfast will be served approximately 2 hours post GSK3915393 oral dose or start of IV infusion. (The Day 1 fasting requirements may be adjusted based on the emerging data from Part B.) • Itraconazole administration on Days -3 to -1 and Days 2 and 3 may be administered following a standard meal. • All other meals will be served as per the site schedule. • Water permitted on an ad lib basis. • Other decaffeinated drinks allowed by the protocol will be permitted except during fasting periods

Procedure (Part C)	**Screening (up to 28 days before Day 1)**	**On admission to unit (Day -4 for periods 2 and 5. Day -1 for periods 1, 3 and 4)**	**Periods 2 and 5 only**			**Periods 1 – 5**			**Early Withdrawal**	**FU**	**Notes**
			Day -3	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**			
Blood samples for GSK3915393 PK						X	X	X			• **IV dosing**: - Pre-dose (within 30 minutes prior to dose) then at the following timepoints post the infusion start time; 20mins, 40mins, 1h (immediately before end of infusion), 1h 5mins, 1h 10mins, 1h 20mins, 1h 40 mins, 2, 2.5, 3, 3.5, 4, 5, 6, 7, 8, 10 h. • For Period 2, additional PK samples to be collected 12, 24, 36, 48 and 60 h post-dose • **Oral dosing** - Pre-dose within 30 minutes prior to dose then at 20mins, 40mins, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24h post dose. • For Period 5, additional PK samples to be collected 36, 48, and 60 h post-dose . The PK sampling times and number of PK sample may be adjusted based on the observed half-life in period 2

Procedure (Part C)	**Screening (up to 28 days before Day 1)**	**On admission to unit (Day -4 for periods 2 and 5. Day -1 for periods 1, 3 and 4)**	**Periods 2 and 5 only**			**Periods 1 – 5**			**Early Withdrawal**	**FU**	**Notes**
			Day -3	**Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**			
Blood sample for Itraconazole/ Hydroxy Itraconazole PK						X	X				• Periods 2 and 5 only • Pre-dose, 30 min, 1 h (prior to dosing GSK3915393), 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h and 24 h hours post itraconazole dose
AE review			X	X	X	X	X	X	X	X	
SAE review	X	X	X	X	X	X	X	X	X	X	
Concomitant medication review		X	X	X	X	X	X	X	X	X	

2. INTRODUCTION

2.1. Study Rationale

GSK3915393 is being developed as an orally administered inhibitor of the enzyme transglutaminase 2 (TG2) for the treatment of patients with Celiac Disease (CeD). This study is the first time into human study (FTIH) for GSK3915393. Parts A and B of the study will evaluate the safety, tolerability and pharmacokinetics (PK) of single ascending and repeat oral doses of GSK3915393 in healthy adult participants. In addition, during Part A the PK following a single intravenous (IV) microdose of GSK3915393 will be evaluated and during Part B, the impact of food on the PK of GSK3915393 will be assessed. Part C will evaluate the impact of co-administration of GSK3915393 with grapefruit juice and itraconazole on the PK of GSK3915393.

The results of this study are intended to identify well tolerated dose(s) of GSK3915393 to be used in further studies. The victim drug interaction potential of GSK3915393 with CYP3A4 inhibitors will be evaluated. In addition, the results will also inform the anticipated pharmacological effect by enabling prediction of the concentration of GSK3915393 at the target site of action in patients with Celiac Disease.

2.2. Background

CeD is a common T cell-mediated disorder triggered by dietary gluten with a worldwide prevalence estimated at one percent [Ludvigsson, 2014]. Presenting symptoms include abdominal pain, extreme weakness and tiredness, diarrhea, anemia, and vomiting while long-term complications include the development of cancer, such as small intestinal adenocarcinoma and enteropathy-associated T-cell lymphoma.

The only treatment currently available for CeD is strict adherence to a gluten-free diet (GFD), which improves mucosal villous atrophy and reduces symptoms in most patients. However, gluten cross-contamination has been demonstrated in the majority of patients adhering to a GFD as determined from gliadin immunogenic peptides in urine and feces [Stefanolo, 2020] [Syage, 2018]. A significant number of patients continue to experience symptoms on a GFD and have incomplete mucosal healing [Pulido, 2013] [Silvester, 2017]. A normal diet contains 5–15 g gluten/day while the average inadvertent exposure to gluten by celiac patients on a GFD is estimated to be 150–400 mg/day [Syage, 2018]. However daily intake of 50 mg has been shown to be harmful to most patients [Catassi, 2007] suggesting that inadvertent gluten exposure even on a GFD contributes to persistent enteropathy, continued symptoms, and a reduced quality of life [Leffler, 2007] [Hall, 2013] [Pulido, 2013]. Given the challenges in diet adherence and the persistence of mucosal injury and symptoms, there is an urgent need for the development of nondietary therapies for this widespread but overlooked disease.

The ingestion of gluten in genetically predisposed patients leads to inflammation and damage of the small intestine. This is trigged by immunodominant gluten peptides that are deamidated by transglutaminase 2 (TG2) in the lamina propria and bind with very high affinity to disease-associated human leukocyte antigen (HLA) alleles, (DQ2, DQ8).

on antigen presenting cells. This interaction results in activation of antigen specific $CD4^+$ T cells, triggering an inflammatory cascade in gastrointestinal tissue which drives mucosal injury.

By reducing the generation of deamidated gluten peptides (dGP), treatment with a TG2 inhibitor should decrease the sensitivity of patients to gluten thereby reducing persistent mucosal damage and symptoms on a GFD and ensuring that inadvertent exposure to gluten will not invoke inflammation or symptoms.

2.3. Benefit/Risk Assessment

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s)		
Idiosyncratic hepatotoxicity	Covalent binding in hepatic microsomes and the formation of glutathione adducts were observed in vitro. 4-week GLP rat and dog studies have not revealed any adverse effects on the liver. The in vitro findings suggest a potential for immune-mediated idiosyncratic hepatotoxicity. However, idiosyncratic hepatotoxicity is a rare event, and the risk to participants in early clinical trials of short treatment duration is low.	Participants with hepatic disorders or liver laboratory abnormalities will be excluded from the study. Standard monitoring of LFTs will be implemented per Section 1.3, Section 10.2, and Section 10.5. Liver chemistry stopping criteria will be used as per Section 7.1.1 and Section 10.5. Paracetamol usage will be restricted (max 2g/d, 500 mg at a time).
Effect on vital signs (HR and BP)	Increased blood pressure and/or heart rate have been observed in rats and dogs. These changes in vital signs were mild and transient, and the risk of significant changes in heart rate	Monitoring of vital signs will be conducted as per Section 1.3. Stopping criteria related to changes in vital signs will be implemented as per Section 7.1.3.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	or blood pressure in humans is considered low.	
Effect on human embryo/fetus	Preliminary animal embryofetal studies suggest minimal risk for the developing human embryo or fetus. Females of reproductive potential (FRP) can receive GSK3915393 in a clinical study if they use proper contraception as required by the study protocol to avoid pregnancy while taking part in the study.	Pregnant women will not be eligible to participate. Participating FRPs will agree to comply with the study contraception requirements. Participants will be withdrawn from the study if the participants become pregnant during the study Pregnancy tests will be done at screening, before dosing, and after completion of dosing.
Drug Drug Interaction (DDI) (perpetrator) (risk of CYP3A4 induction and CYP3A4 metabolism dependent inhibition)	In vitro, GSK3915393 is a weak CYP3A4 inducer and a CYP3A4 metabolism dependent inhibitor (MDI). Physiologically based pharmacokinetic [PBPK] modelling integrating the in vitro CYP3A4 parameters with the predicted human pharmacokinetics predicts that the risk of significant CYP3A4 inhibition is low at the GSK3915393 doses planned in	Co-medications are prohibited in FTIH except for paracetamol and hormonal contraceptives.,

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	FTIH (<1.6-fold change in AUC with doses up to 160 mg BID with a sensitive CYP3A4 substrate). The risk of loss of efficacy of oral contraceptives due to induction of CYP3A4 is also low (<0.96-fold change in AUC with doses up to 160 mg BID with a sensitive CYP3A4 substrate).	
DDI (victim) in Part C	In vitro, GSK3915393 is metabolised by intestinal and hepatic CYP3A4. Administration of itraconazole, a potent inhibitor of both gut and hepatic CYP3A4, could result in a substantial increase in systemic exposure to GSK3915393 when administered orally due to inhibition of 1st pass CYP3A4 (gut and liver) as well as by inhibition of hepatic CYP3A4 metabolism of systemically available GK3915393.	An IV microdose (100ug) of GSK3915393 will be used to evaluate the impact of itraconazole hepatic inhibition of CYP3A4 on the systemic exposure to GSK3915393. Any observed fold-increase in systemic exposure when IV GSK3915393 is administered with itraconazole, compared to IV GSK3915393 alone, will be used to predict the potential increase in exposure for oral GSK3915393 with the addition of inhibition of first-pass clearance. The oral dose of GSK3915393 in the victim drug interaction study (Part C) will not exceed 20 mg. The oral dose selection will be based on maintaining the predicted exposure to GSK3915393 in the presence

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		of itraconazole to within the systemic exposures already achieved in Parts A and B of the study.
Study Procedures		
Bile Sampling (Entero-Tracker)	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 from the gut in the feces.	The string will be securely taped to the side of the participants face during the collection time to minimize risk of swallowing the entire string. Participants undergoing bile-sampling should not be exposed to magnetic resonance imaging (MRI) for at least 72 hours after swallowing of the capsule device – such time will allow the stainless-steel ball to be expelled into the feces.
Other		
COVID-19	Participation within an inpatient environment may increase risk of contracting COVID-19. Exposure to other participants and staff may increase risk of exposure.	Monitoring of clinical presentation of COVID-19 signs/symptoms. Conduct study at sites which have appropriate mitigation strategies in place.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Itraconazole	Risk of hepatotoxicity. Rare cases of severe hepatotoxicity have been observed with ITZ.	Subjects with liver disease or abnormal liver enzyme tests will be excluded from the study. Subjects with history of liver toxicity from other drugs will be excluded. LFTs will be monitored in the periods when ITZ is administered. Liver chemistry stopping criteria will be used as per Section 7.1.1 and Section 10.5.

2.3.2. Benefit Assessment

The proposed study with GSK3915393 will be conducted in healthy participants; no medical benefit will be derived by volunteer's participation.

2.3.3. Overall Benefit: Risk Conclusion

The potential risks associated with GSK3915393 in study 213585 can be appropriately mitigated by the careful selection of study participants and the proposed safety monitoring procedures. As such, the risk to potential participants is considered low. Safety and tolerability will be evaluated from reported AEs, scheduled physical examinations, vital sign measurements, 12-lead ECGs, and clinical laboratory test results as well as continued observation by clinical staff.

The study will be conducted in an accredited unit set up for dealing with medical emergencies. The in-house periods as detailed in the SoA will allow for continuous medical monitoring for all participants following first dose until discharge. Participants will only be discharged from the unit if the Investigator deems it safe to do so.

