Clinical Study Protocol

Primary Study Intervention(s)	GSK5464714
Other Study Intervention(s)	Not Applicable
Study Identifier	221852 (Ph1 Hepatic impairment (HI) study)
US IND Number	142905
Approval Date	25 Apr 2024
Title	A phase 1, open-label study to investigate the pharmacokinetics and safety of camlipixant in male and female participants aged 18-75 years of age with hepatic impairment compared to matched healthy participants with normal hepatic function.
Compound Number/Name	GSK5464714, camlipixant
Brief Title	A study to investigate the pharmacokinetics and safety of camlipixant in male and female healthy participants and participants with hepatic impairment aged 18-75 years of age.
Sponsor	BELLUS Health (a wholly owned subsidiary of GSK) 275 Armand-Frappier Blvd Laval, Quebec Canada, H7V 4A7.
Sponsor signatory	David A. Lipson, MD. VP Disease Area Lead, Respiratory Development Clinical Sciences, GSK.

Medical monitor name and contact can be found in local study contact information document

Protocol Investigator Agreement

I agree:

- To conduct the study in compliance with this protocol, any future protocol amendments, with the terms of the clinical trial agreement and with any other study conduct procedures and/or study conduct documents provided by GSK.
- To assume responsibility for the proper conduct of the study at this site.
- That I am aware of and will comply with GCP and all applicable regulatory requirements.
- That I will comply with the terms of the site agreement.
- To comply with local bio-safety legislation.
- To ensure that all persons assisting me with the study are adequately informed about the GSK study intervention and other study-related duties and functions as described in the protocol.
- To supervise any individual or party to whom I have delegated study-related duties and functions conducted at the study site.
- To ensure that any individual or party to whom I have delegated study-related duties and functions conducted at the study site are qualified to perform those study-related duties and functions.
- To acquire the reference ranges for laboratory tests performed locally and, if required by local regulations, obtain the laboratory's current certification or Quality Assurance procedure manual.
- To ensure that no clinical samples (including serum samples) are retained on-site or elsewhere without the approval of GSK and the express physical and/or digital informed consent of the participant.
- To perform no biological assays on the clinical samples other than those described in the protocol or its amendment(s).
- To co-operate with representative(s) of GSK in the monitoring and data management processes of the study with respect to data entry and resolution of queries about the data.
- To have control of all essential documents and records generated under my responsibility before, during, and after the study.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply, as necessary, details about the investigator(s)' ownership interest in the sponsor or the study intervention(s), and more generally about their financial ties with the sponsor. GSK will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply GSK with any necessary information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to promptly update this information if any relevant changes occur during the study and for 1 year following completion of the study.
- Agree that GSK may disclose any information about such ownership interests and financial ties to regulatory authorities.
- Agree to provide GSK with an updated Curriculum Vitae and all other documents required by regulatory agencies for this study.

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Investigator name	
Signature	
Date of signature (DD Month YYYY)	

Protocol Amendment Summary Of Changes Table

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	25 Apr 2024
Original Protocol	15 December 2023

Amendment 1 25 Apr 2024

Overall rationale for the current Amendment:

Protocol Amendment 1 is a substantial amendment meant for the purpose of clarification, CCI [redacted] CCI [redacted] Other global changes also made to increase clarity/brevity or correct formatting errors.

List of main changes in the protocol and their rationale:

Section # and title	Description of change	Brief rationale
1.3 Schedule of Activities (SoA) Table 9.3.3. Exploratory Endpoint Analysis 10.2. Appendix 2: Clinical laboratory tests	CCI [redacted]	
5.2.1.4 Diagnostic assessments Exclusion Criteria # 12	Updated the criterion to allow for rapid and/**or** PCR testing as per local guidelines.	Changed to allow some flexibility in the type of test required.
5.2.3.2 Other exclusion criteria Exclusion Criteria # 22	This criterion was not given a number in the original protocol and had to be moved to the end of the list of exclusions.	Correction of a formatting issue – no change to the criterion
8.4.4 AESIs 8.4.5 Regulatory Reporting Requirements for SAEs 8.4.8 Contact Information for Reporting SAEs, Pregnancies and Study Holding Rules 10.3.7 Recording, assessment and follow-up of AE, SAE, AESIs and pregnancies	The requirement to report AESIs (taste questionnaire results) to the sponsor within 24 hours was removed. The AESIs continue to be collected and monitored by the sponsor if they were to occur.	The reporting requirement was removed because this is a single (low) dose study.
CCI [redacted]		

Section # and title	Description of change	Brief rationale
CCI [redacted]		
1.1 Synopsis 3. Objectives and Endpoints and/or Estimands	Additions made to estimand text to better define the intentions.	For clarity.
10.2. Appendix 2: Clinical laboratory tests	Tests added to Table 9: HBcAb test; serum albumin concentration and indirect bilirubin Urine culture removed and update made to HBsAG timing of reflexive test.	Changes in this section were made for clarity
1.1 Synopsis 1.3 Schedule of Activities (SoA) Table 3. Objectives and Endpoints and/or Estimands 9.3.3. Exploratory Endpoint Analysis	CCI [redacted]	
6.8. Prior or concomitant therapy	Timing of this investigational agent following any other investigational agent updated from 30 days to 90 days.	Concomitant medication statement corrected to align with Exclusion Criterion #9
1.3 Schedule of Activities (SoA) Table	'Meal' was only marked for Day 1 in SoA table. Days 2 -5 were also marked.	Oversight
10.1.7 Dissemination of clinical study data	'Randomization codes' removed from fourth bullet.	Correction for clarity as this is an open label study.
10.1 Appendix 1: Regulatory, ethical and study oversight considerations 10.6 Appendix 6: Liver safety: suggested	Text added throughout section.	To align with current GSK Core Protocol Template.

Section # and title	Description of change	Brief rationale
actions and follow-up assessments		
11. References	The previous Investigator's Brochure has been replaced with the current IB.	For information.
Global	Correction of grammar, formatting, or spelling and addition of text for clarity/brevity	To correct minor errors and/ or add clarifying text.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AD	Atopic dermatitis
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the concentration-time curve
BCRP	Breast cancer resistance protein
BID	Twice daily
BMI	Body mass index
CAR	Chimeric antigen receptors
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent oral clearance
CCI	CCI
CCI	CCI
CCI	CCI
C_{max}	Maximum observed concentration
COVID-19	Coronavirus Disease-2019
CV%	Coefficient of variation percentage
CYP	Cytochrome P450
DDI	Drug-drug interaction
DMP	Data Management Plan

Abbreviation	Definition
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDC	Electronic Data Capture
eCRF	Electronic case report form(s)
ex	Extrapolation
FDA	Food and Drug Administration
FIH	First-in-human
FSH	Follicle-stimulating hormone
CCI	CCI [redacted]
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HI	Hepatic impairment
HIV	Human immunodeficiency virus
HRT	Hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IUD	Intrauterine device
LSLV	Last subject (participant) last visit
LSM	Least-squares mean
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
N	Number
No.	Number
NOAEL	No observed adverse effect level
OATP	Organic anion-transporting polypeptide
oz	Ounce
P-gp	P-glycoprotein
PBPK	Physiologically based pharmacokinetic
PI	Principal Investigator
PK	Pharmacokinetic(s)
PXR	Pregnane X receptor
QA	Quality Assurance
QTcF	Corrected value of the interval between the Q and T waves on the electrocardiogram tracing, corrected QT interval using Fridericia formula
RCC	Refractory chronic cough
REC	Research Ethics Committee
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SUSARs	Suspected “unexpected” serious adverse reactions
TEAE	Treatment-emergent adverse event
t½	Half-life
T_{max}	Time of occurrence of Cmax
ULN	Upper limit normal
US	United States

Abbreviation	Definition
USA	United States of America
V_z/F	Apparent volume of distribution
CCI	CCI
WHO	World Health Organization
WOCBP	Women of childbearing potential
WONCBP	Women of non-childbearing potential

Definition of Terms

Term	Definition
Blinding	A procedure in which 1 or more parties to the study are kept unaware of the intervention assignment in order to reduce the risk of biased study outcomes. The level of blinding is maintained throughout the conduct of the study, and only when the data are cleaned to an acceptable level of quality will appropriate personnel be unblinded or when required in case of a SAE. In an open-label study, no blind is used. Both the investigator and the participant know the identity of the intervention assigned.
Certified copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Co-administered (concomitant) products	A product given to clinical trial participants as required in the protocol as part of their standard of care for a condition which is not the indication for which the IMP is being tested and is therefore not part of the objective of the study.
Eligible	Qualified for enrollment into the study based upon strict adherence to inclusion/exclusion criteria.
Essential documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
Investigational medicinal product	A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

Term	Definition
Investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator. The investigator can delegate study-related duties and functions conducted at the study site to qualified individual or party to perform those study-related duties and functions.
Participant number	A unique identification number assigned to each participant who consents to participate in the study.
Participant	Term used throughout the protocol to denote an individual who has been contacted to participate or who participates in the clinical study as a recipient of the study intervention (vaccine(s)/product(s)/control). Synonym: subject.
Pharmacogenomics	The ICH E15 Guidance for Industry defines pharmacogenomics as the "Study of variation of DNA and RNA characteristics as related to drug or treatment response." Pharmacogenetics, a subset of pharmacogenomics, is "the study of variations in DNA sequence as related to drug response." Pharmacogenomic biomarkers include germline (host) DNA and RNA as well as somatic changes (e.g., mutations) that occur in cells or tissues. Pharmacogenomic biomarkers are not limited to human samples but include samples from viruses and infectious agents as well as animal samples. The term pharmacogenomic experiment includes both the generation of new genetic or genomic (DNA and/or RNA) data with subsequent analysis as well as the analysis of existing genetic or genomic data to understand drug or treatment response (PK, safety, efficacy or effectiveness, mode of action). Proteomic and metabolomic biomarker research is not pharmacogenomics.

Term	Definition
Primary Completion Date	The date on which the last participant in a clinical study was examined or received an intervention to collect final data for the primary outcome measure. Whether the clinical study ended according to the protocol or was terminated does not affect this date. For clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all the primary outcome measures.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).
Study intervention	Term used throughout the clinical study to denote a set of investigational product(s) or marketed product(s) or placebo intended to be administered to a participant. Note: “Study intervention” and “study treatment” are used interchangeably unless otherwise specified.
Study completion date	The date on which the last participant in a clinical study was examined or received an intervention/treatment to collect final data for the primary outcome measures, secondary outcome measures, and AEs (that is, the last participant's last visit or LSLV).
Study monitor	An individual assigned by the sponsor and responsible for assuring proper conduct of clinical studies at 1 or more investigational sites.

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A phase 1, open-label study to investigate the pharmacokinetics and safety of camlipixant in male and female participants aged 18-75 years of age with hepatic impairment compared to matched healthy participants with normal hepatic function.

Brief Title: A study to investigate the pharmacokinetics and safety of camlipixant in male and female healthy participants and participants with hepatic impairment aged 18-75 years of age.

Rationale:

As per the FDA hepatic guidance, a sponsor should evaluate the PK of its investigational drug in participants with HI when hepatic metabolism and/or excretion accounts for substantial portion (>20% of the absorbed drug) of the elimination of the parent or active metabolite. Camlipixant meets this criterion.

Camlipixant is primarily eliminated through liver metabolism, the main routes of metabolism are de-alkylation, oxidation, oxidation followed by glucuronidation, oxidation and ring opening, and oxidation to the carboxylic acid, de-methylation. Camlipixant is metabolized by CYP3A4, 2C8, 1A1 and 2D6 enzymes. Total camlipixant AUC is predicted to increase by approximately 1.4-fold in moderate HI participants and by 1.6-fold in severe HI participants compared to control participants with an increase of up to 3-fold for the unbound AUC in the severe category. The purpose of this study is to determine the effect of HI on the PK profile and safety of camlipixant. The data generated will provide guidance on the administration of camlipixant to participants with impaired hepatic function.

