Protocol

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Official Title of Study: A PHASE 1, 2-PART, OPEN-LABEL, FIXED-SEQUENCE STUDY EVALUATING POTENTIAL DRUG-DRUG INTERACTIONS BETWEEN GEMFIBROZIL (PART 1) OR DABIGATRAN ETEXILATE (PART 2) AND CAMLIPIXANT (BLU-5937) 50 mg TABLET IN HEALTHY PARTICIPANTS UNDER FASTING CONDITIONS

Date of Document: 29 June 2023

PROTOCOL 220265
Bellus Health Study Number: BUS-P1-12

A PHASE 1, 2-PART, OPEN-LABEL, FIXED-SEQUENCE STUDY EVALUATING POTENTIAL DRUG-DRUG INTERACTIONS BETWEEN GEMFIBROZIL (PART 1) OR DABIGATRAN ETEXILATE (PART 2) AND CAMLIPIXANT (BLU-5937) 50 mg TABLET IN HEALTHY PARTICIPANTS UNDER FASTING CONDITIONS

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Contract Research Organization:

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Protocol Version: Final

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CONFIDENTIAL

Protocol Historical File

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I have carefully read this study protocol and agree that it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol (including any amendments) and in accordance with the clinical site's Standard Operating Procedures (SOPs), ICH Good Clinical Practice (GCP), all other applicable regulations, and the recommendations laid down in the most recent version of the Declaration of Helsinki.

PPD

29-Jun-2023

Bruno Francoeur, M.D. Date

PPD

PPD

Facilities and Responsible Staff

Clinical Research Facilities

This study will be conducted by CCI [redacted] at the following facility:

CCI [redacted]

Screening and/or visits may also be performed at the CCI [redacted] facility:

CCI [redacted]

Biomedical Laboratory Facilities

Biomedical laboratory testing will be performed by the following laboratories:

CCI [redacted]

CCI [redacted]

CCI [redacted]

If another biomedical laboratory is used, this will be documented and annexed to the protocol.

CCI [redacted]

CCI [redacted]

Institutional Review Board

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List of Abbreviations

AE	adverse event
AEMI	adverse event of medical interest
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
$AUC_{0\text{-}inf}$	area under the concentration-time curve from time zero to infinity (extrapolated)
$AUC_{0\text{-}t}$	area under the concentration-time curve from time zero until the last observed concentration
BCRP	breast cancer resistance protein
CCI	[redacted]
BMI	body mass index
BUN	blood urea nitrogen
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CK	creatine kinase
Cl/F	apparent clearance
C_{max}	maximal observed concentration
COVID-19	coronavirus 2019
CrCl	creatinine clearance
CRO	contract research organization
CTA	Clinical Trial Application
CV%	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DMP	data management plan
DVT	deep vein thrombosis
eCRF	electronic case report form
ECG	electrocardiogram
EFD	embryo-fetal development
ET	early termination
FDA	Food and Drug Administration

FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GEM-1-O-gluc	gemfibrozil-1-O-beta-glucuronide
GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
HPMC	hydroxypropylmethylcellulose
IB	Investigator's Brochure
IBS	irritable bowel syndrome
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IME	important medical event
INR	international normalized ratio
K_{el}	terminal elimination rate constant
LFT	liver function test
Max	maximum
MDMA	3,4-methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
MRHD	maximum recommended human dose
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NOL	No Objection Letter
OATP	organic anion transporter polypeptide
OTC	over-the-counter
PBPK	physiologically based pharmacokinetic
PC	pharmacokinetic concentration
PCP	phencyclidine
PE	pulmonary embolism
PEPT1	peptide transporter 1

P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PT	prothrombin time
CCI	CCI [redacted]
QT	QT interval
QTcF	Fridericia's corrected QT interval
RBC	red blood cell
RCC	refractory and unexplained chronic cough
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SD	standard deviation
SOP	standard operation procedure
SUSAR	suspected, unexpected, serious adverse reaction
$T_{½\ el}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
THR	total hip replacement
TKR	total knee replacement
T_{max}	time when the maximal concentration is observed
CCI	[redacted]
UGT1A1	UDP glucuronosyltransferase 1 A1
ULN	upper limit of normal
VLDL	very low density lipoprotein
VTE	venous thromboembolic events
V_z/F	apparent volume of distribution
WBC	white blood cell
WHODrug	World Health Organization Drug