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with GSK3915393 are justified by the anticipated benefits that may be afforded by the future development of a new therapy in an area of unmet need.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Part A Dose Escalation Single Dose • To evaluate the safety and tolerability of single escalating oral doses of GSK3915393 administered in the fed state in healthy adult participants **Part B Dose Escalation Repeat Dose** • To evaluate the safety and tolerability of repeat escalating oral doses of GSK3915393 twice daily (BID) administered in the fed and fasted state in healthy adult participants	**Part A and B** • Occurrence of serious adverse events (SAEs), adverse events (AEs) and treatment related AEs • Occurrence of clinically significant changes in physical examination, vital signs, laboratory parameters, and 12-lead electrocardiogram (ECG) findings.

Objectives	Endpoints
Part C CYP3A4 Victim Interaction • To characterize the PK profile of IV GSK3915393 administered alone and when co-administered with itraconazole in healthy adult participants • To characterize the PK profile of oral GSK3915393 administered alone and when co-administered with grapefruit juice or with itraconazole in healthy adult participants	**Part C** • Cmax, Tmax, AUC(0-t), (AUC(0-∞)) and (t1/2) as appropriate
Secondary	
Part A Dose Escalation Single Dose • To characterize the PK profile of single oral doses of GSK3915393 in healthy adult participants • To characterize the PK profile of a single intravenous dose of GSK3915393 in healthy adult participants • To evaluate the safety and tolerability of single microdose doses of GSK3915393 in healthy adult participants	**Part A** • Maximum observed plasma drug concentration (Cmax), time to maximum observed plasma drug concentration (tmax), area under the plasma drug concentration versus time curve from time zero to last quantifiable concentration (AUC(0-t)), AUC from time zero to infinity (AUC(0-∞)), and apparent terminal half-life (t1/2) as appropriate. • Clearance (CL) and volume of distribution (Vd) following IV administration and absolute bioavailability (F) of oral administration • Fraction of drug escaping hepatic metabolism (F_H) and product of fraction of drug absorbed (F_A) and fraction of drug escaping gut metabolism (F_G) i.e., (F_A*F_G). • Clinical safety and tolerability data including adverse events (AEs) and serious adverse events (SAEs), clinically significant changes in laboratory values, vital signs and 12 lead electrocardiogram (ECG) readings and physical examinations
Part B Dose Escalation Repeat Dose	**Part B**

Objectives	Endpoints
• To characterize the PK profile of single doses and repeat oral doses of GSK3915393 in healthy adult participants • To assess the impact of food on the PK of GSK3915393 in healthy adult participants • To evaluate time to steady-state	• Cmax, Tmax, AUC(0-t), and AUC over the dosing interval AUC(0-τ) • Cmax, Tmax and AUC(0-τ) following 1st dose of day • Pre-dose concentrations on Days 2, 3, 5, 7 and 14
Part C CYP3A4 Victim Interaction • To evaluate the safety and tolerability of a single oral dose of GSK3915393 when administered with grapefruit juice or with itraconazole in healthy adult participants • To evaluate the safety and tolerability of single intravenous dose of GSK3915393 when administered with itraconazole in healthy adult participants • To investigate absorption characteristics and first pass clearance of GSK3915393	**Part C** • Occurrence of serious adverse events (SAEs), adverse events (AEs) and treatment related AEs • Occurrence of clinically significant changes in physical examination, vital signs, laboratory parameters, and 12-lead electrocardiogram (ECG) findings. • F_A F_G and F_H
Exploratory	
• To investigate metabolites of GSK3915393 in plasma and urine following oral dosing (Part A and B) • To investigate metabolites of GSK3915393 in duodenal bile following oral dosing (Part B, highest dose only)	• Metabolites of GSK3915393 in plasma and urine. The analyses will be conducted and reported separately • Metabolites of GSK3915393 in duodenal bile. The analyses will be conducted and reported separately

Objectives	Endpoints
• To assess potential effect of repeat doses of GSK3915393 on Cytochrome P450 3A4 (CYP3A4) enzyme activity (Part B). • To assess the effect of single dose GSK3915393 on Holter ECG in healthy volunteers. Waveforms will be stored for potential future analysis.	• Plasma 4β-hydroxycholesterol to cholesterol ratio at pre-treatment and following repeat dosing of GSK3915393 • If analyses conducted: Centrally read ECG parameters and correlation between plasma levels of GSK3915393 and QTc changes

4. STUDY DESIGN

4.1. Overall Design

This FTIH study will be a randomized, single centre trial in three parts. Parts A and B are double blind and placebo controlled and Part C is open label. Please see Section 4.2 for scientific rationale for study design.

1. **Part A** is a crossover design, single-dose (SD), dose escalation study in one cohort of healthy participants. Participants will receive single ascending doses of GSK3915393 or matching placebo as an oral dose in periods 1, 2, 4 and 5 and as a single IV microdose dose in period 3. The initial dosing for all periods in which the dose level has been escalated will be staggered so that 2 participants will be dosed as sentinel participants, one with study drug and one with placebo. After approximately 24 hours, and provided the investigator considers the safety and tolerability of the sentinels to be acceptable, the remainder of the participants scheduled for the period may be dosed. Sentinel dosing is not required in the IV dosing period.

2. **Part B** is a parallel group, 14-day, repeat oral dose, dose escalation study in 3 cohorts of healthy participants. Participants will receive GSK3915393 or matching placebo BID in each of the sequential cohorts. The initial dosing for all periods in which the dose level has been escalated will be staggered so that 2 participants will be dosed as sentinel participants, one with study drug and one with placebo. After at least 4 days of dosing, and provided the investigator considers the safety and tolerability of the sentinels to be acceptable, the remainder of the participants scheduled for the period may be dosed.

3. **Part C** consists of 5 SD periods in healthy adult participants. In period 1 all participants will receive an IV microdose of GSK3915393. In period 2 all participants will receive oral doses of itraconazole for 6 days and an IV microdose of GSK3915393 on the 4th day of itraconazole dosing. In periods 3 and 4, participants will receive oral GSK3915393 with or without grapefruit juice in a randomized crossover design. In period 5, all participants will receive oral doses

of itraconazole for 6 days and a single oral dose of GSK3915393 on the 4th day of itraconazole dosing

The participants, investigator, and study staff are all blinded in parts A and B. The schematic of each part is provided in Section 1.2.

4.1.1. Number of Participants

A sufficient number of participants will be screened to ensure a minimum of 60 participants are eligible to be randomized. It is estimated that Part A will have 12 randomized participants, Part B will have 36 randomized participants and Part C will have 12 randomized participants.

Up to 12 additional participants in Part A or Part B may be enrolled to allow for evaluation of additional dose levels, i.e. up to a maximum of 72 randomised participants in total in the study, excluding replacements.

4.1.2. Study Intervention Groups and Duration

Part A

Part A will be a double-blind, single dose, dose-escalating, placebo controlled, randomized (with respect to placebo allocation) study. A sufficient number of healthy participants will be screened to enroll 12 participants. Participants will be randomized to one of the sequences shown in Table 1 Participants will participate in 5 dosing periods and will receive 1 oral placebo dose and 4 active doses; 3 as an oral GSK3915393 dose and 1 as a single GSK3915393 IV microdose dose in period 3. Participants will be dosed in the fed state.

Table 1 Part A Treatment Sequences

Number of Participants	Period 1	Period 2	Period 3	Period4	Period 5
3	P	D2	IV	D3	D4
3	D1	P	IV	D3	D4
3	D1	D2	IV	P	D4
3	D1	D2	IV	D3	P

Each dosing period where the dose is escalated will be staggered so that only 2 participants will be administered study drug initially, 1 active and 1 placebo. Once approximately 24 hours have elapsed, and provided there are no safety concerns, the remainder of participants scheduled for that dosing period may be dosed. Sentinel dosing is not required in period 3 when the IV microdose is administered. A review of safety, tolerability, and PK will occur prior to administration of the next oral dose level. Participants will return for their next scheduled dosing period once at least 5 half lives have elapsed and once all information for dose adjustment/ escalation has been received

and reviewed, which is anticipated to be at least 7 days after administration of the study drug from the prior dosing period. Review of PK data is not required prior to proceeding to the IV dose.

The actual doses to be administered may be adjusted based on emerging safety, tolerability and PK data; these dose adjustments may involve either an increase or a decrease in the planned dose or to repeat a dose level. Sentinel dosing will not be required should the dose be equivalent to, or lower than a dose already given in Part A. The decision to proceed to the next oral dose level will be made by the Dose Escalation Committee based on safety, tolerability and available PK data. The IV dose will be 100 µg.

Participants in part A will be enrolled in the study for at least 11weeks (up to 28 days screening, 5 in house dose assessment periods of up to 5 days each, 1 washout period between each dose of at least 7 days and up to 14 days follow up period).

If a participant withdraws prematurely from Part A of the study, additional participants may be recruited and assigned to the same treatment sequence, starting from the current dosing period of the early withdrawal at the discretion of the sponsor in consultation with the investigator.

Part B

Part B will be a double-blind, 14 day repeat oral dosing, placebo controlled, randomized (with respect to placebo allocation,) dose escalation study with 3 repeat dose levels in 3 separate cohorts of participants who are not enrolled in part A of the study. A sufficient number of healthy participants will be screened to enroll approximately 36 participants (12 participants/cohort). Participants will be randomized to receive either GSK3915393 (9 participants) or placebo (3 participants) in each cohort. Each cohort will be staggered so that only 2 of the 12 participants will be administered study drug initially, 1 active and 1 placebo. After at least 4 days and provided the investigator considers the safety and tolerability of the sentinels to be acceptable, the remainder of the participants scheduled for the period may be dosed. Since the half-life of GSK3915393 is predicted to be <2h, PK steady state is expected to be achieved on day 1 (see dose justification section, Section 4.3). The 4 day (120 h) time frame was selected to provide sufficient duration of dosing to assess safety data, however this duration may be increased based on emerging PK data.

It is planned that participants will be dosed twice daily (approximately 10h and 14h dosing intervals). The impact of food on the PK of GSK3915393 will be investigated following the AM dose on three days in all cohorts (day 3 = fasted, day 5 = high fat meal, day 7 = standard meal). Timings of meals are detailed in Section 5.3.1. The BID dosing regimen and the timing of meals relative to dosing may be adjusted based on emerging PK data.

Blood samples for PK analysis will be collected following both the morning and evening dose on days 1 and 14 following administration of standard meals in order to evaluate any diurnal changes on the rate or extent of absorption and to evaluate the extent of accumulation upon repeat dosing. Additional blood samples for PK analysis will be collected for 10 hours following the first dose on days 3 (fasted), 5 (high-fat), 7 (standard breakfast) to evaluate the impact of food by comparing day 5 and day 7 PK profiles with

day 3. The study days for food effect evaluation may change if emerging PK data suggests that steady-state is not predicted to be achieved by day 3.

The starting dose for part B will be selected after review of safety, tolerability and PK data from at least two oral dose levels in part A (IV dosing is not required to make the part B dose decision. The actual doses to be administered may be adjusted based on emerging safety, tolerability and PK data; these dose adjustments may involve either an increase or a decrease in the planned dose or to repeat a dose level. Sentinel dosing will not be required in a Cohort should the dose be equivalent to, or lower than a dose already given in Part B. Preliminary safety and tolerability from 14 days of dosing and PK data from 7 days of dosing for each cohort will be reviewed prior to dose escalation and will be used to determine the dose to be administered in the subsequent cohort. The decision to proceed to the next dose level will be made by the Dose Escalation Committee based on safety, tolerability and available PK data.