Objectives, Endpoints, and Estimands:

Objective(s)	Endpoint(s)
Primary	
To assess the effect of HI on the PK of camlipixant in participants with HI compared to healthy control participants.	$AUC_{(0-\infty)}$ and C_{max}.
Secondary	
To evaluate the safety and tolerability of camlipixant in participants with HI compared to healthy control participants.	Incidence of Adverse Events, Serious Adverse Events and Adverse Events of Special Interest. Incidence of participants with clinically relevant changes in clinical laboratory tests, ECG and vital signs assessments.
To assess the effect of HI on other PK parameters of camlipixant in participants with HI compared to healthy control participants.	Tmax, $t_{½}$, CL/F, and Vz/F.
Exploratory	
CCI [redacted]	

Primary Estimand:

The geometric mean of PK parameters area under the concentration-time curve from time zero extrapolated to infinity [$AUC_{(0-\infty)}$] and maximum observed plasma concentration [C_{max}] in adult participants with HI vs. adult healthy control participants receiving 50 mg of camlipixant (or 25 mg in scenario 3) where issues that affect exposure to study drug such as emesis, dosing errors, or important protocol violations will be handled while on-treatment strategy. The primary PK estimand is described by the following attributes:

- Population: male and female adult participants 18 to 75 years of age inclusive with mild, moderate, or severe HI vs. healthy male and female adult participants 18 to 75 years of age inclusive.
- Treatment condition: single dose of 50 mg camlipixant or a single dose of 25 mg in the severe hepatic impairment group in Scenario 3.
- Variable: area under the concentration-time curve from time zero extrapolated to infinity [$AUC_{(0-\infty)}$] and maximum observed plasma concentration [C_{max}].
- Summary measure: ratio of the geometric mean of each HI group vs. Healthy matched participants for $AUC_{(0-\infty)}$ and C_{max}.
- Intercurrent events: issues that affect exposure to study drug such as emesis, dosing errors, or important protocol violations will be handled while on-treatment strategy. Interest lies in estimating the effect of HI on the PK of camlipixant, when patients receive the single dose of camlipixant and while patients are sufficiently compliant with camlipixant to accurately assess exposure.

Overall design:

This will be a phase 1, open-label, multi-center (3 planned), non-randomized, parallel-group, single dose, adaptive study in adults with moderate (Part 1) and mild and/or severe hepatic impairment (Part 2) and matched healthy control participants with normal hepatic function (Part 1 and 2). All participants will undergo screening within 28 days prior to dosing. A decision to progress from Part 1 to Part 2 and which groups to dose on Part 2 will be made based on the available safety and PK study results from Part 1.

A total of up to 48 male and female participants will be enrolled.

In Part 1, enrollment will begin for participants with moderate HI (Child-Pugh score of 7-9; n=8). Healthy control participants (n=8) will be matched in gender, race, age (±10 years), and weight (±20%) to participants with moderate HI. All participants will receive 50 mg of camlipixant as a single oral dose in the fasted state. Following safety and PK data review by the study team of a minimum of n=6 in each group of Part 1 a decision will be made about which HI category to be dosed on Part 2.

- Scenario 1: CCI [redacted]
- Scenario 2: CCI [redacted]
- Scenario 3: CCI [redacted]

In Part 2, a single oral dose of camlipixant 50 mg (or 25 mg for severe HI in Scenario 3) will be administered to the selected group(s) and their matched healthy control participants in a fasted state.

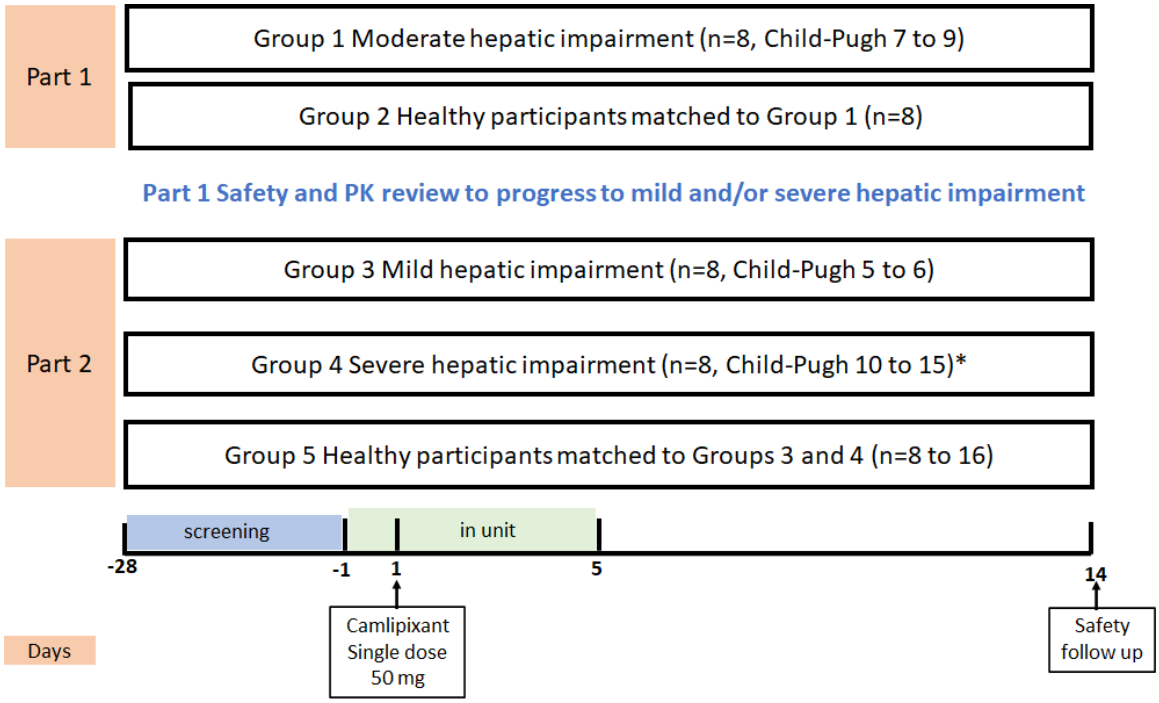
In both Parts, PK samples for camlipixant total plasma concentration will be collected pre-dose and up to 96 hours post-dose. Participants will be confined to the investigator site from Day -1 at the time indicated by the investigator site (at least 10 hours prior to Day 1 dosing), until after the 96-hour blood draw and/or study procedures. CCI [redacted]

Number of Participants: Refer to Section 9.5.

Data Monitoring/Other Committee: Refer to Section 10.1.6.

1.2. Schema

Figure 1 Study design overview



*In Scenario 3, severe HI participants may receive a single dose of 25 mg Camlipixant on Day 1.

1.3. Schedule of activities (SoA)

Table 1 Schedule of Activities

Procedure (refer to Section 8)	**Screening** (up to 28 days before Day 1)	**Study Days in Each Group**																						**ED**	**Telephone Follow-up** (14 ±2 days post-dose)/End of study	**Notes**
Days	**-28**	**-1**	**1**																**2**		**3**	**4**	**5**			Follow – up: Phone call to be conducted using site standard procedures for all participants that received study drug, including those that withdraw early from the study, to determine if any AE has occurred since the last study visit
Allowed interval (Hours)		C-I	P	0	0.25	0.5	0.75	1	1.5	2	2.5	3	4	6	8	10	12	16	24	36	48	72	96			
Administrative procedure																										
Informed consent	●																									See Section 10.1.3 for details
Inclusion and exclusion criteria	●	●																								Recheck clinical status before 1st dose of study medication. See Section 5.1 and Section 5.2 for Inclusion and Exclusion criteria
Demography	●																									See Section 8.1.1 for more information
Medical History	●																									Substances: [Drugs, Alcohol, tobacco and caffeine.

																									Premature CV disease: female participant <65 years or male participant <55 years in first degree relatives only. See Section 8.1.2 for more information.
	Safety Evaluation																								
Full physical examination	•	•																				•	•		See Section 8.3.1 for more information. To be performed on Day 5 or prior to early termination from the study.
Height	•																								
Weight	•	•																							
Assessment of Hepatic Function (Including Child-Pugh Classification [for HI Participants Only])	•	•																							If there is a shift in score leading to a change of grade in reference to the screening visit, that is considered clinically significant by the PI, then the participant will be screen failed for the study. The participant may be re-screened later on if the hepatic condition stabilized.
Vital Signs (HR, BP, RR and T)	•		•																•		•	•	•	•	To be performed within 3 hours prior to dosing on Day 1. See Section 8.3.2 for more information. Day 5 or prior to early termination from the study.
12-Lead Safety ECG	•		•						•														•	•	To be performed on Day 5 or prior to early

																									termination from the study. See Section 8.3.3 for more information.
Hem, Serum Chem, Coag, and UA	•	•																					•	•		Samples for serum chemistry will be obtained after a fast of at least 8 hours. See section 10.2 for exceptions. Day 5 or prior to early termination from the study.
CCI																										
Serum/Urine Pregnancy Test (Females Only)	•	•																					•	•		At screening, pregnancy test will be performed in serum; other pregnancy test can be performed in serum or urine as per local guidelines. See Section 8.4.6 for more information.. Day 5 or prior to early termination from the study.
Serum FSH (as needed in WOCBP Only)	•																									
Urine Drug and Breath Alcohol Screen	•	•																								
HIV, Hepatitis B and C screening]	•																									

AE Monitoring		•																							•	•	Day 5 or prior to early termination from the study.
SAE/Pregnancy Monitoring	•	•																							•	•	Pregnancy will be reported at any time following study drug administration (or up to 30 days following dosing).
Concomitant medications monitoring	•	•																							•	•	
	Study Intervention administration and PK assessments																										
Meal		•	•																•	•	•	•	•				
Camplixant Dosing				•																							Participants in all groups will be dosed at approximately the same clock time in the morning in a fasted state.
Blood for camlipixant total plasma concentration			•		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•			

CCI [redacted]

	Other procedures																												
Clinical Confinement																													
Visit	●																												Participants will be admitted to the site on Day -1, at least 10 hours prior to Day 1 dosing.

AE = Adverse event(s), BP = Blood pressure, C-I = Check-in, Chem = Chemistry, Coag = Coagulation, ConMeds = Concomitant medication, ED: Early discontinuation; ECG = Electrocardiogram, FSH = Follicle-stimulating hormone, F/U = Follow-up call, Hem = Hematology, HI = Hepatic impairment, HIV = Human immunodeficiency virus, HR = Heart rate, P = Pre-dose, PMP = Postmenopausal, RR = Respiratory rate, S = Screening, SAE = Serious adverse events, T = Temperature, UA = Urinalysis.

● Is used to indicate a study procedure that requires databasing (either in eCRF, device, laboratory or other third party vendor).

The timing of planned study assessments may change during the course of the study based on emerging data/in-stream data review (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

The CA and IEC will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the ICF. The changes will be approved by the CA and the IEC before implementation.

2. INTRODUCTION

2.1. Study rationale

The liver is involved in the clearance of many drugs through a variety of oxidative and conjugative metabolic pathways and/or through biliary excretion of the unbound drug or metabolites. Alterations of these excretory and metabolic activities by HI can lead to higher drug exposure. Liver disease may also alter kidney function, which can lead to higher drug/metabolites exposure; even in cases where the liver is not the primary route of elimination/excretion. Hence, hepatic disease can alter the absorption and disposition of drugs as well as their efficacy and safety. In accordance with the FDA hepatic guidance [FDA, 2003], a sponsor should evaluate the PK of its investigational drug in participants with HI when hepatic metabolism and/or excretion accounts for substantial portion (>20% of the absorbed drug) of the elimination of the parent or active metabolite. Camlipixant meets this criterion [IB, 2023].

Camlipixant is CCI [redacted] [IB, 2023].

CCI [redacted]

The purpose of this study is to determine the effect of HI on the PK profile and safety of camlipixant. The data generated will provide guidance on the administration of camlipixant to participants with impaired hepatic function.

2.2. Background

P2X3 receptors are ATP cation-gated channels located on primary afferent neurons in various tissues, including respiratory tract. ATP released from damaged or inflamed tissues acts on P2X3 receptors, triggering pain or irritation signals transmitted by sensory afferent fibers to the brain. Specifically, the P2X3 receptor appears to play a role in cough hypersensitivity and has been identified as an important target in RCC. Camlipixant (previously identified as BLU-5937) was shown to reduce significantly cough frequency in patients with baseline awake cough frequency ≥25 coughs/hour in a phase 2b clinical study. It is currently being investigated in phase 3 clinical trials in RCC patients at doses of CCI and CCI mg twice daily (BID).