Synopsis of Protocol

Project Number:	220265 Bellus Health study number: BUS-P1-12
Title:	A Phase 1, 2-Part, Open-label, Fixed-sequence Study Evaluating Potential Drug-Drug Interactions between Gemfibrozil (Part 1) or Dabigatran Etexilate (Part 2) and Camlipixant (BLU-5937) 50 mg Tablet in Healthy Participants under Fasting Conditions
Investigational Product:	Camlipixant (BLU-5937) 50 mg Tablet
Study Phase and Type:	Phase 1 – Drug-Drug Interaction (DDI)
Objectives:	Primary objectives: • To assess the effect of repeated oral doses of gemfibrozil, a cytochrome P450 (CYP) 2C8 inhibitor, on the pharmacokinetics (PK) of a single oral dose of camlipixant (Part 1) administered to healthy participants. • To assess the effect of repeated oral doses of camlipixant on the PK of a single oral dose of dabigatran etexilate, a P-glycoprotein (P-gp) substrate (Part 2), administered to healthy participants. Secondary objective: • To evaluate the safety and tolerability of camlipixant when administered alone and in combination with gemfibrozil or dabigatran etexilate to healthy participants.
Endpoints:	Primary endpoints: • PK parameters: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} of camlipixant (Part 1) and dabigatran (Part 2*) Secondary endpoints: • PK parameters: T_{max}, $T_{½\ el,}$ Residual area, K_{el}, Cl/F, and V_z/F of camlipixant (Part 1) and dabigatran (Part 2*) *For Part 2, both total and free dabigatran will be assayed, and their PK parameters generated. • Safety evaluation: o Adverse events (AEs), serious adverse events (SAEs), adverse events of medical interest (AEMIs), vital signs measurements (blood pressure, heart rate, respiratory rate, and oral temperature), 12-lead electrocardiogram (ECG) recordings, physical examinations, and clinical laboratory test results, including hematology, biochemistry, coagulation, and urinalysis.
Study Design:	This is a single-center, 2-part, Phase 1, open-label, fixed-sequence, DDI study designed to compare the PK of camlipixant when administered with

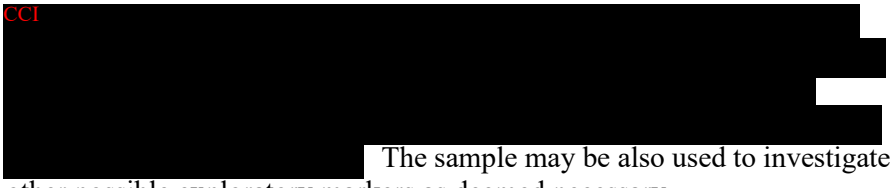
	and without gemfibrozil (Part 1) or to compare the PK of dabigatran when administered with and without camlipixant (Part 2) in healthy participants under fasting conditions. Participants will be enrolled to either Part 1 or Part 2. In each part, participants will receive the assigned treatment. The start of study conduct for Part 2 is independent from Part 1 study conduct. In Part 1, participants will receive a single oral dose of 1 x 50 mg camlipixant tablet on Day 1, followed by 72 hours of PK and safety assessments. Repeated oral doses of CCI mg gemfibrozil tablet will be administered CCI CCI, (total daily dose of CCI mg) on Days 5 to 11, with co-administration of a single oral dose of 1 x 50 mg camlipixant tablet with the morning dose of gemfibrozil on Day 9. Administration of camlipixant on Day 9 will occur 1 hour (± 2 minutes) after administration of gemfibrozil, followed by 72 hours of PK and safety assessments. In Part 2, participants will receive a single oral dose of CCI mg dabigatran etexilate capsule on Day 1, followed by 72 hours of PK and safety assessments. Repeated oral doses of 1 x 50 mg camlipixant tablet will be administered on Days 5 to 10 (CCI mg, on Days 5 to 9), with same time co-administration of a single oral dose of CCI mg dabigatran etexilate capsule and the dose of camlipixant in the morning of Day 10. This will be followed by 72 hours of PK and safety assessments. The study will include a screening visit from Day -28 to Day -1. In each part of the study, eligible participants will be admitted to the clinical site on Day -1 and will be confined until completion of the assessments on Day 12 (Part 1) or Day 13 (Part 2). There will be a washout period of at least 4 days between the first dose of camlipixant on Day 1 and the first dose of gemfibrozil on Day 5 (Part 1), and a washout period of at least 4 days between the first dose of dabigatran etexilate on Day 1 and the first dose of camlipixant on Day 5 (Part 2). A follow-up phone call will be performed 7 ± 2 days after discharge (Day 19 ± 2 in Part 1 and Day 20 ± 2 in Part 2).
Study Population:	A total of 36 healthy participants are planned to be enrolled, with 16 participants enrolled in Part 1 and 20 participants enrolled in Part 2. Participants must be males or females, ≥ 18 and ≤ 55 years of age, and non-smoker for enrollment in the study.
Inclusion/Exclusion Criteria:	<u>Inclusion Criteria:</u> 1. Male or female, non-smoker (no use of tobacco or nicotine products within 3 months prior to screening), ≥18 and ≤55 years of age, with body mass index (BMI) >18.5 and <30.0 kg/m^2 and body weight ≥50.0 kg. 2. Healthy as defined by: a. the absence of clinically significant illness and surgery within 4 weeks prior to dosing. b. the absence of clinically significant history of neurological, endocrine, cardiovascular, respiratory, hematological,