Participants will be enrolled in the study for approximately 8 weeks (up to 28 days screening, approximately 16 days in-house assessment period, and up to 14 day follow up period).

If a participant withdraws prematurely from Part B of the study, additional participants may be recruited and assigned to the same repeat dose level, starting from baseline at the discretion of the sponsor in consultation with the investigator.

Part C

Part C consists of 5 single dose periods of GSK3915393. In period 1, all participants will receive an IV microdose of GSK3915393. In period 2 all participants will receive oral doses of itraconazole for 6 days and an IV microdose of GSK3915393 on the 4th day of itraconazole dosing. In periods 3 and 4, participants will receive oral GSK3915393 with water or with grapefruit juice in a randomized crossover design. In period 5, all participants will receive oral doses of itraconazole for 6 days and a single oral dose of GSK3915393 on the 4th day of itraconazole dosing. A sufficient number of healthy participants will be screened to enroll 12 participants. Participants will be randomized to one of the 2 sequences shown in Table 2. Participants will participate in 5 dosing periods and will receive an IV microdose of GSK3915393 in periods 1 and 2 and three active oral doses of GSK3915393 in periods 3, 4 and 5; either dosed alone, with grapefruit juice or with itraconazole. Participants will be dosed in the fasted state.

Table 2 Part C Treatment Sequences

Number of Participants	Period 1	Period 2	Period 3	Period 4	Period 5
6	IV microdose GSK3915393	IV microdose GSK3915393 + ITZ	GSK3915393 + water	GSK3915393 + GFJ	GSK3915393 + ITZ
6	IV microdose GSK3915393	IV microdose GSK3915393 + ITZ	GSK3915393 + GFJ	GSK3915393 + water	GSK3915393 + ITZ

The IV microdose of GSK3915393 will be 100 µg. The oral dose of GSK3915393 to be given in periods 3-5 will be selected after review of the IV PK data from periods 1 and 2 and will not exceed 20 mg (see Section 4.3.9 for more details on oral dose selection in Part C).

Participants in part C will be enrolled in the study for at least 10 weeks (up to 28 days screening, 5 in house dose assessment periods of between 3 and 6 days each, 1 washout period between each dose (see Section 1.2 Schema for minimum duration of washout periods) and up to 14 days follow up period).

If a participant withdraws prematurely from Part C of the study, additional participants may be recruited and assigned to the same treatment sequence, at the discretion of the sponsor in consultation with the investigator. The treatment period in which a replacement volunteer will start from will be at the discretion of the sponsor in consultation with the investigator.

4.2. Scientific Rationale for Study Design

The study design is based on well-established and published methods to evaluate the first single and repeat dose administration of experimental drugs including the use of sentinel dosing. This study includes a placebo arm to allow for a valid evaluation of adverse events attributable to treatment versus those independent of treatment.

A cross-over design is preferred for part A where each participant receives placebo as it allows assessment of safety in the same individual thus reducing the influence of inter-individual variability.

An IV microdose arm has been included Part A in order to determine the absolute bioavailability of GSK3915393 at clinically relevant doses.

Initial evaluation of safety, tolerability, and PK of GSK3915393 in the single ascending dose and multiple ascending dose phases of the study will be conducted in healthy participants. It is prudent to examine safety in participants for 14 days in part B to inform future clinical studies.

Because the solubility of GSK3915393 is pH dependent (high solubility at low pH and low solubility at higher pH), it is likely that the absorption of GSK3915393 will be higher when administered with food particularly at higher doses due to longer retention time in the stomach which will allow greater dissolution time for GSK3915393. For the single ascending dose phase GSK3915393 will therefore be administered in the fed state, following a standard breakfast. In part B, the impact of prandial state (high-fat meal, standard meal and fasted) on the PK of GSK3915393 will be determined at each dose level to determine the appropriate dosing conditions for future clinical studies

Recent *in-vitro* studies have shown that GSK3915393 is a substrate for both intestinal (gut) and hepatic CYP3A4. The impact of moderate CYP3A4 inhibitors and CYP3A4 inducers that may be included in future clinical trials can be modelled based on data from

a strong inhibitor such as itraconazole therefore coadministration of GSK3915393 with itraconazole will be evaluated in part C. Initially an IV microdose (100 µg) of GSK3915393 will be used in Periods 1 and 2 to evaluate the impact of itraconazole inhibition of hepatic CYP3A4 on the systemic exposure to GSK3915393. This data will be used to select the oral dose of GSK3915393 to be used in Periods 3 to 5 (Section 4.3.9). The oral dose to be used in Part C will not exceed 20 mg.

Since expression of intestinal CYP3A4 is altered in patients with CeD, determining the impact of intestinal CYP3A4 on the predicted exposure of GSK3915393 in the lamina propria (the site of TG2 activity in CeD) is important to understand the predicted pharmacological activity of GSK3915393 in patients. Grapefruit juice administered as a single dose has been shown to inhibit CYP3A4 gut metabolism but not CYP3A4 hepatic metabolism, so in Periods 3 and 4 of Part C, GSK3915393 will be administered with and without coadministration of grapefruit juice (GFJ) to determine the fraction of GSK3915393 which escapes gut metabolism by CYP3A4 in healthy volunteers. Coadministration of GSK3915393 with GFJ will occur in either period 3 or 4, per the randomization schedule, to minimize impact of period effects to the GFJ interaction assessments.

Itraconazole 200mg will be dosed for 6 days with GSK3915393 dosed on Day 4. The 3-day lead-in of ITZ dosing allows for accumulation of ITZ to maximise the degree of CYP3A4 inhibition. Continuing to dose ITZ on Days 5 and 6 will maintain maximal CYP3A4 inhibition to fully characterise the impact of ITZ on the elimination of GSK3915393. Since the half-life of GSK3915393 may be significantly extended upon coadministration with itraconazole, there is increased potential for carryover effects after these regimens compared to the other regimens. For this reason, the itraconazole regimens will be given in fixed periods (2 and 5) rather than in randomized sequence, An extended washout period of at least 7 days is incorporated between periods 2 and 3.

Holter monitor data will be collected and stored for future evaluation of the correlation between plasma levels of GSK3915393 and changes in the QTc interval, if appropriate. Emerging literature suggests that frequent QT evaluation early in development may mitigate the need for a formal thorough QT/QTc (TQT) study [Darpo, 2014]. Therefore, Holter monitor data will be collected during Parts A and B of this study. This data will be held by ERT and may be analysed in the future, if necessary, for a potential TQT waiver in further development of the compound. This will not be reported in the primary clinical study report (CSR).

In order to characterize potential biliary elimination pathways, this study will also employ the Entero-Tracker for sampling of duodenal bile to conduct qualitative assessment of drug metabolites in this matrix. The Entero-Tracker is based on a similar device, Entero-Test which has been shown to be an easy-to-use and minimally invasive method for sampling bile from the duodenum. The Entero-Tracker is a recent replacement device for Entero-Test which is a FDA 510k exempt device. Information on the biliary disposition of drug-related material derived in the current study may avoid the need for invasive methods of bile collection in future studies. The specific cohort and dose level (aiming for the highest

dose level) in part B that will undergo bile sampling will be determined based upon emergent pharmacokinetic data as agreed by the Dose Escalation Committee (DEC). The Entero-Tracker bile sample collected from placebo-dosed participants will be considered as the control. In addition, urine will be collected and used to investigate the urinary elimination of parent drug and any metabolites alongside bile analysis as well as analysis of residual PK plasma samples for drug and metabolites. The results of the metabolite investigations in these matrices will be reported under a separate GSK protocol.

4.2.1. Participant Input into Design.

Participants in this study are healthy volunteers and therefore input into design is not applicable.

4.3. Justification for Dose

The dose justification provided below is based on the supporting information from the first time in human dose justification report [GlaxoSmithKline Document Number 2020N445405_00].

4.3.1. Predicted Human Pharmacokinetics

The predicted human therapeutic dose of GSK3915393 is based on PBPK modelling [GlaxoSmithKline Document number 2020N441210_00]. This approach is mechanistically robust and allows the utilisation of the predicted time course of GSK3915393 concentrations in the human lamina propria. The PBPK model predicts complete absorption of GSK3915393 (100%) with high first pass extraction (FPE) resulting in a low overall bioavailability of 4%.

The human pharmacokinetic (PK) concentration-time profiles and PK exposure parameters (Cmax and AUC) of GSK3915393 were also predicted using in vitro to in vivo extrapolation (IVIVE) and allometric scaling to evaluate the range of likely exposures and predicted maximum TG2 inhibition following a range of single doses of GSK3915393 [GlaxoSmithKline Document number 2020N445405_00].

For both the IVIVE and allometric scaling approaches, human clearance and volume of distribution values were estimated assuming a weight of 70 kg and the bioavailability was assumed to be 10% (based on the range of mouse, rat and dog bioavailability values from 2 to 20%). The absorption rate constant (k_a) was assumed to be 2 h^{-1}. For all methods the human half-life ($t_{½}$) of GSK3915393 is predicted to be short (<2h).

4.3.2. Anticipated Pharmacological Dose Range of GSK3915393

The site of action for TG2 inhibition for the treatment in CeD is in the lamina propria of the gut. The predicted GSK3915393 concentration-time profile in the lamina propria from the PBPK model was used to predict TG2 inhibition.

The predicted human PK parameters along with the experimentally obtained human in vitro kinetics values of K_i (244 nM) and k_{inact} (0.13 min^{-1}) were incorporated into a mechanistic pharmacokinetics/pharmacodynamics (PKPD) model to predict levels of

TG2 inhibition at various dose levels. The rate of regeneration of TG2 activity in the tissue was assumed to be 2.5x slower than that observed in mouse (i.e. t½=93h).

Based on the predicted percentage inhibition of TG2, for the same total daily dose, twice daily dosing (BID) provided improved trough TG2 inhibition over QD dosing whereas increasing the frequency to three times daily dose (TID) did not provide additional improvement on the trough TG2 inhibition. Therefore, the anticipated pharmacological dose range of GSK3915393 is based on a BID dosing regimen. It is anticipated that GSK3915393 would be dosed prior to or at the same time as breakfast and evening meal, therefore the BID dosing regimens were simulated assuming 10 h and 14 h dosing intervals (e.g. dosing at 8am and 6 pm). Based on these simulations a dose of 20 mg BID is predicted to provide a mean of 90% TG2 inhibition over a 24 hour period [GlaxoSmithKline Document number 2020N441210_00].

4.3.3. Starting Dose Selection for Part A

Although, TG2 is not expected to be activated in the small intestine of healthy participants, it is proposed that the starting dose is based on using the 'Minimal Anticipated Biological Effect Level' (MABEL) approach. Based on the average predicted maximum TG2 inhibition across the 4 human PK prediction methods, a starting dose of 15 mg is predicted to provide a maximum of approximately 46% inhibition of TG2 in the lamina propria and 5% inhibition systemically following single dose administration of GSK3915393 (Table 3).