Camlipixant has been administered to healthy participants as CCI [redacted] CCI [redacted]. Two drug-drug interaction (DDI) studies have been conducted with camlipixant as a victim to evaluate the effect of strong inhibitors of CYP3A4 (itraconazole) and CYP2D6 (paroxetine) on camlipixant PK. The results showed a weak interaction between camlipixant and itraconazole (27% increase in AUC) and no effect of paroxetine on camlipixant PK. CCI [redacted]

A detailed description of the chemistry, pharmacology, efficacy, and safety of camlipixant is provided in the IB and any associated IB Supplements [IB, 2023].

2.3. Camlipixant benefit/risk assessment

CCI [redacted]

Detailed information about the known and expected benefits and risks and reasonably expected AEs of camlipixant may be found in the IB and DSUR.

2.3.1. Risk assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention- camlipixant		
Ocular effects	In long term toxicity studies in rats and dogs, camlipixant had non-adverse effects leading to very minor anterior cortical lens opacities in the lens of rats and partially reversible small, faint, slight to very slight, focal or multifocal corneal opacities in dogs.	Exposure to camlipixant is limited to a single dose Close monitoring of AEs to assess ocular effects

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	No AEs related to corneal or lens lesions or other eye disorders suggestive of treatment-related ocular injury were reported in the completed Phase 1 and Phase 2 studies.	
Testicular effects	In long term toxicity studies in rats and dogs, adverse effects were observed in the testis with decreased sperm in the epididymis which were fully reversible and demonstrated safety margins for the 50 mg BID dose in humans of >25-fold of the NOEL in rats and >6-fold of the NOAEL in dogs. No effect on reproductive hormone levels was seen. No AEs related to male reproductive disorders were reported in the completed Phase 1 and Phase 2 clinical trials. Reproductive hormone levels were tested in a subset of men enrolled in SOOTHE (25 males with mean age of 58.3 years), and results showed no effects at any dose of camlipixant.	Exposure to camlipixant is limited to a single dose. Close monitoring of AEs to assess any potential testicular effects.
Cardiovascular effects – QT prolongation	In vitro studies indicated that camlipixant is a weak inhibitor of hERG channels. Camlipixant has a dose-dependent QT prolongation effect as shown in a thorough QT study. The study showed the likelihood of a clinically relevant prolongation of QT interval (i.e., a $\Delta\Delta$QTcF) of 10ms or more) is considered low at doses up to 200 mg BID. No cardiac rhythm disturbances (e.g., Torsade de pointes, ventricular or atrial arrythmias, prolonged QT interval) were reported in the completed Phase 1 and Phase 2 clinical trials. ECG results did not suggest an imbalance in cardiac conduction-related abnormalities or an effect on QTc interval at doses up to 200 mg BID.	Exposure to camlipixant is limited to a single dose and at a dose which a clinically relevant prolongation of QT interval is not anticipated. ECGs are performed at baseline, 1.5 hours post-dose (at the anticipated time of C_{max}) and at Day 5 to monitor for any abnormalities. Close monitoring of AEs to assess any that may be secondary to QT prolongation.
Hepatic effects	Hepatocellular findings were observed with repeat dosing with camlipixant in mice (28-day study) and rats (26-week study) consistent with xenobiotic nuclear receptor CAR and/or PXR induction. No adverse liver findings were reported in the repeat-dose toxicity studies in dogs. In clinical studies, reversible elevations of ALT and AST >3×ULN not associated with concurrent increase in bilirubin have been observed in participants receiving higher doses of camlipixant (≥200 mg BID). Mild hyperbilirubinemia was also observed at higher doses of camlipixant (≥200 mg BID). It was not associated with transaminase elevations and appears likely due to OATP inhibition.	Exposure to camlipixant is limited to a single dose. Liver enzymes will be monitored during the study. Close monitoring of AEs to assess any potential hepatic effects.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Gastrointestinal (GI) disturbances	Camlipixant-related decreased motility and mucosal erosions were observed in repeat-dose toxicity studies in rats up to 6 months duration and in dogs up to 9 months duration. These findings were reversible and demonstrated safety margins for the 50 mg BID dose in humans of >8-fold of the NOAEL in rats and >25-fold of the NOAEL in dogs. Mild to moderate GI dysmotility AEs have been reported in the completed Phase 1 and Phase 2 clinical studies; none caused treatment discontinuation, and no dose relationship was observed. No GI ulcers or bleeding was reported.	Exposure to camlipixant is limited to a single dose. Close monitoring of AEs to assess any potential gastrointestinal disturbances.
Taste disturbances	Taste disturbance has been reported in clinical studies of camlipixant and other P2X3 antagonists. In completed Phase 1 and Phase 2 studies, most taste disturbances were mild to moderate in intensity, started within a week of the first dose, and resolved by the end of the study. In phase 2 studies of 4 weeks duration and doses up to 200 mg BID, taste disturbances were more frequent among participants who received camlipixant than among those who received placebo (4.6% vs. 0% in SOOTHE and 15.3% vs. 2.9% in BLUEPRINT).	Exposure to camlipixant is limited to a single dose. Close monitoring of AEs to assess taste disturbance.
Study Procedures		
Venipuncture	Participants will be required to have blood samples taken. Risk of bruising, and rarely infection.	Trained personnel will perform venipuncture.
Risks of ECG pad removal	Some discomfort and rash may occur where the ECG pads are applied and subsequently removed.	ECGs will be conducted by appropriately trained personnel and effort made to minimize contact time for application of the pads.

Reproductive risks: Currently we are not fully aware of the effects of the study drug on unborn babies, or pregnant or breastfeeding women. In the oral study of the effects of camlipixant on embryo-fetal development (EFD) in rats, no test article-related effects on maternal survival, clinical findings, or ovarian and uterine parameters were observed at any camlipixant dose levels evaluated. Lower maternal and gestational mean body weights and reduced food consumption were observed in pregnant female rats at the highest dose administered. Lower fetal body weights and increased incidence of fetal tail abnormality and skeletal variations were observed at this highest dose. The NOAEL for both maternal toxicity and for developmental toxicity was considered 100 mg/kg/day.

2.3.2. Benefit assessment

There will be no direct therapeutic benefit for participants from receipt of study drug. An indirect health benefit to the participants enrolled in this study are the free medical tests received at screening and during the study.

2.3.3. Overall benefit-risk conclusion

The dose of camlipixant administered in this study is not anticipated to induce any potential risk to participants participating in this study, as it is within doses assessed in prior clinical studies that have been demonstrated to be well tolerated at CCI [redacted] in healthy volunteers. The safety monitoring practices employed by this protocol (i.e., AEs, clinical laboratory tests, vital sign measurements, 12-lead ECG, and physical examination) are adequate to protect the participants' safety and should detect all TEAEs.

3. OBJECTIVES, ENDPOINTS AND ESTIMANDS

Objective(s)	Endpoint(s)
Primary	
To assess the effect of HI on the PK of camlipixant in participants with HI compared to healthy control participants.	$AUC_{(0-\infty)}$ and C_{max}.
Secondary	
To evaluate the safety and tolerability of camlipixant in participants with HI compared to healthy control participants.	Incidence of Adverse Events, Serious Adverse Events and Adverse Events of Special Interest. Incidence of participants with clinically relevant changes in clinical laboratory tests, ECG and vital signs assessments.
To assess the effect of HI on other PK parameters of camlipixant in participants with HI compared to healthy control participants.	T_{max}, $t_{½}$, CL/F, and V_z/F.
CCI [redacted]	

$AUC_{(0-\infty)}$: Area under the concentration-time curve from 0 extrapolated to infinity, CL/F: Apparent oral clearance, CCI [redacted] C_{max}: Maximum observed concentration, HI: Hepatic impairment, PK: Pharmacokinetics, Tmax: Time of occurrence of C_{max}, $t_{½}$: Half-life, CCI [redacted], Vz/F: Apparent volume of distribution, CCI [redacted]

Primary Estimand:

The geometric mean of PK parameters area under the concentration-time curve from time zero extrapolated to infinity [$AUC_{(0-\infty)}$] and maximum observed plasma concentration [C_{max}] in adult participants with HI vs. adult healthy control participants receiving 50 mg

of camlipixant (or 25 mg in scenario 3) where issues that affect exposure to study drug such as emesis, dosing errors, or important protocol violations will be handled while on-treatment strategy. The primary PK estimand is described by the following attributes:

- Population: male and female adult participants 18 to 75 years of age inclusive with mild, moderate, or severe HI vs. healthy male and female adult participants 18 to 75 years of age inclusive.
- Treatment condition: single dose of 50 mg camlipixant or a single dose of 25 mg in the severe hepatic impairment group in Scenario 3.
- Variable: area under the concentration-time curve from time zero extrapolated to infinity [$AUC_{(0-\infty)}$] and maximum observed plasma concentration [C_{max}].
- Summary measure: ratio of the geometric mean of each HI group vs. healthy matched participants for $AUC_{(0-\infty)}$ and C_{max}.
- Intercurrent events: issues that affect exposure to study drug such as emesis, dosing errors, or important protocol violations will be handled while on-treatment strategy. Interest lies in estimating the effect of HI on the PK of camlipixant, when patients receive the single dose of camlipixant and while patients are sufficiently compliant with camlipixant to accurately assess exposure.

4. STUDY DESIGN

4.1. Overall design

This will be a phase 1, open-label, multi-center (3 planned), non-randomized, parallel-group, single dose, adaptive study in adults with moderate (Part 1) and mild and/or severe HI (Part 2) and matched healthy control participants with normal hepatic function (Part 1 and 2). All participants will undergo screening within 28 days prior to dosing. A decision to progress from Part 1 to Part 2 and which groups to dose on Part 2 will be made based on the available safety and PK study results from Part 1.

A total of up to 48 male and female participants will be enrolled.

In Part 1, enrollment will begin for participants with moderate HI (Child-Pugh score of 7-9; n=8). Healthy control participants (n=8) will be matched in gender, race, age (±10 years), and weight (±20%) to participants with moderate HI. All participants will receive 50 mg of camlipixant as a single oral dose in the fasted state. Following safety and PK data review by the study team of a minimum of n=6 in each group of Part 1 a decision will be made about which HI category to be dosed on Part 2 according to the following criteria (see Section 9.4 for additional details).

- Scenario 1: CCI [redacted]
- Scenario 2: CCI [redacted]

- Scenario 3: CCI [redacted]

In Part 2, a single oral dose of camlipixant 50 mg (or 25 mg in Scenario 3) will be administered to the selected group(s) and their matched healthy control participants in a fasted state. If the camlipixant dose is reduced to 25 mg for the severe HI participants, the matching healthy controls to the severe HI group will also be dosed with 25 mg.

In both Parts, PK samples for camlipixant total plasma concentration will be collected pre-dose and up to 96 hours post-dose. Participants will be confined to the investigator site from Day -1 at the time indicated by the investigator site (at least 10 hours prior to Day 1 dosing), until after the 96-hour blood draw and/or study procedures. CCI [redacted]

A follow-up visit will occur 14 days (±2 days) after the dose of study treatment. The investigator site will attempt to contact over the phone all participants who received the study intervention (including participants who withdrew early from the study) using their standard procedures 14 ± 2 days after dosing to determine if any AE has occurred since the last study visit.

A participant's total involvement with the study will be up to 6 weeks (including screening window).

Table 2 Study Cohorts

Study Part	Group	Sample Size	Treatment[1]
Part 1	1 (Moderate HI)[2]	8	Camlipixant 50 mg tablet
	2 (Matched Healthy Controls to Group 1)[3]	8	
Part 2	3 (Mild HI)[2]	8	
	4 (Severe HI)[2]	8	
	5 (Matched Healthy Controls to Groups 3 and 4)[3,4]	8 to 16	

[1] All participant will receive a single 50 mg oral dose of camlipixant in a fasted state (or 25 mg for severe HI in scenario 3).

[2] Hepatic impairment categorized by Child-Pugh classification system (see Table 3: Mild: Score 5-6; Moderate: Score 7-9; Severe: Score 10-15) in conjunction with the specification listed in Section 5.

[3] Healthy control participants are matched to the HI participants in gender, race, age (±10 years), and weight (±20%).

[4] A healthy control participant in group 5 can be matched to both a mild HI and a severe HI participant (Scenario 2 only).