	immunological, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease. 3. Female participants of non-childbearing potential must be: a. post-menopausal (spontaneous amenorrhea for at least 12 months prior to dosing) with confirmation by documented follicle-stimulating hormone (FSH) levels ≥40 mIU/mL; or b. surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy) at least 3 months prior to dosing. 4. Females of childbearing potential who are sexually active with a non-sterile male partner (sterile male partners are defined as men vasectomized since at least 3 months) must be willing to use one of the following acceptable contraceptive methods throughout the study and for 90 days after the last study drug administration: a. simultaneous use of intra-uterine contraceptive device without hormone release system placed at least 4 weeks prior to study drug administration, and condom for the male partner; b. simultaneous use of diaphragm or cervical cap with intravaginally applied spermicide and male condom for the male partner, started at least 21 days prior to study drug administration. c. tubal ligation at least 3 months prior to dosing. 5. Female participants must be willing not to donate ova for 90 days after the last dose. 6. Male participants who are not vasectomized for at least 3 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 the first dose and for 90 days after the last dose: a. simultaneous use of condom and hormonal contraceptive (e.g., oral, patch, depot injection, implant, vaginal ring, intrauterine device) or non-hormonal intrauterine device used for at least 4 weeks prior to sexual intercourse for the female partner; b. simultaneous use of condom and a diaphragm or cervical cap with spermicide for the female partner. 7. Male participants (including men who have had a vasectomy) with a pregnant partner must agree to use a condom from the first dose and for 90 days after the last dose. 8. Male participants must be willing not to donate sperm for 90 days after the last dose. 9. Able to understand the study procedures and provide signed informed consent to participate in the study.