Table 3 Predicted maximum percentage TG2 inhibition in the gut lamina propria (LP) and blood following single dose administration of GSK3915393

Dose	PBPK		IVIVE lower CL		IVIVE higher CL		Allometric scaling		Average Across Human Prediction Methods	
	LP	Blood	LP	Blood	LP	Blood	LP	Blood	LP	Blood
10 mg	35	1	48	5	35	4	21	2	35	3
15 mg	47	2	61	8	47	6	30	3	46	5
20 mg	57	3	71	10	57	7	37	4	56	6

Safety margins are calculated using the Cmax and AUC values from the scaling approach predicting the highest exposure for a given dose level. At the 15 mg dose, the highest predicted mean plasma C_{max} (12.6 ng/mL) and $AUC_{(0\text{-}inf)}$ (50.7 ng.h/mL) values are expected to have 763-fold and 669-fold safety cover, respectively, based on Day 28 gender averaged mean C_{max} (9620 ng/mL) and $AUC_{(0\text{-}t)}$ (33900 ng/mL) values observed at the NOAEL in dog [60 mg/kg BID] in the 4 week safety assessment study. Thus, a starting dose of 15 mg in human provides sufficient safety margins against the preclinical toxicological findings to ensure the safety of study participants.

4.3.4. Top Dose Selection for Part A

GSK3915393 can generate reactive metabolites in the liver, which has the potential to cause idiosyncratic hepatoxicity in a small number of people. Although generally a rare event, the risk of this occurring is greatly reduced if the dose is less than 100 mg/day [Sakatis, 2012]. The highest dose intended to be taken into Phase 2 for chronic dosing is 40 mg BID (80 mg/day). In part B it is proposed to evaluate a dose of 160 mg BID (320 mg/day) [see Dose Selection for Part B for rationale]. To support dosing of 160 mg BID dose in part B, it is proposed to administer 320 mg as the top dose in part A.

The top dose of 320 mg is predicted to provide up to a 16-fold higher Cmax than the anticipated therapeutic unit dose of 20 mg which supports supratherapeutic concentrations for evaluation of QT. However, if intestinal CYP3A4 plays a significant role in the metabolism of GSK3915393, these margins may be narrower due to higher Cmax in CeD patients compared with healthy individuals.

At the 320 mg dose, the predicted highest mean plasma C_{max} (268 ng/mL) and $AUC_{(0-\infty)}$ (1082 ng.h/mL) values are expected to have approximately 36-fold and 31-fold safety cover, respectively, based on gender averaged Day 28 C_{max} and $AUC_{(0-t)}$ values observed at the NOAEL in the dog (60 mg/kg BID) in the 4 week safety assessment study (Table 4).

4.3.5. IV Microdose in Part A

Predictions of human GSK3915393 PK following IV administration were based on the PBPK model. Human PK estimates derived assuming a weight of 70 kg were; clearance = 72.2 L/h, volume = 106 L.

The IV dose of GSK3915393 to be administered is a microdose of 100 µg, which will be infused over 1 h. The predicted Cmax and AUC(0-inf) have greater than 5000 and 15000-fold safety margins compared with the gender averaged Day 28 Cmax and AUC values observed at the NOAEL in the dog 4 week safety assessment study (Table 4).

A 100 µg total dose of GSK3915393A will be formulated as a 0.1 mg/mL solution (prepared in 20mM Acetate buffer). In an in vitro hemolysis assay using human erythrocytes, GSK3915393 IV Solution for Infusion at concentrations 0.1 mg/mL (prepared in a 20mM acetate buffer) did not produce hemolysis when added to human blood.

4.3.6. Safety Margins for Proposed Doses for Part A

Table 4 Proposed doses for Part A, with predicted exposure and safety cover.

Dose Level	Dose	Predicted Cmax (ng/mL)	Predicted fold below NOAEL[1]	Predicted AUC (ng.h/mL)	Predicted fold below NOAEL[2]
1	15 mg PO	12.6	763	50.7	669
2	60 mg PO	50.1	192	203	167
3	160 mg PO	133	72.3	541	62.7
4	320 mg PO	268	36.2	1082	31.3
	100 ug IV	1.4	6871	2.14	15841

[1] Calculated based on gender averaged Week 4 toxicokinetic Cmax (9620 ng/mL) in dogs following oral dosing at NOAEL of 60 mg/kg BID
[2] Calculated based on gender averaged Week 4 toxicokinetic AUC(0-t) (33900 ng.h/mL) in dogs following oral dosing at NOAEL of 60 mg/kg BID

4.3.7. Dose Selection for Part B

The dose level of GSK3915393 selected to be administered in Part B will not exceed the maximum daily dose investigated in Part A of the study. Twice-daily (BID) dosing of GSK3915393 for 14 days is currently planned for Part B. Dose selection for Part B is based on providing safety cover for the dose to be used in future studies in patients with CeD. It is proposed that three dose levels will be evaluated in part B (e.g. 20, 60 and 160 mg BID). Since t½ of GSK3915393 is predicted to be <2h, a BID regimen is not expected to result in any accumulation of GSK3915393 upon repeat dosing. The safety margins for the proposed top dose of 160 mg BID in part B are the same as for the 320 mg (for AUC) and 160 mg (for Cmax) single dose margins in part A.

In-vitro data has shown that GSK3915393 is a substrate for intestinal and hepatic CYP3A4. Patients with CeD have reduced intestinal CYP3A4 activity, therefore drugs which are subject to intestinal CYP3A4 metabolism may have increased systemic exposure compared to healthy subjects. This has been observed for felodipine which is completely absorbed but has an oral bioavailability of 16% as a result of intestinal and hepatic first pass clearance. Approximately 50% of an administered dose of felodipine is cleared via CYP3A4 intestinal metabolism [Xie, 2016]. A study in patients with CeD showed that the systemic exposure (AUC) to felodipine was approximately 1.7-fold higher in patients with mild mucosal abnormalities compared to healthy controls and was approximately 2.3-fold higher in patients with moderate to severe mucosal abnormalities [Chretien, 2020]. This suggests that the majority of felodipine that is cleared by intestinal CYP3A4 in healthy controls is not cleared in patients with CeD. A review of 15 orally administered CYP3A4 substrate drugs showed that the majority had between 35 to 55% eliminated by intestinal metabolism [Xie, 2016]. However, buspirone has 78% of administered drug elimination via intestinal CYP3A4 metabolism. If GSK3915393 were to have a similar proportion of drug eliminated via intestinal CYP3A4, the systemic exposure in patients CeD could be around 4.5-fold higher than in healthy subjects

(i.e.100% available for absorption vs 22%). Therefore, it is proposed to evaluate higher doses in the healthy participants in Part B of the study than the highest dose that is planned to be evaluated in future studies in CeD: e.g. upto 160 mg BID in Part B to cover for 40 mg BID in CeD. As described above in Section 4.3.4, the highest dose which may be evaluated in future studies in CeD is 40 mg BID.

4.3.8. Dose Escalation in Parts A and B

Dose escalation will be guided by the principles listed below, the criteria in Section 6.5 and the stopping criteria detailed in Section 7.2

Part A

The following rules will guide dose selection in Part A:

1. The highest dose escalation step to the next dose will be 5-fold.
2. Once the dose exceeds 80 mg (the planned maximum daily dose to be taken into Phase 2), any further dose escalation will be no higher than 3-fold in order to minimize the risk of adverse events.
3. The highest dose in part A will not exceed 320 mg.

Part B

The following rules will guide dose selection in Part B:

1. The starting daily dose in part B will be selected after review of safety, tolerability and PK data from at least two dose levels in Part A.
2. The highest dose escalation step to the next dose will be 4-fold; Once the dose is ≥ 80 mg/d (the planned maximum daily dose to be taken into phase 2), any further dose escalation will be no higher than 3-fold.
3. The highest daily dose in part B will not exceed 320 mg/day (160 mg BID).

4.3.9. Dose Selection for Part C

There is a potential of substantial increase in exposure to GSK3915393 following oral administration of GSK3915393 with itraconazole, therefore the interaction of itraconazole will initially be evaluated with an IV micro-dose of GSK3915393 (100 µg). This will allow the impact of itraconazole inhibition of hepatic CYP3A4 on systemic exposure to GSK3915393 to be evaluated and inform the selection of the oral dose of GSK3915393 to be administered in periods 3 to 5

Preliminary PK data from Part A of the study showed that following administration of the IV micro-dose (100 µg), the observed mean Cmax and AUC values (5 ng/mL and 5

ng.h/mL, respectively) have approximately 1900 and 6800-fold safety margins compared with the gender averaged Day 28 Cmax (9620 ng/mL) and AUC (33900 ng.h/mL) values observed at the NOAEL in the dog 4 week safety assessment study. Therefore there is no risk that the exposures observed in the presence of itraconazole will approach the specified PK stopping criteria.

All available PK data, including information from the IV microdose in the presence of itraconazole will be used to set the oral dose for periods 3-5. The selection of the oral dose will be based on maintaining the predicted exposure to GSK3915393 in the presence of itraconazole in accordance with the defined PK stopping criteria and within the systemic exposures already achieved in Parts A and B of the study and will not exceed 20 mg. See Section 6.5 for further details on dose selection for Part C.

4.4. End of Study Definition

The end of the study is defined as the date of last scheduled procedure at FU (LSLV) shown in the Schedule of Activities for the last participant in the trial globally.

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

5.1.1. Inclusion Criteria

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

Study Specific Criteria:

AGE
1. Between 18 and 50 years of age inclusive, at the time of signing the informed consent.
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Healthy Participants who are overtly healthy as determined by medical evaluation including medical history, physical examination, laboratory tests, and cardiac monitoring. 3. Negative COVID-19 test on admission.

WEIGHT
4. Body weight ≥40 kg and body mass index (BMI) within the range 18.5-29.9 kg/m2 (inclusive).
SEX
5. Male or females **a. Male participants:** • No restrictions for male participants. **b. Female participants:** • A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies: o Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4 Contraception and Barrier Guidance. OR o Is a woman of childbearing potential (WOCBP) and using an acceptable contraceptive method as described in Section 10.4 from 30 days prior to first dose until follow up visit. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated in relationship to the first dose of study intervention). • A WOCBP must have a negative highly sensitive pregnancy test (serum) at screening and on admission to the clinical unit, see Section 8.2.6 Pregnancy Testing. • Additional requirements for pregnancy testing during and after study intervention are located in Section 8.2.6. • The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

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

5.2. Exclusion Criteria

5.2.1. Exclusion Criteria

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

MEDICAL CONDITIONS
1. History or current evidence of cardiovascular, respiratory, hepatic, renal, gastrointestinal (Irritable bowel syndrome [IBS], Gastroesophageal reflux disease [GERD], nausea, vomiting or dysphagia), endocrine, hematological, neurological, or psychiatric disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study treatment; or interfering with the interpretation of data.
2. Current evidence of active infection.
3. Participants with signs/symptoms suggestive of COVID-19 (i.e. fever, cough, etc) within the past 14 days prior to screening and admission to clinical unit.
4. Participants with known COVID-19 positive contacts in the past 14 days prior to screening and admission to clinical unit.
5. Any history of suicidal behavior within the past 6 months or any history of attempted suicide in a participant's lifetime.
6. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN).
7. Bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
8. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
9. History of GI surgery (with exception of appendectomy).
10. Average QTcF >450 msec at screening
11. Any clinically relevant abnormality on the screening medical assessment, laboratory examination, or ECG
12. History of QTc prolongation, symptomatic cardiac arrhythmias or cardiac arrest.
13. For Part C only, history of liver toxicity resulting from drug administration.
14. For Part C only, history of intolerance to itraconazole.