Child-Pugh classification of HI:

The Child-Pugh classification will be used to categorize HI due to its widespread use and acceptance by regulatory agencies (including the US FDA [FDA, 2003] and the European Medicines Agency [EMA, 2005]). This study design is supported by FDA guidelines for drugs that undergo substantial hepatic metabolism and for which a dosage guideline is sought for participants with HI.

In the current study, participants with chronic, stable HI (i.e., has a diagnosis of chronic [≥6 months], stable (no acute episodes of illness within 30 days prior to dosing due to deterioration in hepatic function) hepatic insufficiency with features of cirrhosis due to any etiology) will be enrolled, and the Child-Pugh scale will be used to classify the severity of liver disease. The scale employs 5 clinical measures of liver disease listed in Table 3. Each clinical measure is scored 1 to 3, with 3 indicating the most severe condition. A composite of all 5 scores for each clinical measure is determined for each participant.

Participants with composite scores of 5 to 6, 7 to 9, and 10 to 15 on this Child-Pugh scale are classified as having mild, moderate, and severe HI, respectively (see Table 4 and Table 5).

Table 3 Derivation of Child-Pugh Classification Score[1]

Parameters	1 point	2 points	3 points
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Total serum bilirubin (mg/dL)	<2.0	2.0 to 3.0	>3.0
Prothrombin time (sec prolonged) or International normalized ratio	<4.0 <1.70	4.0 to 6.0 1.70 to 2.30	>6.0 >2.30
Ascites	Absent	Slight or participant on one medication to control ascites	Moderate or participant on medications to control ascites
Hepatic encephalopathy grade (see Table 4)	None	Grade 1 or 2 (or suppressed with medication)	Grade 3 or 4 (participant receiving medication(s) to prevent encephalopathy)

[1] Adapted from U.S. Department of Health and Human Services. Guidance for Industry. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling [FDA, 2003].

Table 4 Determination of Encephalopathy Grade[1]

Encephalopathy Grade	Definition
0	Normal consciousness, personality, neurological examination
1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting

Encephalopathy Grade	Definition
2	Lethargic, time-disoriented, inappropriate, asterixis, ataxia
3[a]	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity
4[a]	Unrousable coma, no personality/behavior, decerebrate

[1] Adapted from U.S. Department of Health and Human Services. Guidance for Industry. Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling [FDA, 2003].

[a.] Participants with clinically active Grade 3 or 4 encephalopathy are excluded.

Safety will be monitored throughout the study by repeated AE assessments, vital signs, physical examinations, clinical laboratory tests, and ECGs.

Discontinued participants may be replaced at the discretion of the sponsor if they were not discontinued due to AEs or SAEs.

4.2. Scientific rationale for study design

This study will be an open-label, single dose, parallel-group, adaptive study for assessment of camlipixant in participants with HI and matched control participants. The study design is consistent with the recommendations outlined in the FDA guidance, [FDA, 2003] and the European Medicines Agency [EMA, 2005].

This study will be open-label as the primary endpoint is PK.

A single dose of camlipixant will be used in this study as camlipixant PK is linear and time independent.

Part 1 of the study will be conducted in participants with moderate HI and matched healthy controls. The adaptive design of this study allows for review of the moderate HI (group 1) PK and safety data before dosing mild and/or severe HI participants (groups 3 and 4) depending on the extent of change in camlipixant $AUC_{(0-\infty)}$ in the moderate HI participants (group 1) relative to matched healthy controls (group 2) (see Section 9.4). The adaptive nature of the study will allow reviewing dosing the severe HI group if the increase in exposure in the moderate group is significantly higher than predicted. CCI [redacted] although a 50 mg dose in the severe group may still be within the safety margins, a dose reduction to 25 mg may be considered as it could be more informative to generate PK data at a dose less likely to approach the saturation of the liver capacity. At the same time, the adaptive nature of the study will avoid dosing the mild HI group if a minimum effect is observed in CCI [redacted] vs healthy controls has been set as the limit for which camlipixant PK is considered not affected by moderate HI impairment as such difference would be unlikely to warrant a dose adjustment.

C_{max} is not included in the decision criteria to move from Part 1 to Part 2 as HI is expected to affect the clearance of camlipixant and therefore mainly the AUC. Based on the camlipixant PK characteristics, any effect of HI on C_{max} is expected to be of lower magnitude than an effect of HI on AUC.

To ensure participants in the healthy control group are comparable (by gender, age, race and body weight) to the hepatically impaired group, each participant with HI (Group 1 and Groups 3 and 4)) will be matched to a healthy control participant (Groups 2 and 5). Healthy participants will be matched to participants with different degrees of HI by age (± 10 years), race, body weight (±20%), and gender (1:1).

CCI [redacted]; therefore, light smokers may be enrolled in this study as no significant impact on the PK of camlipixant is anticipated.

Camlipixant plasma protein binding CCI [redacted] [IB, 2023]. CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted]

CCI [redacted] CCI [redacted]

4.3. Justification for dose

Camlipixant was well tolerated at CCI [redacted] in healthy participants, and expected exposures in this study are lower than exposures from the highest single dose in the single ascending dose/multiple ascending dose and exposures in the 28-day phase 2 studies. The anticipated therapeutic oral doses of camlipixant of CCI [redacted] and CCI [redacted] BID are being investigated in phase 3 clinical trials in RCC participants. Camlipixant PK is relatively linear across the dose range being evaluated in the phase 3 studies. Therefore, a single dose of 50 mg camlipixant was selected for this study CCI [redacted]. CCI [redacted]

4.4. End-of-study definition

A participant is considered to have completed the study if the participant has completed the study including the last contact or the last scheduled procedure shown in the SoA (Section 1.3).

The end of the study is defined as the date of the last contact with the last participant. Following an unresolved AE/SAE to resolution or ongoing concomitant medication, or an unscheduled assessment that occurs after the last scheduled assessment, is considered last contact.

5. STUDY POPULATION

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

Participants who do not qualify based on a reversible medical condition or mild intercurrent illness may be re-evaluated after further testing/examination or re-screened after the condition is resolved following discussion with the sponsor. Screening tests may be repeated per discretion of the PI or the sponsor.

5.1. Inclusion criteria

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

5.1.1. Inclusion criteria for all participants

1. Adult male or female participant, ≥ 18 years and ≤ 75 years of age at the screening visit.
2. Male and female participants must follow protocol-specified contraception guidance as described in Section 10.4.

- Female Participants: A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
  - Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4: Contraceptive and Barrier Guidance.

  OR

  - Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.4 during the study intervention period and for at least 14 days after the last dose of study intervention. The investigator should evaluate 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 urine or serum as required by local regulations) within specify timeframe before the first dose of study intervention. See Section 8.3.5 Pregnancy Testing.
  - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5.
- 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.

3. Must weigh at least 50 kg and have a BMI ≥ 18.0 and ≤ 40.0 kg/m^2, at the screening visit.
4. Continuous non-smoker who has not used nicotine- and tobacco-containing products or light smoker (≤ 5 cigarettes/day or the equivalent) for the last 3 months prior to study screening.
5. Understands the study procedures in the informed consent form (ICF) and is willing and able to comply with the protocol.

5.1.1.1. Additional inclusion criteria for hepatic impaired participants

6. Aside from HI, be sufficiently healthy for study participation based upon medical history, physical examination, vital signs, ECGs, and screening clinical laboratory profiles, as deemed by the PI or designee, including the following:
   - Seated blood pressure is ≥ 90/40 mmHg and ≤160/100 mmHg at the screening visit.
   - Seated heart rate is ≥40 bpm and ≤99 bpm at the screening visit.
   - QTcF interval is ≤480 msec and has ECG findings considered normal or not clinically significant by the PI or designee at the screening visit.
   - Estimated creatinine clearance ≥80 mL/min at the screening visit.
   - Total bilirubin ≤6 mg/dL.
7. Has a score on the Child-Pugh scale at the screening visit as follows:
   - Severe HI: ≥10 and ≤15; or
   - Moderate HI: ≥7 and ≤9; or
   - Mild HI: ≥5 and ≤6.
8. Has stable HI as defined by a diagnosis of chronic (≥ 6 months), stable (no acute episodes of illness within 30 days prior to dosing due to deterioration in hepatic function) hepatic insufficiency with features of cirrhosis due to any etiology.

5.1.1.2. Additional inclusion criteria for healthy control participants

9. Medically healthy with no clinically significant medical history, physical examination, screening clinical laboratory profiles, vital signs and ECGs, as deemed by the PI or designee, including the following:
   - Seated blood pressure is ≥90/40 mmHg and ≤140/90 mmHg at the screening visit.
   - Seated heart rate is ≥40 bpm and ≤99 bpm at the screening visit.
   - QTcF interval is ≤450 msec and has ECG findings considered normal or not clinically significant by the PI or designee at the screening visit.
   - QTc ≤480 msec in participants with bundle branch block

   NOTE:
   - The QTc is the QT interval corrected for heart rate according to Fridericia's formula (QTcF). It is either machine-read or manually over-read.
   - AST, ALT, direct bilirubin, indirect bilirubin, and total bilirubin within normal ranges at the screening visit and check-in. Only abnormal values up to 1.5 x upper limit of normal may be repeated once.

5.2. Exclusion criteria

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

5.2.1. Exclusion criteria for all participants

5.2.1.1. Medical conditions

1. Mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or are expected during the conduct of the study.
2. Surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the participant's safety in case of participation in the study.
3. History or presence of liver or other solid organ transplant.
4. History of acute pancreatitis within 1 year of study entry.

5.2.1.2. Prior/concomitant therapy

5. History or presence of hypersensitivity or idiosyncratic reaction to the study drug or related compounds.
6. Has received any COVID-19 vaccine within 14 days prior to dosing.
7. Unable to refrain from or anticipates the use of prohibited prescription or non-prescription medication, herbal remedies, or supplements as listed in Section 6.8.

8. History or presence of drug abuse within the past 6 months prior to dosing. Positive drug screen due to prescription drug use in hepatic impaired participants will be allowed if approved by PI on a case by case basis.

5.2.1.3. Prior/concurrent clinical study experience

9. Participation in another clinical study within 30 days (or 5 half-lives, whichever is longer) prior to dosing. The 30-day window will be derived from the date of the last blood collection or dosing, whichever is later, in the previous study to Day 1 of the current study.

5.2.1.4. Diagnostic assessments

10. Positive pre-study drug/alcohol screen, including THC (tetrahydrocannabinol) at the screening visit or at check-in, unless the positive drug test is due to prescription drug use that is approved by the PI or designee and sponsor.
11. Positive results for HIV.
12. Has positive coronavirus (SARS-CoV-2) rapid test and/or positive polymerase chain reaction test (based on local procedures) at check-in.
13. Presence of hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) at screening or within 3 months prior to first dose of study intervention.
14. Positive hepatitis C antibody test result at screening or within 3 months prior to starting study intervention. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, after performing a reflex test for HCV RNA and documenting the negative hepatitis C RNA test is obtained before the enrollment of participant.

5.2.1.5. Other exclusion criteria

15. Unhealthy alcohol use, defined as use more than 24 g pure alcohol per day for male and 12 g for female (12 g equals to approximately 300 mL beer, 100 mL wine, or 25 mL spirits).
16. Has been on a diet incompatible with the on study diet, in the opinion of the PI or designee, within the 30 days prior to dosing.
17. Donation of blood or plasma greater than 400 ml within the last 90 days prior to dosing.
18. Donation of bone marrow within the last 6 months prior to dosing.

5.2.2. Additional exclusion criteria for hepatic impaired participants

5.2.2.1. Medical conditions

19. History or presence of clinically significant medical or psychiatric condition or disease (aside from HI) in the opinion of the PI or designee and Sponsor medical representative.

5.2.3. Additional exclusion criteria for healthy control participants

5.2.3.1. Medical conditions

20. History or presence of clinically significant medical or psychiatric condition or disease in the opinion of the PI or designee and Sponsor medical representative.

5.2.3.2. Other exclusion criteria

21. History or presence of alcoholism or drug abuse within the past 2 years prior to dosing.
22. Female participant with a positive pregnancy test at the screening visit or at check-in or who is lactating (also applies to female HI participants).

5.3. Lifestyle considerations

5.3.1. Meals and dietary restrictions

- Water (except water provided with dosing) will be restricted 1 hour prior to and 1 hour after dosing, but will be allowed ad libitum at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.
- Participants will be required to fast overnight for at least 10 hours prior to dosing and will continue the fast for at least 4 hours post-dose.
- After dosing, if a participant exhibits symptom(s) of hypoglycemia, a sugary beverage may be provided at the discretion of the PI and must be documented.
- Each meal and/or snacks served at the investigator site will be standardized and will be similar in caloric content and composition and will be taken at approximately the same time.
- When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the investigator site, participants will be required to fast from all food and drink except water between meals and snacks.
- Refrain from consumption of red wine, Seville oranges, grapefruit, or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from at least 14 days before the start of study intervention until the last PK sample collection.

5.3.2. Caffeine, alcohol, and tobacco

Participants will refrain to use the following:

- During the 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 until after collection of the final PK sample.

- During the dosing session, participants will abstain from alcohol and alcohol containing foods or beverages for 48 hours before the start of dosing until after collection of the final PK sample.
- Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.

5.3.3. Activity

Participants will remain ambulatory or seated upright for the first 4 hours after the morning camlipixant dosing, except when they are supine or semi-reclined for study procedures. However, should AEs occur at any time, participants may be placed in an appropriate position or will be permitted to lie down on their right side.

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

5.4. Screen failures

Within 28 days prior to dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2), and tobacco use (including number of cigarettes smoked per day) will be recorded. At the screening visit, each participant will be assessed by collection of AEs, SAEs, clinical laboratory tests, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, and a physical examination.

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, any protocol deviations and any serious adverse events (SAEs). If there is a shift in score leading to a change of grade in reference to the screening visit, then the participant will be screen failed for the study. The participant may be re-screened later on if the hepatic condition stabilized.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once. Re-screened participants should be assigned a new participant number are to be record in the participants' eCRF.

5.5. Criteria for temporarily delaying enrollment/randomization/administration of study intervention

Not applicable.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

The definition of study intervention is provided in the Definition of Terms

Table 5 Study Intervention (s) administered

Intervention Label	BLU-5937
Intervention Name	Camlipixant BLU-5937 (GSK5464714)
Intervention Description	Camlipixant BLU-5937 (GSK5464714) 50 mg* tablet
Type	Drug
Dose Formulation	Tablet
Unit Dose Strength(s)	50 mg*
Dosage Level(s)	50 mg* single dose At 0 hour on Day 1**
Route of Administration	Oral***
Use	Experimental
IMP and NIMP/AxMP	IMP
Sourcing	Provided centrally by the Sponsor.
Packaging and Labeling	Study intervention will be provided in a container. Each container contains 68 tablets and will be labeled as required per country requirement.

* 25 mg tablets will be supplied if the severe HI group requires a dose reduction.

** The exact clock time of dosing will be recorded. Hour 0 will be set as dosing time. Participants in all groups will be dosed at approximately the same clock time in the morning.

*** Study drugs will be administered orally with approximately 240 mL of water. Participants will be instructed not to crush, split, or chew the study drug.

6.1. Preparation, handling, storage, and accountability

- The investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention.
- All study intervention 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.
- The investigator, institution, the head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy manual.
- Under normal conditions of handling and administration, study intervention is not expected to pose significant safety risks to site staff.
- A 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.

6.2. Assignment to study intervention

Each participant will be assigned a unique identification number upon the screening visit. Participants will receive the treatment on one occasion.

6.3. Blinding

This is an open-label study and all participants will be receiving the same 50 mg dose. The severe hepatic impaired group (Group 4) and the matched healthy controls (Group 5) may receive a reduced dose of 25 mg in Scenario 3 based on the review of safety and PK data in Part 1. The dose used in Group 4 and Group 5 will be communicated to the site prior to the start of screening.

6.4. Study intervention compliance

As participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. A qualified designee will be responsible for monitoring the administration of the timed oral dose. The date and time of the dose administered in the clinic will be recorded in the source documents.

6.5. Dose modification

The dose and administration of the study drug may be modified in the severe HI participants and in matching healthy controls to severe HI participants but may not be modified in other participants.

6.6. Continued access to study intervention after the end of the study

Not applicable.

6.7. Treatment of overdose

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

- Although unlikely to occur as study drug is administered as a single dose under direct supervision, should a participant experience an overdose with camlipixant (with or without an AE/SAE), protocol deviation will need to be documented and reported promptly to the sponsor.
- Evaluate the participant to determine, in consultation with the medical monitor, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 5 days), as medically appropriate.

6.8. Prior and concomitant therapy

All participants must not have received another investigational agent within 90 days prior to dosing.

For all participants, any drugs known to be moderate and strong inhibitors of CCI, and CCI, including St. John's Wort, will be restricted for 14 days or 5 half-lives (or 5 half-lives, whichever is longer) prior to dosing and throughout the study. For all participants, any drugs known to be CCI enzymes will be restricted for 28 days (or 5 half-lives, whichever is longer) prior to dosing and throughout the study. Use of weak inhibitors or inducers may be deemed acceptable following consultation with the sponsor and the PI or designee. Appropriate sources (e.g., Flockhart Table™) will be consulted to confirm lack of potential PK/pharmacodynamic interaction with the study drug.

For all participants proton pump inhibitors and dabigatran will be restricted for at least 14 days prior to dosing and throughout the study.

Healthy participants will be restricted from using any prescription medications/products and any over-the-counter, non-prescription preparations (including vitamins, minerals, dietary supplements, and phytotherapeutic/herbal/plant derived preparations) from at

least 14 days (or 5 half-lives, whichever is longer) prior to dosing and throughout the study. Healthy participants that are on stable medication (i.e., steady dose, drug, and regimen) for at least 8 weeks may be enrolled upon approval by the PI (or designee) and sponsor (e.g., stable/well-managed hypertension and hypercholesterolemia).

Participants with HI who are taking medications to treat manifestations of hepatic disease or medications needed to treat for stable diseases (e.g., diuretics such as Spironolactone, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, beta-blockers, lactulose, rifaximin or antibiotics used for spontaneous bacterial peritonitis like fluoroquinolones) will be allowed to participate in the study at the discretion of the PI (or designee) and following consultation with the sponsor. Participants must be on a stable dose (i.e., steady dose, drug, and regimen) for at least 8 weeks before dosing and able to withhold the use for at least 4 hours post-dose; phosphate binders containing aluminum, calcium, or lanthanum salts; iron supplements or other metal cations; H2-receptor antagonists; or multivitamins containing iron or zinc must be withheld at least 10 hours before dosing and at least 6 hours post-dose.

Following study drug administration, paracetamol (up to 2 g per 24 hours) may be administered at the discretion of the PI or designee. Thyroid hormone replacement medication may be permitted if participant has been on same stable dose for the last 8 weeks prior to study drug administration. Birth control methods are allowed as described in Section 10.4 (Appendix 4), and hormone replacement therapy may also be permitted.

All medications taken by participants during the course of the study will be recorded.

Concurrent medication during the course of the study including both prescription and non-prescription drugs may be permitted based on the timing of study drug administration and its pharmacology, however must first be discussed with the PI or designee and sponsor prior to dosing, unless appropriate medical care necessitates that therapy should begin before the PI or designee and sponsor can be consulted.

If deviations occur, the PI will decide on a case-by-case basis whether the participant may continue participation in the study based on the time the study drug was administered and its pharmacology.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of study intervention

As each participant receives a single dose of study intervention, later discontinuation of study drug is not possible. If an AE or other situation is identified, it is preferred for the participant to remain in the study for full evaluation per the SoA (Section 1.3).

If the participant experiences a liver event, refer to Section 10.6 for required Liver Safety Actions and Follow-up Assessments; the participant does not need to be withdrawn from the study.

The primary reason for premature discontinuation of the study intervention will be documented in the [CRF/eCRF] based on the list below:

Reasons	Additional items/Sub-reasons
Lost to follow-up	Participant Relocated Participant was Incarcerated Other, specify Unknown
Physician Decision	Specify Safety, behavioral
Protocol Deviation	Specify Incorrect dose Or dose not given
Site Terminated by Sponsor	
Study Terminated by Sponsor	
Withdrawal by Participant	Burden of Procedure Participant Relocated COVID-19 Other Unknown
Other	Specify
Death	

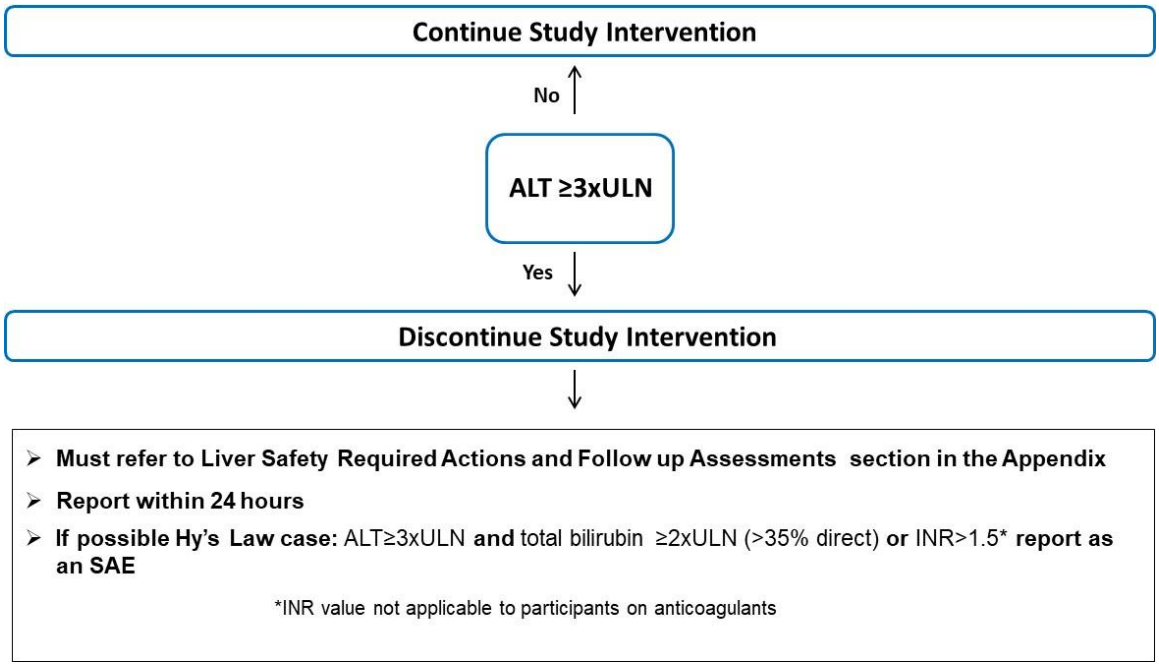
7.1.1. Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in the algorithm or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

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

Due to this being a single dose study, participants will not be discontinued from treatment; however, the monitoring/follow-up criteria will apply.

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 10.6 (Appendix 6) for required Liver Safety Actions and Follow-up Assessments.

For participants with hepatic impairment, liver function tests may be above ULN at baseline. Recruitment and dosing will be stopped, and a safety review will occur following any of the below events:

- Elevation of total bilirubin or hepatic transaminases (within an 8-day window post-dose) beyond the following thresholds:
  - ALT or AST ≥3 x ULN starting from a baseline in the reference range;
  - Increase in ALT or AST >150 U/L for males or >100 U/L for females starting from a baseline outside the reference range
  - A ≥2.5-fold elevation of ALP and/or gamma glutamyl transferase (GGT) relative to the baseline result;
  - Total bilirubin >3 x ULN, with >50% being direct; starting from a baseline in the reference range;
  - Increase in total bilirubin by 2.5 mg/dL starting from a baseline outside of the reference range;

  Note: These findings must be verified by repeated testing following initial observation, OR be part of an upgoing trend.
- Any other event deemed by the Investigator or Sponsor to reflect potentially unacceptable risk to subsequent participant associated with further dosing.

- Severe TEAE or SAE related to IP.

7.1.2. QTc Stopping criteria

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QTcF after enrollment, the investigator or qualified designee will determine if the participant can continue the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

A participant who meets either bulleted criteria based on the average of triplicate ECG readings will be withdrawn from study intervention:

For hepatic impaired and healthy participants:

- QTcF >500 msec
- Change from baseline of QTcF >60 msec

For patients with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
<450 msec	>500 msec
450 – 480 msec	≥530 msec

Due to this being a single dose study, participants will not be discontinued from treatment; however, the monitoring/follow-up criteria will apply.