PRIOR/CONCOMITANT THERAPY
15. History of sensitivity to any of the study medication, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation.

16. Use of any immunosuppressive medications within 6 months prior to entry.
17. Unable to refrain from the use of prescription or non-prescription drugs, including vitamins, probiotics, antacids, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication for each dosing, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise participant safety. (Paracetamol is acceptable at a dose of no more than 500 mg at a time and no more than 2 grams per day).
18. Participants who have received a COVID-19 vaccine within 7 days of admission (or readmission) to the clinical unit or who are demonstrating signs/symptoms attributed to a COVID-19 vaccination that occurred greater than 7 days earlier.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

19. Recent donation of blood or blood products such that participation in the study would result in loss of blood in excess of 500 mL within 56 days.
20. The participant 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).
21. Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day
22. Unwillingness or inability to follow the procedures outlined in the protocol or any other type of medical research within 30 days of randomization.

DIAGNOSTIC ASSESSMENTS

23. Presence of hepatitis B surface antigen (HBsAg) at screening or within 3 months prior to first dose of study treatment
24. Positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. **NOTE:** Participants with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C ribonucleic acid (RNA) test is obtained
25. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment. **NOTE:** Test is optional and participants with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing
26. A positive pre-study drug/alcohol screen
27. Positive human immunodeficiency virus (HIV) antibody test

OTHER EXCLUSIONS
28. History of drug abuse (as defined by the current version of the Diagnostic and Statistical Manual [DSM]) within 2 years before dosing, or a positive drug screen reflecting consumption of illicit drugs. 29. Regular alcohol consumption within 6 months prior to screening: • An average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits. 30. Urinary cotinine levels indicative of smoking or use of tobacco or nicotine-containing products (e.g. nicotine patches or vaporizing devices) at screening or on admission to the unit.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or citrus fruit juices from 7 days before the start of study intervention until after the final dose.

5.3.1.1. Part A

- On Day 1 in all oral dosing periods participants will fast for 8hr and a standard breakfast will be served approximately 30 minutes prior to dosing.
- All other meals will be served as per the site schedule.
- In the IV dosing period all meals will be served as per the site schedule.
- 8 fl oz (240 mL) of water to be taken after dosing and water permitted on an ad lib basis.
- Other decaffeinated drinks will be permitted except during fasting periods

5.3.1.2. Part B

- **Breakfast**
  - Participants will fast 8hr and a standard breakfast will be given approximately 30 min pre dose (except on Day 3 and Day 5 (see below)). On day 7 breakfast will be eaten within 20 minutes.
  - Day 3 - Participants will fast 8hr and will be dosed fasted, a low-fat breakfast will be served approximately 2hr after dosing.
  - Day 5 - Participants will fast 8hr and a high fat breakfast meal will be given approximately 30 min. pre dose & eaten within 20 minutes.
- **Lunch**

- Day 12 in the cohort undergoing bile sampling - A high fat small lunch meal will be served at approximately 5 hours post dose.
- On all other day's lunch and snacks will be served according to the sites schedule.

- **Dinner**

- On D1 dinner will be served approximately 1 h before PM dose. On all other days the dinner meal will be given approximately 40 mins prior to the PM dose.

- Fluids

- Water permitted on an ad lib basis
- Other decaffeinated drinks allowed by the protocol will be permitted except during fasting periods and while the EnteroTracker is in place.

5.3.1.3. Part C

- On day 1 participants will fast 8hr prior to dosing (with Itraconazole or GSK3915393 depending on period and day) and a standard breakfast will be served approximately 2 hours post GSK3915393 oral dose or start of IV infusion
    - The day 1 fasting requirements may be adjusted based on the emerging food effect data in Part B. Changes will be documented in a note to file.
- Itraconazole administration on Days -3 to -1 and Days 2 and 3 may be administered following a standard meal.
- All other meals will be served as per the site schedule.
- Water or GFJ (volume to be defined in SRM) to be taken with GSK3915393 dosing (depending on period) and water permitted at other times on an ad lib basis.
- Other decaffeinated drinks will be permitted except during fasting periods

5.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing (with itraconazole or GSK3915393 depending on period) until after collection of the final PK and/or pharmacodynamic sample.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing (with itraconazole or GSK3915393 depending on period) until after collection of the final PK and/or pharmacodynamic sample.
- Use of tobacco products will not be allowed from screening until after the final follow-up visit.

5.3.3. 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 (e.g., watching television, reading, walking).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. 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, any protocol deviations and any SAEs.

Individuals who do not meet the criteria for participation in this study may be rescreened. Rescreened participants should be assigned a new participant number. Screening assessments that yield aberrant results (e.g., safety laboratory samples) may be repeated once within the screening window at the discretion of the investigator. Individuals who failed initial screening but passed rescreening may be admitted into the study based upon clinical judgement and after consultation with the GSK medical monitor.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

The following products will be received by the participant as per the protocol design.

Part A - Participants will receive GSK3915393 extemporaneous formulations: API filled capsules and placebo capsules according to the treatment sequence to which they are assigned. For the IV dose, participants will receive GSK3915393 at a dose of 100 µg within 24 hours from compounding.

Part B - Participants will receive GSK3915393 extemporaneous formulations: API filled capsules and placebo capsules according to the treatment to which they are assigned.

Part C - Participants will receive GSK3915393 extemporaneous formulations: API filled capsules for 3 Periods. For the IV dose, participants will receive GSK3915393 at a dose of 100 µg within 24 hours from compounding. In periods 2 and 5, 200 mg Itraconazole will be given as an oral solution or tablets (depending on emerging data from Part B). In periods 3 or 4 participants will receive GFJ according to the randomisation.

Intervention Name	**GSK3915393 Solution for Infusion**	**GSK3915393 Capsules**	**GSK3915393 Placebo to Match Capsules**	**Itraconazole**	**Grapefruit Juice**
Type	Drug	Drug	Drug	Drug	Food Stuff
Dose Formulation	IV	Capsule	Capsule	Solution or capsule	Drink
Unit Dose Strength(s)	IV infusion to be prepared by extemporaneous compounding to 100 µg.	API alone in capsule to be prepared by extemporaneous compounding to required weight. Multiple Capsules can be used as required. Fill weight can span from 2mg to 100mg as required	To match oral active. (*No placebo for IV infusion arm.)*	Solution 10 mg/ml or 100 mg capsule	Volume to be defined in SRM
Dosage Level(s)	100 µg once	Starting dose single dose of 15 mg subsequent doses to be determined at dose escalation meetings	To match oral active. (*No placebo for IV infusion arm.)*	200 mg	Volume to be defined in SRM
Route of Administration	IV infusion	Oral	Oral	Oral	Oral
Use	Experimental	Experimental	Placebo	Experimental	Experimental
IMP and NIMP	IMP	IMP	IMP	NIMP	NIMP

Intervention Name	**GSK3915393 Solution for Infusion**	**GSK3915393 Capsules**	**GSK3915393 Placebo to Match Capsules**	**Itraconazole**	**Grapefruit Juice**
Sourcing	Extemporaneous compounding facility to provide, labelled, solution for injection via Extemporaneous Compounding	Extemporaneous compounding facility to provide blinded, labelled, API in Capsule and Placebo capsules via Extemporaneous Compounding	TBC Extemporaneous compounding facility to provide blinded, labelled, API in Capsule and Placebo capsules via Extemporaneous Compounding	Kleva Pharmaceuticals (Generic substitution is permitted)	Provided by GSK
Packaging and Labelling	Syringe which is capped	Capsules provided in labelled HDPE bottles	Capsules provided in labelled HDPE bottles	N/A	N/A

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual.
5. Under normal conditions of handling and administration, study intervention 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.

6. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

6.3. Measures to Minimize Bias: Randomization and Blinding

On Day 1 of the first dosing period for each cohort, participants will be assigned a unique randomisation number in ascending numerical order. In parts A and B, the randomisation number encodes the participant's assignment to either GSK3915393 or placebo, according to the randomisation schedules generated prior to the study by the Statistics Department at GSK, using validated internal software. The PI or delegated responsible person will assign the randomisation numbers as described above and the randomisation number will be entered in the case report form (CRF). Subjects will receive GSK3915393 in all periods in Part C, and the randomisation schedule defines the period in which GFJ will be co-administered with GSK3915393.

The unblinded pharmacist will receive a copy of the randomisation schedules from the GSK randomisation co-ordinator to enable dispensing of study medication.

Parts A and B of the study are double blind. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. In order to maintain this blind, an unblinded pharmacist will be responsible for the reconstitution and dispensation of all study intervention.

Unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to un-blinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

Code break envelopes, which contain the treatment codes if required in an emergency, will be prepared by the unblinded pharmacist/unblinded site personnel. Code break envelopes will be stored in a secure fire-proof environment that is inaccessible to blinded personnel, but can be directly accessed 24 hrs a day by the investigator in case emergency unblinding is required.

The investigator or treating physician may unblind a participant's treatment assignment, using the code break envelopes, 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 participant as judged by the investigator.

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 participant'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 participant, unless that information is important for the safety of participants currently in the study.

The date and reason for the unblinding must be fully documented in the CRF. A participant will be withdrawn if the participant's intervention code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention 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 intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

Part C is being conducted open label as placebo-to-match ITZ and GFJ are not currently available. The time periods for ITZ coadministration are fixed as opposed to randomised (see Section 4.2). The primary endpoint for Part C is pharmacokinetic, and there is no risk of bias with this objective measure. There is however potential for carry over/period effects to confound the safety evaluation within Part C, but since safety is a secondary objective in Part C and the exposures within Part C are expected to remain within the range studied in the randomised double blind phases of the study (Parts A and B), there is minimal risk to the overall integrity of the study by adopting this approach in Part C.

6.4. Study Intervention 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 intervention 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 intervention 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 intervention. In oral dosing periods study site staff will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Dose Modification

Dose justification and stopping criteria are detailed in Section 4.3 and Section 7.1 respectively.

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum daily dose will not exceed 320mg in parts A and B.

The decision to proceed to the next dose level of GSK3915393 (either an increase, a decrease or to repeat a dose level) during parts A and B will be made by a DEC consisting of the Principal Investigator (or appropriate designee), Medical Monitor, GSK

Study Team Leader, GSK Clinical Pharmacology Modelling and Simulation (CPMS) representative, a GSK GCSP representative and a GSK Statistician (or appropriate designees for GSK DEC members). The DEC will review blinded data. Unblinded data may be reviewed by the GSK Medical Monitor, GSK CPMS representative, and a GSK Biostats representative. The decision to progress from part A to part B and the oral dose to be used in Part C will also be made by the DEC.

In parts A and B, dose escalation or adjustment decisions will be based on data review which includes at least 6 participants on active treatment (two thirds of planned 9 participants on active treatment) at the prior dose level. The review data set will at minimum consist of AE listings, safety labs, vital signs and ECG and PK results up to 24 h post-dose in part A, and up to 10 h post-Day 7 dose in part B. Laboratory findings will also be reviewed.

In Part C, data review will be conducted prior to initiating period 3 and will comprise a minimum of 8 subjects dosed with GSK3915393 IV + ITZ and GSK3915393 IV to enable the selection of the oral dose of GSK3915393 to be co-administered with GFJ and ITZ in periods 3-5. The review data set will comprise of PK data and AE listings, safety labs, vital signs and ECG from periods 1 and 2 in conjunction with available safety data from Parts A and B.