7.2. Participant discontinuation/withdrawal from the study

A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).

A participant may be withdrawn at any time at the discretion of the investigator for safety, behavioral, or compliance reasons.

Investigators will attempt to contact participants who do not return for scheduled visits or follow-up.

At the time of discontinuing from the study, if possible, an ED 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 from the study intervention and the study at that time.

All data and samples collected up to and including the date of withdrawal of/last contact with the participant will be included in the study analyses. 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, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

In addition, participants may be withdrawn from the study by the PI or designee for the following reasons but not limited to:

- AEs/SAEs
- Difficulties in blood collection
- Positive pregnancy test
- Positive drug or alcohol test

If a participant is discontinued prior to study completion, efforts should be made to perform all procedures scheduled for the end-of-treatment (i.e., Day 4) or early termination as outlined in the SoA (Section 1.3).

Participants who are withdrawn from the study because of AEs/SAEs must be clearly distinguished from participants who are withdrawn for other reasons. Investigator will follow participants who are withdrawn from the study due to an AE/SAE until the event is resolved (see Section 10.3.7.5).

7.3. Lost to follow-up

A participant will be considered lost to follow-up if the participant 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, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether 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, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the Schedule of activities (SoA) (Section 1.3). Protocol waivers or exemptions are not allowed.
- 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. Participants who have signed informed consent but are not eligible to proceed should be recorded in the eCRF with a status of 'screen failure'.
- Procedures conducted as part of the participant's routine clinical management [(e.g., blood count)] and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.

The SoA (Section 1.3) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the sponsor for reasons related to participant safety.

For this study, the blood collection for camlipixant is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time in the following order (except for the screening visit and check-in): ECGs, vital signs, PK sampling, and other procedures.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

Blood Volume drawn for study assessment:

Table 6 Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point * (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, coagulation, and serology), FSH (for postmenopausal female participants only), and serum pregnancy (for female participants only).	1	16	16
On study hematology, serum chemistry, and coagulation (this includes serum pregnancy for female participants only when scheduled at the same time)	2	16	32
Blood for camlipixant PK	20	2	40
CCI [redacted]			
Total Blood Volume (mL)→			CCI [redacted]

* Represents the largest collection tube that is expected to be used (a smaller tube may be used).
** If additional safety or PK analysis are necessary, additional blood may be obtained (up to a maximum of 50 mL).

8.1. Administrative procedures

8.1.1. Collection of demographic data

Record demographic data such as date of birth, sex, race, and ethnicity in the participant's eCRF.

Collection of sex, race and ethnicity data is necessary to assess and monitor the diversity of the trial participants, and to determine if the trial participants are truly representative of the impacted population.

8.1.2. Medical/vaccination history

Obtain the participant's medical/vaccination history including tobacco use (including number of cigarettes smoked per day) by interviewing the participant and/or review of the participant's medical records. Record any pre-existing conditions, signs and/or symptoms present prior to the first dose of study intervention/study intervention/study start in the eCRF.

8.2. Efficacy and/or immunogenicity assessments

Not applicable.

8.3. Safety assessments

AEs, SAEs and other safety reporting will be captured as per GSK standard procedures (see Appendix 3, Section 10.3).

Planned timepoints for all safety assessments are provided in the SoA (See Section 1.3).

8.3.1. Physical examination

A full physical examination including body weight (kg) will be performed as outlined in the SoA (Section 1.3). Additional physical examinations may be performed at other times, if deemed necessary by the PI or designee.

8.3.2. Vital signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured as outlined in the SoA (Section 1.3). Additional vital signs may be taken at any other times, if deemed necessary by the PI or designee.

Blood pressure and heart rate measurements will be performed with participants in a seated position for at least 5 minutes, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the PI or designee.

Vital signs will be measured within 3 hours prior to Day 1 dosing. When scheduled post-dose, vital signs will be performed within approximately 15 minutes of the scheduled time point.

8.3.3. Electrocardiograms

Single 12-lead ECGs will be performed as outlined in the SoA (Section 1.3). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

ECGs will be performed with participants in a supine position for at least 5 minutes. All ECG tracings will be reviewed by the PI or designee.

ECGs will be measured within 3 hours prior to Day 1 dosing. When scheduled post-dose, ECGs will be performed within approximately ±20 minutes of the scheduled time point.

8.3.4. Clinical safety laboratory tests

- See Section 10.2 for the list of clinical laboratory tests to be performed in accordance with lab manual and the SoA (Section 1.3).
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
  - In the absence of a diagnosis, abnormal laboratory findings assessments PI or designee or other abnormal results the investigator considers clinically significant will be recorded as an AE or SAE, if they meet the definition of an AE or SAE (refer to Section 10.3.1 and Section 10.3.2).
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
  - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g, SAE or AE or dose modification), then the results must be recorded.

8.3.5. Pregnancy testing

- Female participants of childbearing potential must perform a urine/blood pregnancy test before the administration of study intervention. Pregnancy testing must be done even if the participant is menstruating at the time of the study visit. The study intervention may only be administered if the pregnancy test is negative.
- Refer to Section 8.4.6 for the information on study continuation for participants who become pregnant during the study.

8.3.6. Study stopping rules/holding rules, safety monitoring AND/OR Committee

The investigator sites and/or PPD reserve the right to terminate the study in the interest of participant welfare.

The sponsor reserves the right to suspend or terminate the study at any time.

- Participant safety will be continuously monitored by the Medical Monitor, designated Safety Lead (or delegate) throughout the study. Pertinent findings and

conclusions are shared with the product's SRT for review of the overall benefit- risk profile of the product.

8.4. Adverse Events (AEs) serious adverse events (SAEs), and other safety reporting

For definitions relating to safety information see Section 10.3.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and other safety information and remain responsible for following up [all AEs OR AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study] (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

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.

8.4.1. Time period and frequency for collecting AE, SAE, and other safety information

All SAEs will be collected from the start of study intervention until the final follow-up telephone call at the time points specified in the SoA (Section 1.3).

SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product (non-IMP) will be recorded from the time a participant consents to participate in the study.

All AEs will be collected from the start of study intervention until the final follow-up telephone call at the timepoints 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 Section 10.3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

A poststudy AE/SAE is defined as any event that occurs outside of the AE/SAE reporting period defined in Section 8.4.1.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, after a participant has been discharged from the study, the investigator must record it in the medical records. If the investigator considers the event to be

reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and SAEs. Open-ended and nonleading verbal questioning and/or questionnaires of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.4.4)] will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.7.5.

8.4.4. AESIs

Adverse events of special interest (AESIs) are AEs of scientific interest specific to the drug class. AESIs for this study include the following, but not limited to:

1. Taste disturbance (dysgeusia, hypogeusia, ageusia)
2. Oral paraesthesia
3. Oral hypoesthesia

Participants will be asked to respond to a taste questionnaire, as detailed in Section 10.5 (Appendix 5). This will only be captured if reporting of a taste disturbance AE is initiated spontaneously by the participant, following dosing on Day 1. This is monitored throughout and until the end of the study. One questionnaire per taste disturbance AE is to be completed by the clinical staff for inclusion in the EDC.

8.4.5. 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 toward the safety of participants and the safety of a study intervention under clinical investigation are met. See [Section 8.4.1] for reporting timeframes.
- For SAEs, the investigator must always provide an assessment of causality at the time of the initial report, as defined in the Section 10.3.7.6.
- 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

Table 7 Timeframes for submitting SAE, pregnancy and other events reports to GSK

Type of event	Initial reports		Follow-up of relevant information on a previous report	
	Timeframe	Documents	Timeframe	Documents
SAEs	24 hours*‡	Paper/electronic AEs Report	24 hours*	Paper/electronic AEs Report
Pregnancies	24 hours*	Paper pregnancy notification report/electronic pregnancy report	24 hours *	Paper pregnancy follow-up report/electronic pregnancy report

* Timeframe allowed after receipt or awareness of the information by the investigator/site staff.
‡ Paper AEs Report will be dated and signed by the investigator (or designee). For each SAE, the investigator(s) must document in the medical notes that they have reviewed the SAE and have provided an assessment of causality.

8.4.6. Pregnancy

Female participants who become pregnant after administration of the study intervention may continue the study at the discretion of the investigator.

- Details of all pregnancies in female participants will be collected after the start of study intervention and until time period for reporting pregnancies should align with the time period for postintervention contraception determined in Section 5.1.
- If a pregnancy is reported at any time following study drug administration (or up to 30 days following dosing), the investigator will record pregnancy information on the Pregnancy Notification Form and submit it to the sponsor within 24 hours of learning of the female participant pregnancy.
- 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. See Table 7 for reporting timeframes.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. 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 can continue on the study.

8.4.7. CV and death events

For any CV events detailed in Section 10.3 (Appendix 3) and all deaths, whether or not they are considered SAEs, specific CV and death sections of the eCRF will be required to be completed. These sections include questions regarding CV (including sudden cardiac death) and non-CV death.

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

The death eCRF 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.

8.4.8. Contact information for reporting SAEs, pregnancies and study holding rules

Table 8 Contact information for reporting SAEs, pregnancies and study holding rules

Study contact for questions regarding SAEs, AESIs, and pregnancies Contact GSK's local and/or medical contacts
Contacts for reporting SAEs and pregnancies Available 24/24 hours and 7/7 days uk.gsk-rd-gcsp-ctsm-admin@gsk.com

8.4.9. Participant card

The investigator (or designee) must provide the participant with a "participant card" containing information about the clinical study. The participant must be instructed to always keep the participant card in their possession for the duration of the study. In an emergency, this card serves to inform the responsible attending physician/LAR/caregiver/family member that the participant is in a clinical study and that relevant information may be obtained by contacting the investigator(s) or their back up.

8.5. Pharmacokinetics

- Blood samples of approximately 2 mL will be collected for measurement of total plasma concentrations of camlipixant as specified in the SoA (Section 1.3). CCI
  CCI
  CCI
  CCI
  CCI
  CCI
  CCI

- CCI [redacted]
- A maximum of 3 blood samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (e.g., to fully characterize the elimination phase) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of camlipixant. Each plasma CCI [redacted] sample will be divided into 2 aliquots (1 each for PK analyses, and a backup]). Samples collected for analyses of camlipixant plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these plasma samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained. At visits during which [plasma/serum/whole blood/etc.] samples for the determination of plasma concentration of camlipixant will be taken, one sample of sufficient volume can be used.

8.6. Pharmacodynamics

Not applicable.

8.7. Genetics

Not applicable.

8.8. Biomarkers

Not applicable.

8.9. Immunogenicity assessments

Not applicable.

8.10. Health economics or medical resource utilization and health economics

Not applicable.

9. STATISTICAL CONSIDERATIONS

The SAP 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.

9.1. Statistical hypothesis

No formal hypotheses are being tested in this study.

9.2. Analysis sets

Analysis Set	Definition / Criteria	Analyses Evaluated
Screened	• All participants who were screened for eligibility.	• Study Population
Enrolled	• All participants who entered the study (who received study intervention or underwent a post screening study procedure). • Note screening failures (who never passed screening even if re-screened) and participants screened but never enrolled into the study (Met eligibility but not needed) are excluded from the Enrolled analysis set as they did not enter the study.	• Study Population
Assigned	• All participants who were assigned to study intervention in the study.	• Study Population
Safety	• Participants who received study intervention.	• Safety
PK	• All participants in the Safety analysis set who had at least 1 non-missing PK assessment (NQ values will be considered as non-missing values). • Data will be reported according to the actual study intervention.	• PK

9.3. Statistical analyses

9.3.1. Primary endpoints analysis

9.3.1.1. Pharmacokinetics analysis

Samples from all participants will be assayed even if the participants do not complete the study.

PK parameters for the primary, secondary and exploratory endpoints will be calculated by CCI [redacted] analysis in Phoenix WinNonlin. Further details will be described in the SAP.

The primary PK parameters are:

$AUC_{(0-\infty)}$	The area under the concentration-time curve, from time 0 extrapolated to infinity
C_{max}	Maximum observed concentration

Descriptive statistics:

The plasma camlipixant concentrations and the PK parameters listed above will be summarized using the appropriate descriptive statistics which will be fully outlined in the SAP.

Analysis of variance:

A linear model will be fitted to the log-transformed blood PK parameters ($AUC_{0-\infty}$, and C_{max}) to assess the effect of HI on the PK of camlipixant. The model will constitute moderate HI vs. Healthy participants in Part 1.