In parts A and B the dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety and/or PK findings at a given dose level to add cohorts to evaluate up to 1-2 additional dose levels. The study procedures for these additional participant(s)/cohort(s) will be the same as those described for other study participants/cohorts. Additional dose levels will not exceed the doses described in Section 4.3.8.

The Dose Escalation Plan will outline how the study team will ensure data integrity is maintained in dose selection decisions by performing clinical data review and appropriate quality control of data prior to making dose selection decisions or decisions to transition into a subsequent part of the study.

The DEC charter will also outline the responsibilities of the investigators and site staff for reporting safety data, participation during dose escalation/ adjustment meetings and confirmation that the data used for dose escalation/ adjustment are accurate and complete.

6.6. Continued Access to Study Intervention after the End of the Study

Participants will not receive any additional treatment from GSK, or with GSK3915393, after completion of the study because this is a Phase 1 study

6.7. Treatment of Overdose

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

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

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities for at least 4 days.
3. Obtain a plasma sample for PK analysis immediately unless a PK sample has already been obtained after the overdose.
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 participant.

6.8. Concomitant Therapy

Participants must abstain from taking prescription or non-prescription drugs (including vitamins, recreational drugs, 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) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol, at doses of ≤2 grams/day, 500mg at a time is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Medical Monitor if required.

Oral contraception as detailed in Section 10.4 are permitted.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study until the end of that treatment period to be evaluated for safety and tolerability. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

A participant may be withdrawn from the study if:

a) A participant experiences a serious or severe clinically significant non-serious AE that in the clinical judgement of the Investigator, is at least possibly related to investigational product.

b) The participant initiates treatment with any prohibited medications.

c) If any of the protocol individual stopping criteria are met.

- In addition, study treatment may be permanently discontinued for any of the following reasons:
  a) Deviation(s) from the protocol
  b) Withdrawal of consent by participant (or proxy)
  c) Discretion of the Investigator
  d) Participant is lost to follow-up

7.1.1. Liver Chemistry Stopping Criteria

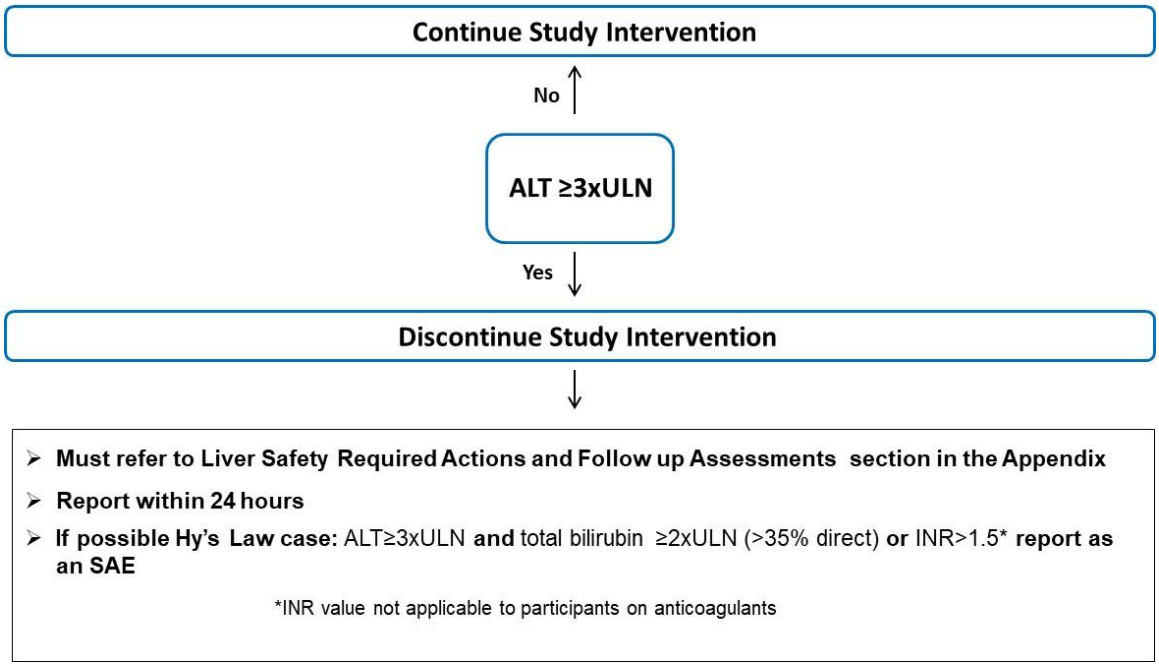
Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.

Study intervention will be discontinued **for a participant** if liver chemistry stopping criteria are met:

Phase 1 Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal.

Refer to Section 10.5 for required Liver Safety Actions and Follow up Assessments.

7.1.2. QTc Stopping Criteria

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

- QTcF >500 msec,
- Change from baseline in healthy volunteer participants: QTcF >60 msec

The QTcF correction formula must be used for each participant to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled. If an ECG demonstrates a prolonged QT interval, two more ECGs should be obtained over 5-10 mins and the average QTcF value of the three ECGs should be used to determine if the participant meets the QTc stopping criteria see Section 8.2.3.

7.1.3. Vital signs Stopping Criteria

A subject will be withdrawn if any of the following cardiovascular changes are detected up to 24 h post last dose in each session.

- Clinically significant and sustained (i.e., for greater than 2 hours) increase in systolic or diastolic blood pressure, for example:
- - systolic blood pressure >160 mmHg or >30 mmHg increase from baseline or,
- - diastolic blood pressure >100 mmHg or >20 mmHg increase from baseline
- Clinically significant and sustained increase in resting heart rate (for example, >120 beats/minute for more than 2 hours)

Withdrawal is to be based on an average value from triplicate blood pressure or heart rate readings. If any blood pressure or heart rate readings are flagged as clinically significant, they are to be repeated in triplicate and checked every 20 minutes until they are no longer clinically significant.

7.1.4. Rechallenge

If any stopping criteria are met by any participant in this study, study treatment restart or rechallenge is not allowed.

7.1.5. COVID-19 Discontinuation

- If a participant develops COVID-19 like symptoms during the study the following actions should be taken:
    - During Part A and C, participants who develop signs/symptoms highly suggestive of COVID-19 disease should be isolated and tested for COVID-19 in accordance with site procedures.

- During Part B, study treatment should be halted for any participants who develop signs/symptoms highly suggestive of COVID-19 disease; they should be isolated and tested for COVID-19 in accordance with site procedures.

- In both cases, assessments should be continued as per the protocol where possible; withdrawal of participants from the study will be at the discretion of the Principal Investigator but should first be discussed and agreed with the GSK Medical Monitor.

7.2. Study Stopping Criteria.

7.2.1. Safety Stopping Criteria

In the event of any of the following, ongoing dosing will be halted.

- Two or more participants in the same dose group/cohort experience non-serious severe adverse events considered at least possibly related to the administration of GSK3915393.
- Any participant experiences a serious adverse event considered at least possibly related to the administration of GSK3915393.

The dosing will be temporarily halted, and no further participants will be dosed until a full safety review of the study has taken place. Relevant reporting and discussion with the GSK medical monitor, relevant GSK personnel, and with the CA and IRB / IEC will then take place prior to any resumption of dosing, which may also include the evaluation of lower doses. If following an internal safety review, it is appropriate to restart the trial, a substantial amendment will be submitted to the MHRA and REC. The trial will not restart until the amendment has been approved by the MHRA and REC.

7.2.2. Pharmacokinetic Stopping Criteria

The following dose adjustment / PK stopping criteria will **apply:**

- If exposure in an individual subject and/or mean cohort exposure exceeds or is predicted to exceed the gender averaged PK exposures in dogs following oral dosing at the NOAEL of 60 mg/kg BID (Cmax of 9620 ng/mL or total daily AUC(0-24) of 33900 ng.h/mL), dose escalation will be stopped
- If the PK stopping criteria is reached with initial doses, the dose escalation will be stopped. The GSK team will decide based on safety and PK whether to evaluate any lower doses or repeat doses already evaluated in remaining periods to collect additional safety and PK data. Throughout all parts of the study, noncompartmental PK analysis will be used to help inform the choice of the next dose level as part of dose escalation discussions.

7.3. Participant Discontinuation/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, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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.

7.4. 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.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed
- Immediate safety concerns will be managed by the investigator with discussions with the GSK Medical Monitor as required to determine if the participant should continue or discontinue study intervention.
- 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 (e.g., 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.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Efficacy assessments will not be performed in this study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A full physical examination will include, at a minimum, assessments of the Skin, 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 skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in the semi-recumbent position 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 (e.g., television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded.

8.2.3. Electrocardiograms

- Triplicate OR Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.1.2 for QTc withdrawal criteria.
- 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.
- If an ECG demonstrates a prolonged QT interval, then obtain 2 more ECGs over a brief period of time and then use the mean QTcF values of the 3 ECGs.
- Safety ECGs will be printed and interpreted on-site by the Investigator to ensure participant safety. Refer to Section 7.1.2 for QTc withdrawal criteria.
- Continuous cardiac telemetry will be performed at time points indicated in the SoA (Section 1.3). Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents.

8.2.3.1. Cardiodynamic assessment (ECGs extracted from Holter recordings)

The 12-lead Holter/ECG equipment will be supplied and supported by ERT. All continuous ECG (Holter) data will be collected using a Global Instrumentation (Manlius, NY, USA) M12R ECG continuous 12 lead digital recorder. The continuous 12-lead digital ECG data will be stored onto SD memory cards. In case the cardiodynamic evaluation is undertaken, 12-lead ECGs will be extracted in replicates from the continuous ECG recording at pre-determined time points as defined in the SoA and will be read centrally by ERT. If a decision is taken to undertake cardiodynamic evaluations, details will be outlined in a separate analysis plan.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study including at follow up should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, further investigations to determine the etiology should be undertaken in coordination with the sponsor.
- All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If laboratory values from non-protocol specified laboratory tests require a change in participant management or are considered clinically significant by the investigator, the results must be recorded.

8.2.5. COVID-19 testing

Participants will be tested for Covid-19 according to local site procedures, at a minimum participant will be tested at the timepoints in the SoA.

Subjects who report symptoms suggestive of COVID-19 while in the research unit should be isolated according to local site procedures in the unit or at home and tested for COVID-19 infection using an approved molecular test.

8.2.6. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of AE or SAEs can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified 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 intervention or the study, or that caused the participant to discontinue the study intervention or study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).
- All AEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions not as AEs.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. 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 information on AEs or SAEs after the conclusion of the study participation. 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 intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. 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.

8.3.3. 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, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is given in Appendix 3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local CA and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the CA, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) 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.
- 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.

8.3.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until completion of the final follow up visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.6. Cardiovascular and Death Events

For any cardiovascular (CV) events detailed in Section 10.3 and all deaths, whether or not they are considered SAEs, specific CV and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.4. Pharmacokinetics

Instructions for the collection, handling and shipping of biological samples will be provided in the SRM. The actual date and time (24-hour clock time) of each sample will be recorded.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Samples collected for analyses of GSK3915393 plasma concentration may also be used to evaluate safety aspects related to concerns arising during or after the study.