In the case of Scenario 1, only severe HI participants will be enrolled in Part 2. In this scenario, the model will constitute severe HI vs. Healthy participants in Part 2.

In the case of Scenario 2, both mild HI and severe HI participants will be enrolled in Part 2 at the same dose. The model then will constitute severe, mild HI vs. Healthy participants in Part 2. In this scenario, healthy participants in Part 2 can be matched to both mild and severe HI participants. The model tackles this by pooling healthy participants in Part 2.

In the case of Scenario 3, healthy participants can only be matched to either a mild or severe HI participant in order to accommodate the two doses. In this scenario, a separate model will be fit for each of the severe and mild HI groups in Part 2. If severe HI participants are not dosed in Part 2, then a separate model will be fit only for mild HI participants.

CCI [redacted]

CCI [redacted]

CCI [redacted]

The analyses of interest are as follows:

- Moderate HI (Group 1) compared to their matched control participant (Group 2)
- Mild HI (Group 3) compared to their matched control participant (Group 5)
- Severe HI (Group 4) compared to their matched control participant (Group 5). Note: Healthy participants in Group 5 can be matched to both mild (Group-3) and severe (Group-4) HI participants.

Note: In Scenario 2, healthy participants in Group 5 can be matched to both mild (Group-3) and severe (Group-4) HI participants. In Scenario 3, healthy participants can only be matched to either a mild or severe HI participant.

9.3.2. Secondary endpoint analysis

Other PK parameters of interest are T_{max}, $t_{1/2}$, CL/F and V_z/F. If there is not sufficient data to analyze $AUC_{(0-\infty)}$ with a linear model, then $AUC_{(0-t)}$ will be calculated and analyzed.

Descriptive statistics as described in Section 9.3.1.1 will also be performed on the secondary PK endpoints.

9.3.2.1. Safety analyses

All safety data will be listed by participant in the final report.

AEs will be coded using the most current version of the MedDRA available at PPD and summarized by treatment for the number of participants reporting the TEAE and the number of TEAEs reported. A by participant AE data listing including verbatim term, coded term, treatment, severity, and relationship to treatment will be provided.

Secondary Endpoint: Summary of incidence of AEs, SAEs and AESIs will be provided. Additionally, for participants with clinically relevant changes in clinical laboratory tests, ECG and vital signs assessments will also be reported during the study period. Safety data including clinical laboratory results, vital signs assessments, and ECG will be summarized by time point of collection. Quantitative safety data as well as the change from baseline, when appropriate, will be summarized using the appropriate descriptive statistics. In addition, a shift table describing out of reference range shifts will be provided for clinical laboratory results, as appropriate.

Concomitant medications will be listed by participant and coded using the most current version of WHO drug dictionary available at PPD.

CCI

9.4. Interim analyses

An informal interim analysis of the primary endpoint will be conducted following completion of Part 1 of the study, with possible progression to Part 2 based on the following criteria:

CCI

The SAP will describe the planned interim analyses in greater detail.

9.5. Pre-dose sample size determination

The sample size chosen for this study was selected based on FDA guidance for industry [FDA, 2003]. It has been determined adequate to meet the study objectives and provide an acceptable level of estimate precision. Eight participants will be enrolled in each HI

group (i.e., Groups 1, 3, and 4). Eight healthy participants will be enrolled in Group 2 and 8 to 16 healthy participants in Group 5 will be enrolled with normal hepatic function, matched to the age (±10 years), weight (±20%), and sex (1:1) of a participant in Group 1, 3, and/or 4.

CCI

[redacted]

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 the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
  - Applicable ICH 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 IRB/IEC 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 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, as applicable:
  - 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/IEC
  - Notifying the IRB/IEC of SAEs 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, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, 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 the investigator's representative will explain the nature of the study, including the risks and benefits, to the participants and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary. They will be required to physically or digitally sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- Sample testing will be done in accordance with the recorded consent of the individual participant.
- By default, collected samples for the study will be stored for a maximum of 20 years. This storage period begins when the last participant completes the last study visit. This timeline can be adapted based on local laws, regulations or guidelines requiring different timeframes or procedures. In all cases, the storage period should be aligned with participant's consent. These additional requirements must be formally communicated to, discussed and agreed with GSK.
- The medical record must include a statement that physical or digital informed consent was obtained before the participant was enrolled in the study and the date the physical or digital consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A physical or digital copy of the ICF(s) must be provided to the participant.
- Participants who are re-screened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

In case of unexpected pregnancy, participant must be informed that personal information such as date of birth, sex of the baby will be collected as part of safety follow-up. Consent for the collection of information about the baby may be obtained from the participant and/or their partner as per local regulations.

10.1.4. Recruitment strategy

Participants will be identified for potential recruitment using clinical database and IEC/IRB-approved advertisements (e.g., newspaper, social media) prior to consenting to take part in this study.

10.1.5. Data protection

- Participants will be assigned a unique identifier by the investigator. 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.
- GSK will ensure protection of the personal data of the investigator and site staff which is collected within the framework of and for the purpose of the study.
- The participant must be informed that their 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, that their data will be used as described in the informed consent.
- The participant must be informed that their 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.
- The contract between sponsor and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. GSK, third parties working on behalf of GSK, and/or institutions working with GSK for the purposes of this study are contractually bound to protect participant coded data. GSK will protect participant coded data and will only share it as described in the ICF.
- GSK has a global, internal policy that requires all GSK staff and complementary workers to report data incidents or breaches immediately, using dedicated tools. Clear procedures are defined for assessing and investigating data breaches to identify and to take appropriate remediation steps, to contain and to mitigate any risks for individuals resulting from a breach, in compliance with applicable laws.

10.1.6. Committees structure

A SRT is in place for each GSK product. It comprises of a global cross-functional team responsible for the ongoing assessment of benefit-risk for a product. The SRT contribute to the continual assessment of incoming new efficacy and safety information.

10.1.7. Dissemination of Clinical Study Data

- The key design elements of this protocol and results summaries will be posted on www.ClinicalTrials.gov and/or GSK Clinical Study Register in compliance with applicable regulations/GSK policy. GSK will aim to register protocols summaries prior to study start and target results summaries submission within 12 months of primary/ study completion date. Where external regulations require earlier disclosure, GSK will follow those timelines.
- Where required by regulation, summaries will also be posted on applicable national or regional clinical study registers.
- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the study report, and provided reasonable access to statistical tables, figures, and relevant reports. GSK will also provide the investigator with the full summary of the study results, including a summary of trial results understandable to laypersons. The investigator is encouraged to share the plain language summary with the study participants, as appropriate. The full study report will be made available upon request, after decision on marketing authorization by regulatory authorities.
- Where required by regulation, the names of the sponsor signatory and investigator signatory will be made public.
- GSK will provide the investigator with the participant-level line listings for their site only after completion of the full statistical analysis.
- GSK intends to make anonymized participant-level data from this study 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 study participants are used to maximum effect in the creation of knowledge and understanding. Data will be shared with researchers in a non-identifying way, and appropriate measures will be taken to protect PI; these measures will comply with data protection and privacy laws that apply.

10.1.8. Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs 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.
- Guidance on completion of eCRFs will be provided in eCRF completion guidelines.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source documents.
- QTLs will be predefined in the QTL Plan to identify systematic issues that can impact participant right, safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- 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, involvement of central reading mechanism) 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 a minimum period of 15 years from the issue of the final CSR/ equivalent summary, or in accordance with Applicable Law, whichever is longer. 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.

10.1.9. Source documents

- For this study there will not be source data recorded directly into the eCRF (i.e., no prior written or electronic record of data is available).
- 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 eCRF 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 e.g. source data acknowledgment.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The sponsor or designee will perform monitoring to confirm that data entered into the eCRF 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.

10.1.10. Study and site start and closure

Start of study and first act of recruitment

The start of study and the first act of recruitment are defined as FSFV (first ICF signature date) at a country-level.

Study/site termination

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 (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or temporarily 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 temporary suspension, as specified by the applicable regulatory requirements. The

investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.11. Publication policy

GSK seeks to publish medically or scientifically significant results in searchable peer-reviewed scientific literature within 18 months from LSLV. We follow International Committee of Medical Journal Editors standards for authorship and use Good Publications practices to guide our publications.

10.2. Appendix 2: Clinical laboratory tests

- The tests detailed in Table 7 will be performed by local laboratories.
- 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.
- Investigators must document their review of each laboratory safety report.

Table 9 Protocol-required safety laboratory tests

Laboratory Tests	Parameters	
Hematology	• Platelet count	
	• Red blood cell (RBC) count	
	• RBC indices	– Mean corpuscular volume (MCV) – Mean corpuscular hemoglobin (MCH) – %Reticulocytes
	• WBC count with differential:	– Neutrophils – Lymphocytes – Monocytes – Eosinophils – Basophils
	• Hemoglobin	
	• Hematocrit	

Laboratory Tests	Parameters
Serum chemistry*	• Blood urea nitrogen (BUN)/Urea • Potassium • Creatinine** • Sodium • Calcium • Glucose [indicate if fasting or non-fasting] • Creatine phosphokinase (CPK) • Serum Albumin Concentration • CCI [redacted] – Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) – Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) – Alkaline phosphatase2 – Total bilirubin – Direct bilirubin – Indirect bilirubin – Total protein
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal) – Epithelial cells – Red Blood cells – WBC – Casts – Crystals
Coagulation testing	• Prothombin Time • International normalized ratio • Activated partial thromboplastin

Laboratory Tests	Parameters
Additional tests	• HIV text • HBsAg (and DNA test, as applicable) • HBcAb • HCV (and RNA test for participants with HI, as applicable) • Urine drug screen- Opiates, Amphetamines, Cocaine, Cannabinoids • Breath alcohol screen • Serum/urine pregnancy test (for females only)*** • Serum FSH (for postmenopausal females only) • SARS-CoV-2 rapid test and/or polymerase chain reaction test

* Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, participants may not have fasted for 8 hours prior to when the serum chemistry sample is taken.
** At the screening visit, creatinine clearance will be calculated using the Cockcroft-Gault formula.
*** At screening, pregnancy test will be performed in serum; other pregnancy test can be performed in serum or urine as per local guidelines.

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 Meeting 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 condition 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 intervention- intervention 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 that occur as a result of protocol-mandated procedures (i.e. invasive procedures, modification of participant's previous therapeutic regimen).

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the 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, admission for routine examination.).
- 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. Pre-existing diseases will be recorded in the medical history section of the eCRF.
- Hospitalization for elective treatment of a pre-existing condition (known or diagnosed before signing the informed consent) that did not worsen from baseline.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

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 fulfills any

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:
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) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect in the offspring of a study participant.
f. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth,
g. Is a suspected transmission of any infectious agent via an authorized medicinal product
h. Other situations: • Possible Hy's Law case: ALT ≥3x ULN AND total bilirubin ≥2x ULN (>35% direct bilirubin) or 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. Solicited events

Definition of solicited event
• Solicited AEs are predefined local systemic events for which the participant is specifically questioned.

10.3.4. Unsolicited AE

Definition of unsolicited AE
• An unsolicited AE is an AE that was not solicited and that is communicated by a participant who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a healthcare provider). The participants will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by the participant will be collected during an interview with the participants and by review of available medical records at the next visit.

10.3.5. Definition of CV events

CV definition:
Investigators will be required to fill out the specific CV event page of the eCRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

10.3.6. Definition of TEAE

TEAE Definition:
• A TEAE is an event that emerges during treatment, having been absent pre-treatment or worsens relative to the pre-treatment state.

10.3.7. Recording, assessment and follow-up of AE, SAE, AESIs and pregnancies

10.3.7.1. 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 reports, 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 eCRF 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.

10.3.7.2. Assessment of intensity

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

- Mild:
  A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate:
  A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe:
  A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.3.7.3. Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/AESI. The investigator will use clinical judgment to determine the relationship.
- 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.

- 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.
- For causality assessment, the investigator will also consult the IB and/or product information, for marketed products.
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes 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 their 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.

10.3.7.4. Assessment of outcomes

The investigator will assess the outcome of all serious and nonserious unsolicited AEs recorded during the study as:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal (SAEs only).