8.4.1. GSK3915393 PK plasma collection.

Blood samples will be collected at all timepoints in Parts A, B and C for measurement of plasma concentrations of GSK3915393.

GSK3915393 concentration analysis will be performed under the control of In Vitro/In Vivo Translation (IVIVT). Plasma concentrations of GSK3915393 will be determined using approved bioanalytical methodology.

The bioanalytical site will be detailed in the SRM and raw data will be archived in the GSK R&D GLP archives.

8.4.2. Metabolite plasma collection.

Plasma will also be analysed for other compound-related metabolites and the results reported separately.

Blood samples will be collected in part A and part B (Days 1 and 14), as specified in the SoA (Section 1.3) to assess for GSK3915393 metabolites.

8.4.3. Urine Metabolite collection

Urine samples for analysis of GSK3915393 and its metabolites will be collected at the time-points listed in the SoA (Section 1.3). These samples may then be analysed for compound-related material and the results reported separately.

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

8.4.4. Itraconazole and Hydroxy Itraconazole PK plasma collection.

Blood samples will be collected at specified timepoints in Part C for measurement of plasma concentrations of Itraconazole and Hydroxy Itraconazole.

Itraconazole and Hydroxy Itraconazole concentration analysis will be performed under the control of *In-Vitro/In-Vivo* Translation (IVIVT). Plasma concentrations of Itraconazole and Hydroxy Itraconazole will be determined using approved bioanalytical methodology.

The bioanalytical site will be detailed in the SRM and raw data will be archived in the GSK R&D GLP archives.

The concentrations of itraconazole and hydroxy itraconazole will be used as part of the drug interaction modelling initiative (Section 9.4.3.1).

8.4.5. EnteroTracker: Bile Sample Collection

Duodenal bile samples will be collected at the time-points listed in the SoA for the analysis of GSK3915393 and its metabolites for participants in the highest dose part B cohort only.

Bile fluid is recovered on a highly absorbent nylon line which is contained within a weighted gelatin capsule. The 90 cm line unwinds after capsule swallowing as 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 the bile EnteroTracker sample collection, processing, storage and shipping procedures are provided in the SRM. These samples may then be analysed for compound-related material and the results reported separately.

8.4.6. Plasma Sample for CYP3A4 Enzyme Activity

Plasma derived from select PK blood samples in Part B (as in the SoA Table, see Section 1.3), will be analyzed for 4β-hydroxycholesterol and cholesterol as a potential *in vivo* marker of CYP3A4 enzyme activity. Samples collected pre-treatment and at steady-state will be compared to evaluate this potential marker.

Details on CYP3A4 enzyme activity marker plasma sample collection, processing, storage and shipping procedures are provided in the SRM.

Baseline and Day 14, post-treatment plasma samples will be analyzed using a validated, specific, and sensitive liquid chromatography–mass spectrometry (LC-MS/MS) method to determine concentrations of 4β-hydroxycholesterol and total cholesterol. A comparison will be made between the ratio of 4β-hydroxycholesterol: cholesterol at baseline and on Day 14 to assess potential changes in CYP3A4 enzyme activity following GSK3915393 treatment.

Analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of PTS-IVIVT and Third Party Resource, GlaxoSmithKline.

8.5. Pharmacogenomics

Pharmacogenomics are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Statistical analyses will be performed by, or under the direct auspices of, Biostatistics, GlaxoSmithKline.

Reporting of study data will be performed in accordance with applicable GSK and/or contract research organization (CRO) standards.

Complete details of the planned statistical analyses will be provided in the statistical analysis plan (SAP). Any deviations from the planned analyses will be described in a SAP addendum and justified in the final integrated clinical study report.

9.1. Statistical Hypotheses

The primary objectives of parts A and B of this study are to assess the safety and tolerability of single and repeat ascending doses of GSK3915393 in healthy participants. The primary objective of Part C is to assess the victim drug interaction potential of GSK3915393 with the CYP3A4 inhibitors, grapefruit juice and itraconazole. No formal hypotheses will be tested.

9.2. Sample Size Determination

Twelve, 36 and 12 participants are planned to be randomised to study intervention in parts A, B and C respectively. A further 12 healthy volunteers may be randomised in

parts A or B if additional dose levels are required to be studied. The sample sizes for parts A and B were selected to support the planned assessments of safety and tolerability, the primary objective of parts A and B of the study.

In parts A and B, 9 subjects will receive each active oral dose. If 0/9 subjects experience a particular adverse event, the upper limit of the exact 95% CI indicates that a true incidence rate of 33.6% could not be ruled out. Whereas if 1/9 subjects experienced an event, the upper limit of the exact 95% CI indicates that a true incidence rate of 48.2% could not be ruled out.

The sample size for Part C was selected taking into consideration the precision of estimation of the ratios of AUC and Cmax for the following comparisons of interest.

- GSK3915393 PO + GFJ vs GSK3915393 PO + water
- GSK3915393 IV + ITZ vs GSK3915393 IV
- GSK3915393 PO + ITZ vs GSK3915393 PO + water

Assuming a within subject coefficient of variation of 35%, with 12 subjects the upper and lower limits of the 90% CI for the AUC and Cmax ratios will be 0.78 and 1.28 times the point estimate respectively. Increases in AUC and Cmax are expected to be observed when GSK3915393 is dosed in combination with GFJ or ITZ and it is expected that F_G (ratio of AUC for GSK3915393 PO + water: GSK3915393 PO + GFJ) will be less than 1. The resulting confidence intervals for a range of ratio scenarios are illustrated in Table 5.

Table 5 Precision of estimation of AUC and Cmax Ratios in Part C

Ratio Estimate	90% CI with N=12 and CV_W=35%
0.2	(0.16, 0.26)
0.4	(0.31, 0.51)
0.6	(0.47, 0.77)
1	(0.78, 1.28)
2.5	(1.95, 3.21)
5	(3.90, 6.42)
10	(7.79, 12.83)
20	(15.59. 25.66)

9.3. Analysis Sets

The populations for the study are detailed below.

Population	Description
Screened	All participants who were screened for eligibility
Randomized	All participants who were randomly assigned to treatment in the study. This population will be based on the treatment the participant was randomized to.
Safety	All randomized participants who received at least one dose of study treatment. This population will be based on the treatment the participant actually received.
PK	All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). This population will be based on the treatment the participant actually received.

9.4. Statistical Analyses

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. Primary Endpoint(s)

In parts A and B, the primary endpoints are the safety assessments as detailed in Section 3.

Safety data will be summarised in tabular and/or graphical form by dose regimen over time for the safety population. Data for each study part will be summarised separately.

In part C, the primary endpoints are GSK3915393 pharmacokinetic parameters AUC, Cmax, Tmax and t1/2 and these are outlined alongside the pharmacokinetic endpoints for parts A and B within Section 9.4.2.

9.4.2. Secondary Endpoint(s)

Pharmacokinetic Endpoints

All pharmacokinetic analyses will be performed on the Pharmacokinetic Population.

Plasma concentration-time data of GSK3915393 will be analysed by non-compartmental methods. Calculations will be based on the actual sampling times recorded during the study. Full details will be described in the reporting and analysis plan.

GSK3915393 pharmacokinetic parameters, including but not limited to the following will be determined from the plasma concentration-time data, as data permit:

Part A

- Maximum observed plasma concentration (Cmax)
- Time to Cmax (Tmax)
- Area under the plasma concentration-time curve (AUC) from time zero to the last quantifiable concentration (AUC(0-t))
- AUC from time zero to infinity (AUC(0-∞))
- Apparent terminal phase half-life (t1/2)
- Plasma clearance (CL) (iv only)
- Plasma volume of distribution (Vd) (iv only)
- Absolute bioavailability (F)
    - Where F=[AUC(0-∞) po /dose po]/[AUC(0-∞) iv/dose iv])
- Fraction of drug escaping hepatic metabolism (F_H)
    - Where, $F_H = (1-E_H)$ (E_H = hepatic extraction ratio)
    - $E_H = CL_{H,b} \div Q_{H,b}$
        - $CL_{H,b}$= hepatic blood clearance; $Q_{H,b}$ = hepatic blood flow (1.26 L/h/kg)
    - $CL_{H,b}$ (Dose IV ÷ Plasma AUC(0-inf)) IV ÷ 0.64 (Blood : Plasma)
- Fraction of drug absorbed intact * Fraction of drug escaping gut metabolism (F_A*F_G)
    - Where $(F_A*F_G) = F \div F_H$

Part B repeat dose comparison day 1 and day 14

- Cmax after 1st and 2nd dose
- Tmax after 1st and 2nd dose
- AUC over the 1st and 2nd dosing interval (AUC(0-T))
- AUC over 24 hours (AUC(0-24))
- Trough concentrations C_T
- AUC(0-∞) after 1st dose on Day 1, if data allow
- t1/2 after 1st dose on Day 1, if data allow
- Cmax accumulation $Cmax_{D14}/Cmax_{D1}$
- Observed accumulations ratio Ro $(AUC(0\text{-}T)_{D14} / AUC(0\text{-}T)_{D1})$
- Steady-state accumulations ratio Rs $(AUC(0\text{-}T)_{D14} / AUC(0\text{-}\infty)_{D1})$, if data permit

Part B food effect comparison (high fat meal v fasted and standard meal v fasted)

- Cmax after 1st dose
- Tmax after 1st dose

- AUC over 1st dosing interval (AUC(0-T))

Part B time to steady-state

- Pre-dose concentrations on days 2, 3, 5, 7 and 14.

Part C (CYP3A4 victim assessment)

- Cmax
- Tmax
- AUC(0-t)
- AUC(0-∞) and t1/2, if data allow
- $F_G = AUC_{H2O} \div AUC_{GFJ}$ (oral administration of GSK3915393)
- F, F_A, F_H:
    - F and F_H are defined as above under Part A
    - $F_A = (F \div F_H) \div F_G$

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

Statistical Analyses of Pharmacokinetic Data

Dose linearity (Part A): Single dose linearity will be assessed by visual inspection of dose normalised AUC (0-∞) [or if not available AUC(0-t) or AUC (0-t')] and Cmax values versus dose. Analysis of loge-transformed parameters may be carried out, using the power model.

Food effect (Part B): The ratio of fed state to fasted state will be assessed for parameters Cmax and AUC (0-T) after 1st dose.

Repeat vs Single dose (Part B): The extent of accumulation after repeat dosing will be determined based on the observed Cmax accumulation, Ro. An assessment of time to achieve steady state will be made based on visual inspection of the trough concentrations by day. Dose proportionality may be assessed using similar methods to the single dose.

Impact of Grapefruit Juice (Part C) Log transformed AUC(0-∞) [or if not available AUC(0-t) or AUC (0-t')] for periods 3 and 4 will be analysed using a mixed model with fixed regimen and period effects and random subject effect. Between regimen differences will be computed and back transformed to provide point estimates and 90% CI for the ratio of AUC for GSK3915393 PO with GFJ: GSK3915393 PO + water, and an estimate of F_G defined as the ratio of AUC GSK3915393 PO with water: GSK3915393 PO + GFJ Similar analysis will be conducted for log transformed Cmax to provide an estimate of the ratio of Cmax for GSK3915393 PO with GFJ: GSK3915393 PO + water.

Impact of itraconazole (Part C): Log transformed AUC(0-∞) [or if not available AUC(0-t) or AUC (0-t')] will be analysed for periods 1 and 2 utilising a mixed model with regimen fixed effect and subject random effect. Between regimen differences will be computed and back transformed to provide point estimates and 90% CI for the ratios of AUC for GSK3915393 IV + ITZ: GSK3915393 IV: A similar mixed model analysis utilizing period 3-5 data will be conducted to provide point estimates and 90% CI for ratio of AUC for GSK3915393 PO + ITZ: GSK3915393 PO + water. These analyses will also be conducted for log transformed Cmax to derive point estimates and 90% CI for the Cmax ratios of interest.

Safety – Part C (CYP3A4 victim assessment)

The Part C safety data will be summarised by regimen.

9.4.3. Exploratory Endpoint(s)

9.4.3.1. Modelling Initiatives

Pharmacokinetic data from the current study are being used to support the modelling initiatives outlined below.

- Assess risk for GSK3915393 to be a victim or perpetrator of drug-drug interaction (DDI) to support any restrictions on concomitant drug administration in Phase 2 study
- F_G determined from healthy participants in the current study will be used in conjunction with gut CYP3A4 expression in Celiac Disease subjects to predict exposure to GSK3915393 in the lamina propria (site of action in CeD).
- A population PBPK model will be developed using IV and oral data along with information from predicted exposure to GSK3915393 in lamina propria to assess probability of pharmacological success for Phase 2.
- Tablet formulation development work for Phase 2.

Further information on these modelling approaches are described in the data dissemination plan located in the study Trial Master File. These modelling initiatives will be reported separately from the main CSR. Abbreviated reports may be generated if GSK3915393 does not progress into Phase 2.

9.4.3.2. Cardiodynamic ECG Evaluation

Cardiodynamic ECG evaluation may be performed in the future for Part A (SAD all periods excluding the micro dose period) and Part B (MAD all cohorts). Cardiodynamic ECG evaluation will be described in a separate statistical analysis plan (SAP).

9.5. Interim Analysis

The decision to proceed to higher dose strengths in parts A and B will be made by the DEC (see Section 6.5) based on assessment of safety, tolerability and pharmacokinetic data at the preceding doses. In part C, an interim evaluation of the pharmacokinetic and safety data in periods 1 and 2 (IV GSK3915393 + ITZ or water) in conjunction with

available safety data from parts A and B will be conducted by the DEC to support the selection of the GSK3915393 oral dose to be administered in periods 3-5.

The DEC will review blinded outputs for Parts A and B of the study which may include individual participant data, tabular summaries, graphical presentations and statistical analysis. GSK members of the DEC may additionally review unblinded data in a GSK only closed session of the DEC. Unblinded data will not be shared with the investigators/site who will remain blinded throughout.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., 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.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants 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.
- A participant who is rescreened is not required to sign another ICF.

The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. 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 participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding “No” box.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- 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.

10.1.5. 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 all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients' received. The investigator(s) is/are encouraged to share the summary results with the study subjects, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

- 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 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.

10.1.7. 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 and its origin can be found in Source Data Agreement.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

GSK or 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate participant therapy and/or follow-up

10.1.9. 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.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 6 Protocol-Required Safety Laboratory Tests

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red blood cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	White blood cell (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)	Calcium	Alkaline phosphatase[2]	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	• Highly sensitive Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only)			

Laboratory Assessments	Parameters
	• Urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody • COVID-19 testing (performed at additional time noted in the SoA tables and as required)

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 7.1 and Section 10.5. All events of ALT ≥3 × upper limit of normal (ULN) and total 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 to GSK in an expedited manner (excluding studies of hepatic impairment or cirrhosis).
2. If alkaline phosphatase is elevated, consider fractionating.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. 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 intervention, whether or not considered related to the study intervention. • 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 intervention.

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

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

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

10.3.2. Definition of SAE

An SAE is defined as any serious adverse event 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 admitted (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 fulfils 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 or significant disability/incapacity

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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 for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

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

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

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- 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 required form.
- 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 sufficient 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 intervention 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 intervention 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 submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor/SAE coordinator by telephone.
- Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool 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 data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- 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, confirmation with more than one FSH prior to randomisation is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen contraception methods listed below if they wish to continue their HRT during the study.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.
- **Note:** Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Contraception Guidance:

• **CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:**
• **Highly Effective Methods[b] That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*

• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion

• Azoospermic partner (vasectomized or due to a medical cause)
  • Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
  Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

• **Highly Effective Methods[b] That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*

• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  • oral
  • injectable

• Sexual abstinence   • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria</th></tr>
<tr><td>ALT-absolute</td><td>ALT≥3xULN
If ALT≥3xULN AND bilirubin[1,2] ≥2xULN (>35% direct bilirubin) or INR >1.5, Report as an SAE.
See additional Actions and Follow Up Assessments listed below</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the 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 participants twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, within 48 hours of last dose[4]
• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
• Fractionate bilirubin, if total bilirubin≥2xULN
• Obtain complete blood count with differential to assess eosinophilia
• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications.
• Record alcohol use on the liver event alcohol intake case report form
If ALT≥3xULN AND bilirubin ≥2xULN or INR >1.5:</td></tr>
</table>

Liver Chemistry Stopping Criteria	
perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • 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 participants receiving anticoagulants
3. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

10.6. Appendix 6: Abbreviations and Trademarks

Abbreviation	Explanation
(AUC(0-∞))	AUC from time zero to infinity
(AUC(0-t))	Area under the plasma drug concentration versus time curve from time zero to last quantifiable concentration
µg	Microgram
AE	Adverse event
BID	Twice daily
BMI	Body Mass Index
CA	Competent authority
CeD	Celiac Disease
Cl	Clearance
Cmax	Maximum observed plasma drug concentration
CRF	Case Report Form
CSR	Clinical Study Report
CTFG	Clinical trial facilitation group
DDI	Drug Drug Interaction
DEC	Dose Escalation Commitee
dGP	Deamidated Gluten Peptide
DL	Dose Level
DSM	Diagnostic and Statistical Manual
EC	Ethics committee
ECG	Electrocardiogram
EMA	Endomysial Antibodies
EW	Early Withdrawal
F	Bioavailability
F_A	Product of fraction of drug absorbed
F_G	Fraction of drug escaping gut metabolism
F_H	Fraction of drug escaping hepatic metabolism
FPE	First pass extraction
FRP	Female Reproductive Potential
FTIH	First time into human
FU	Follow Up
GC	Gluten challenge
GDP	Gliadin-derived peptides
GERD	Gastroesophageal reflux disease
GFD	Gluten-free diet
GFJ	Grapefruit Juice
GSK	GlaxoSmithKline
HLA	Human Leukocyte Antigen
IBS	Irritable bowel syndrome
ICF	Informed consent form
IL2	Interleukin-2
ITZ	Itraconazole

Abbreviation	Explanation
IV	Intravenous
IVIVE	In vitro to in vivo extrapolation
LFT	Liver Function Tests
LSLV	Last Subject Last Visit
MABEL	Minimal Anticipated Biological Effect Level
MDI	Metabolism Dependent Inhibitor
MSDS	Material safety data sheet
NOAEL	No Observed Adverse Event Level
PBMC	Peripheral blood mononuclear cell
PBPK	Physiologically based pharmacokinetic
PK	Pharmacokinetics
PKPD	Pharmacokinetics/pharmacodynamics
QC	Quality control
QTcF	QT interval corrected using Bazett's formula
QTL	Quality tolerance limits
RAP	Reporting and analysis plan
RBC	Red blood cells
REC	Research Ethics Committee
RNA	Ribonucleic acid
SAE	Serious adverse events
SAP	Statistical analysis plan
SD	Single-dose
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of Activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
t1/2	Terminal half-life
TBD	To be determined
TG2	Transglutaminase 2
TID	Three times daily dose
tmax	Maximum observed plasma drug concentration
TQT	Thorough QT/QTc
tTG	Tissue Transglutaminase
ULN	Upper limit of normal
Vd	Volume of distribution
WBC	White Blood Cells
WOCBP	Woman of Childbearing Potential
WONCBP	Woman of Non-Childbearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
EnteroTracker

10.7. Appendix 7: COVID-19 Appendix

10.7.1. Overall Rationale for this Appendix

COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, and promote data integrity.

These measures will remain in place until study completion.

10.7.2. Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, you should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrollment and treatment decisions for trial participants.

As outlined in Section 8, Protocol waivers or exemptions are not allowed and every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up however when not possible, for the duration of these special circumstances, the following measures may be implemented for enrolled participants.

- Clinical investigators should document in site files and in participant notes as appropriate how restrictions related to COVID-19 led to the changes in study conduct and duration of those changes and indicate which trial participants were impacted and how those trial participants were impacted (as per the current local COVID-19 related regulatory guidance).
- Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

10.7.3. Protocol Defined Procedures/Visits:

- The protocol defined interval for the collection of samples during the follow-up visit (see Section 1.3 Schedule of Activities), may be extended up to a maximum length of 14 days.

10.7.4. Data Management/Monitoring:

- If a situation arises where on-site monitoring is no longer permitted, GSK will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a participant and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, GSK will work with the site to ensure participant privacy.
- eCRF/CRF Final or Interim Sign off Process: The PI is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing InForm (or other eDC platform) using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.
- Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by GSK

10.8. Appendix 8: Protocol Amendment History

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

Amendment 1 Dated 30-SEP-2020

Overall Rationale for the Amendment: This amendment is in response to questions raised in the MHRA's Grounds for non-acceptance letter dated 23 Sep 2020 (also including ethics committee comments under a Combined Ways of Working process) and includes revisions to the data required for making dose escalation decisions, the threshold for smaller does escalation increments, the process for investigator unblinding, update to contraception guidelines and removal of different nonclinical exposure data thresholds for individual and mean pharmacokinetic stopping criteria.

Section # and Name	Description of Change	Brief Rationale
4.3.8 Dose escalation.	The threshold for smaller escalation increments reduced to 80 mg/day.	The threshold for smaller escalation increments has been aligned to the planned maximum daily therapeutic dose.
6.3 Measures to Minimize Bias: Randomisation and Blinding	Unblinding process has been added.	To describe the process by which the investigator can access the treatment allocation for an individual subject to facilitate emergency unblinding, if required.
6.5 Dose Modification	Increase in the minimum number of subjects required to make a dose escalation decision and the minimum safety data to be reviewed has been updated to clarify it includes all vital signs and ECG data.	To ensure data from at least two-thirds of subjects dosed with GSK3915393 is available for dose escalation decisions and to enable the identification of trends safety data in the absence of any flagged abnormalities.
7.1 Discontinuation of Study Intervention.	Removed the requirement for the Investigator to consult with the Medical Monitor prior to withdrawing a participant who experiences a serious or severe clinically significant non-serious AE that is at least possibly related to investigational product.	To permit the investigator to make the judgement based on the treating investigator's opinion alone.

Section # and Name	Description of Change	Brief Rationale
7.2.2 Pharmacokinetic Stopping Criteria	Removed the different criteria for individual and group pharmacokinetic stopping criteria.	To apply the agreed stopping limits at the individual level in addition to the mean cohort exposure.
10.4.1 Definitions.	Removed reference to effective methods of contraception that are not considered to be highly effective (failure rate ≥1% per year).	To align with the Clinical Trial Facilitation Group document for clarification of effective contraception in a clinical trial.

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