10.3.7.5. Follow-up of AEs, SAEs, AESIs, pregnancies or any other events of interest

- 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/Sponsor with a copy of any postmortem 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.

After the initial AE/SAE/AESI/pregnancy or any other event of interest, 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.

Other nonserious AEs must be followed until end of the study or until the participant is lost to follow-up.

Follow-up during the study

AEs/AESIs documented at a previous visit/contact and defined as not recovered/not resolved or recovering/resolving will be reviewed at subsequent visits/contacts until follow-up.

If a participant dies during their participation in the study or during a recognized follow-up period, GSK will be provided with any available postmortem findings, including histopathology.

Follow-up of pregnancies

Pregnant participants will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether full-term or premature, information on the status of the mother and child will be forwarded to GSK using the paper pregnancy follow-up report/electronic pregnancy report and the AE Report if applicable. Generally, the follow-up period does not need to be longer than 6 to 8 weeks after the estimated date of delivery.

Regardless of the reporting period for SAEs in this study, if the pregnancy outcome is an SAE, it should always be reported as such.

Furthermore, the investigator must report any SAE occurring as a result of a poststudy pregnancy that is considered by the investigator to be reasonably related to the study intervention, to GSK as described in the Section 10.3.7.7.

10.3.7.6. Updating of SAE and pregnancy information after removal of write access to the participant's eCRF

When additional SAE or pregnancy information is received after write access to the participant's eCRF is removed, new or updated information should be recorded on the appropriate paper report, with all changes signed and dated by the investigator. The updated report should be sent to the Study contact for reporting SAEs (refer to Section 8.4.3).

10.3.7.7. Reporting of SAEs and pregnancies

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an 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.
- After the study is completed at a given site, the electronic data collection tool will be taken offline 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 offline, then the site can report this information on a paper SAE form (see next section) or to the GSK by telephone.
- If the site during the course of the study or poststudy becomes aware of any serious, nonserious AEs, pregnancy exposure, related to any GSK non-IMP they will report these events to GSK or to the concerned competent authority via the national spontaneous reporting system. These will be classified as spontaneous ICSRs.
- Contacts for SAE reporting can be found in Section 8.4.8.

SAE Reporting to GSK via Paper Data Collection Tool

- Email/facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the GSK.
- In rare circumstances and in the absence of email/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 timeframes.
- Contacts for SAE reporting can be found in Section 8.4.8.

10.4. Appendix 4: Contraceptive and barrier guidance

10.4.1. Definitions

10.4.1.1. Woman of childbearing potential (WOCBP)

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

Adolescents of childbearing potential: Tanner stage ≥2 (post-thelarche) irrespective of the occurrence of menarche or following menarche.

From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

Note: Menarche is the first onset of menses in a young female. Menarche is normally preceded by several changes associated with puberty including breast development and pubic hair growth.

10.4.1.2. Woman of non-childbearing potential (WONCBP)

Women in the following categories are considered WONCBP:

- Premenarchal: Tanner stage 1 (prepubertal)

Permanently sterile due to one of the following procedures:

a. Documented hysterectomy

b. Documented bilateral salpingectomy

c. Documented bilateral oophorectomy

   For permanently sterile individuals 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. If reproductive status is questionable, additional evaluation should be considered.

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

Postmenopausal female

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception guidance

Guidance for Female Participants

Female participants of childbearing potential must agree to one of the following methods of contraception:

- Hysteroscopic sterilization or bilateral tubal ligation at least 6 months prior to dosing.
- Non-hormonal releasing IUD or hormonal contraceptives (e.g., oral, IUD, vaginal ring, transdermal patch, depot, implantable, etc.) for at least 3 months prior to dosing

and with either a physical (e.g., condom, diaphragm, or other) or a chemical (e.g., spermicide) barrier method from the time of the screening visit.

In addition, female participants of childbearing potential will be advised to keep the same birth control method for at least 30 days after dosing.

Female participant must agree not to donate ova from dosing until at least 30 days after dosing.

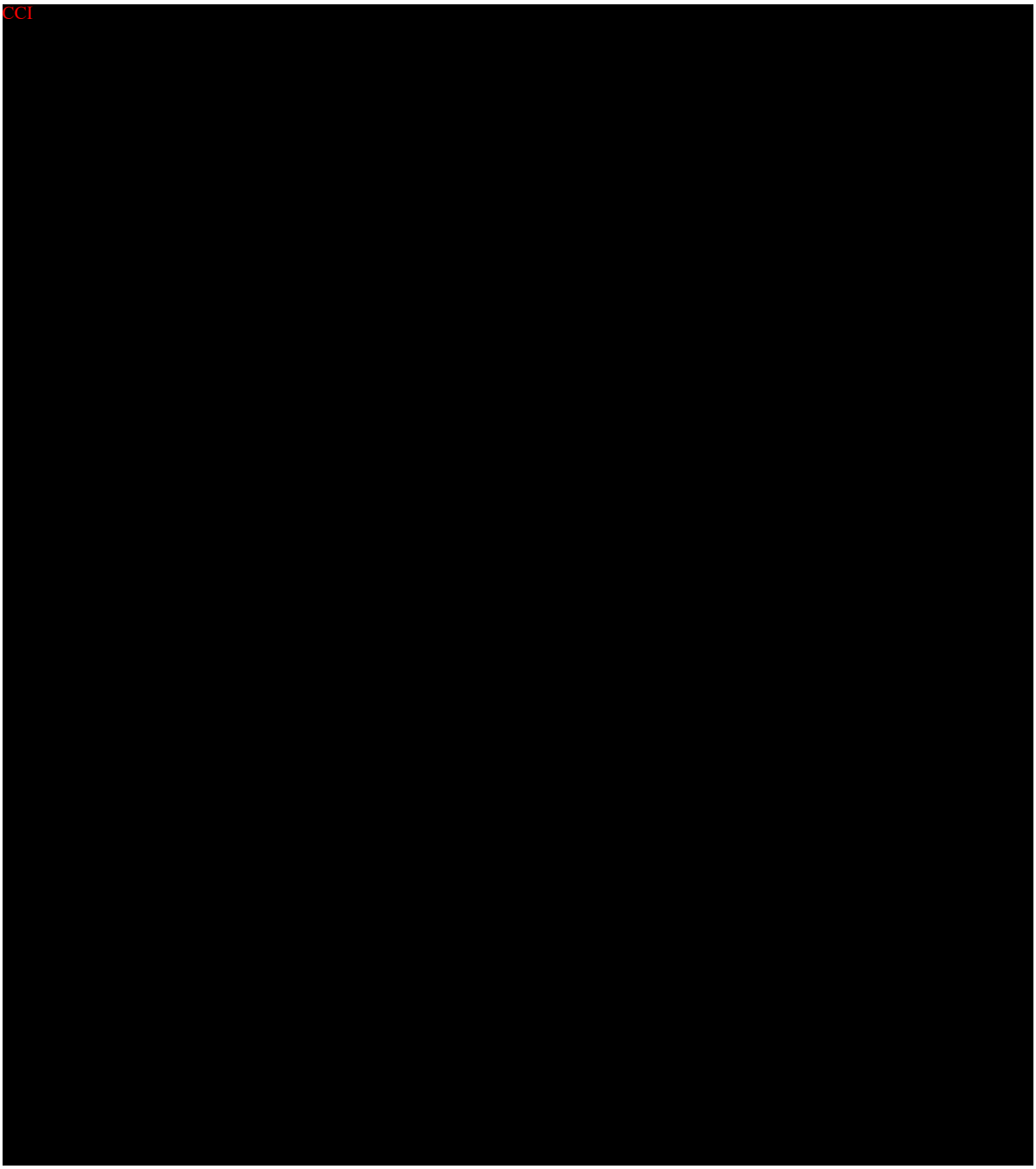
Guidance for male participants

Male participants who are not vasectomized for at least 4 months prior to dosing and who are sexually active with a female partner of childbearing potential must be willing to use one of the following acceptable contraceptive methods from dosing until 90 days after dosing:

- Simultaneous use of condom and hormonal contraceptive (e.g., oral, IUD, vaginal ring, patch, depot, implantable, etc.) or non-hormonal intrauterine device used for at least 3 months prior to dosing for the female partner
- Simultaneous use of condom and a diaphragm or cervical cap with spermicide for the female partner.

No restrictions are required for a vasectomized male provided his vasectomy has been performed 4 months or more prior to dosing. A male who has been vasectomized less than 4 months prior to dosing must follow the same restrictions as a non-vasectomized male.

CCI



10.6. Appendix 6: Liver safety: suggested actions and follow-up assessments

Phase 1 liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event etiology.

Phase 1 Liver Chemistry Stopping Criteria and Required Follow-Up Assessments

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

If ALT ≥3xULN AND total bilirubin[1,2] ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) or ALT ≥3xULN AND INR >1.5, report as an SAE.</td></tr>
<tr><td colspan="3">Required Actions, Monitoring and Follow-up Assessments</td></tr>
<tr><td colspan="2">Actions</td><td>Follow-Up Assessments</td></tr>
<tr><td colspan="2">• Report the event to GSK within 24 hours
• Complete the liver event form, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow-up assessments as described in the Follow-Up Assessment column
• Monitor the participant until liver chemistries (see MONITORING)

MONITORING:

If ALT≥3xULN AND total bilirubin ≥2xULN or INR >1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within 24 hours
• Monitor participant twice weekly until liver chemistries reduce to <3xULN for ALT, <2xULN for total bilirubin or ≤1.5 for INR or return to or remain within baseline or normal limits.A specialist or hepatology consultation is recommended

If ALT≥3xULN AND total bilirubin <2xULN and INR ≤1.5:
• Perform liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within 24-72 hours
• Monitor participant weekly until liver chemistries reduce to <3xULN for ALT or</td><td>• Viral hepatitis serology[3].
• Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins.
• Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend.
• Obtain blood sample for pharmacokinetic (PK) analysis, 96 hr after the dose[4].
• Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT), glutamate dehydrogenase (GLDH) and serum albumin.
• 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 liver event form.
• Record use of concomitant medications on the concomitant medications CRF page including acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications.
• Record alcohol use on the liver event alcohol intake form.

If ALT≥3xULN AND total bilirubin ≥2xULN or INR >1.5 obtain the following in addition to the assessments listed above:</td></tr>
</table>

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT≥3xULN If ALT ≥3xULN AND total bilirubin[1,2] ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) or ALT ≥3xULN AND INR >1.5, report as an SAE.

Required Actions, Monitoring and Follow-up Assessments	
Actions	Follow-Up Assessments
return to or remain within baseline or normal limits.	• Serum acetaminophen adduct assay should be conducted (where available to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week (e.g., where the participant has been resident in the clinical unit throughout). • Liver imaging (ultrasound, magnetic resonance, or computed tomography) to evaluate liver disease; complete liver imaging form. • Liver biopsy may be considered and discussed with local specialists if available for instance: – In participants when serology raises the possibility of autoimmune hepatitis (AIH) – In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention – In participants with acute or chronic atypical presentation. • If liver biopsy is conducted, then complete liver biopsy form

1. Serum bilirubin fractionation should be performed if testing is available. 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 total bilirubin ≥2xULN (for participants with known Gilbert's syndrome these criteria only apply if total bilirubin ≥2xULN, and direct bilirubin ≥2xULN and at least doubled from baseline value) or ALT ≥3xULN and INR >1.5, which may indicate severe liver injury (possible 'Hy's Law'), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis); the INR threshold value stated will not apply to participants receiving anticoagulants.
3. Includes: hepatitis A Immunoglobulin M (IgM) antibody; HbsAg and HBcAb; hepatitis CRNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); hepatitis E IgM antibody and RNA PCR test. HBV DNA quantification, and HDV antibody should be measured if participant known to be HBsAg and/or HBcAb positive prior to onset of the liver event or subsequently found to be HBsAg positive on investigation following the liver event. If hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed and if this is feasible).
4. Record the date/time of the PK blood sample draw and the date/time of the dose of study intervention prior to pk blood sample draw on the CRF. If the date or time of the dose is unclear, provide the participant's best approximation. If the date/time of the 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 pharmacy manual.

11. REFERENCES

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Kim JH, Sherman ME, Curriero FC, et al. Expression of cytochromes P450 1A1 and 1B1 in human lung from smokers, non-smokers, and exsmokers. *Toxicol Appl Pharmacol*. 2004; 199(3): 210-9.

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