	Exclusion Criteria: 1. Any clinically significant abnormal finding at physical examination at screening. 2. Clinically significant abnormal laboratory test results or positive serology test results for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) antigen and antibody, at screening. 3. Any of the following laboratory parameters above the upper limit of normal (ULN) values at screening or baseline (Day -1): aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct bilirubin, indirect bilirubin, and total bilirubin. Only abnormal values up to 1.5x ULN may be repeated once for confirmation to below ULN. 4. Positive pregnancy test or lactating female participant. 5. Positive urine drug screen, urine cotinine test, or alcohol breath test. 6. Positive test for coronavirus 2019 (COVID-19) at admission. 7. Known allergic reactions or hypersensitivity to camlipixant, gemfibrozil (participants in Part 1 only), dabigatran etexilate or dabigatran (participants in Part 2 only), or other related drugs, or to any excipient in the formulation. 8. Clinically significant ECG abnormalities (for example, Fridericia's corrected QT interval [QTcF] > 450 ms) or vital signs abnormalities (systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, or heart rate less than 50 or over 100 bpm) at screening. 9. History of drug abuse within 1 year prior to screening or use of drugs (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) within 3 months prior to screening, except for cannabis, hashish, or any products containing either, which are not allowed within 1 month prior to screening. 10. History of alcohol abuse within 1 year prior to screening or regular use of alcohol within 6 months prior to screening that exceeds 10 units for women or 15 units for men of alcohol per week (1 unit = 340 mL of beer 5%, 140 mL of wine 12%, or 45 mL of distilled alcohol 40%). 11. History of gastrointestinal disorders, such as stomach ulcers, irritable bowel syndrome (IBS), ulcerative or pseudomembranous colitis, intestinal obstruction, previous liver disease or hepatic dysfunction (including primary biliary cirrhosis), hyperbilirubinemia, jaundice, or elevated liver enzymes. 12. Known Gilbert, Rotor, Crigler-Najjar, or Dubin-Johnson syndrome. 13. CCI [redacted] CCI [redacted]. 14. History of gallbladder disease, including cholelithiasis.

	15. History of renal dysfunction and those with estimated creatinine clearance (CrCl) less than 60 mL/min. 16. Participants in Part 1 only: History of myoglobinuria, myopathy, myalgia, myositis or rhabdomyolysis. 17. Participants in Part 1 only: History of Type I hyperlipoproteinemia. 18. Participants in Part 2 only: Participants with haemorrhagic manifestations, clinically significant active bleeding, including gastrointestinal bleeding, bleeding diathesis, spontaneous or pharmacological impairment of haemostasis. 19. Participants in Part 2 only: Participants with lesions, diseases, or procedures at risk of clinically significant bleeding/haemorrhagic risks, such as congenital or acquired coagulations disorders, thrombocytopenia or functional platelet defects, recent cerebral infarction (haemorrhagic or ischemic) within the last 6 months, active ulcerative gastrointestinal disease (including peptic ulcer) with recent gastrointestinal bleeding, bacterial endocarditis, recent biopsy or major trauma, brain, spinal or ophthalmic surgery, prosthetic heart valves, or hemodynamically significant rheumatic heart disease. 20. Participants in Part 2 only: History of antiphospholipid disease. 21. Participants in Part 2 only: Participants having undergone any major surgery within 6 months prior to the start of the study, unless deemed otherwise by the Investigator. 22. Participants in Part 2 only: Any of the following laboratory parameters outside the normal ranges at screening or baseline (Day -1): prothrombin time (PT) and activated partial thromboplastin time (aPTT). 23. Use of medications for the timeframes specified below, with the exception of medications exempted by the Investigator on a case-by-case basis because they are judged unlikely to affect the PK profile of the study drug or participant safety (e.g., topical drug products without significant systemic absorption): a. depot injection or implant within 3 months prior to dosing; b. any drug known to induce or inhibit hepatic drug metabolism, including St. John's wort, within 30 days prior to dosing or 10 half-lives, whichever is longer; c. prescription medications within 14 days prior to dosing; d. any vaccine, including COVID-19 vaccine, within 14 days prior to dosing; e. over-the-counter (OTC) medications and natural health products (including herbal remedies, homeopathic and traditional medicines, probiotics, food supplements such as vitamins, minerals, amino acids, essential fatty acids, and protein supplements used in sports) within 7 days prior to dosing, with the exception of the occasional use of acetaminophen (up to 2 g daily).

	24. Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days prior to dosing, administration of a biological product in the context of a clinical research study within 90 days prior to dosing, or concomitant participation in an investigational study involving no drug or device administration. 25. Donation of plasma within 7 days prior to dosing or donation or loss of 500 mL or more of whole blood within 8 weeks prior to dosing. 26. Any reason which, in the opinion of the Investigator, would prevent the participant from participating in the study.
Study Treatments:	Participants will receive: • Camlipixant (BLU-5937) 1 x 50 mg tablet administered under fasting conditions [CCI] on Day 1 and Day 9 (Part 1), or 1 x 50 mg tablet for 6 consecutive days from Day 5 to Day 9 as [CCI], (total daily dose 100 mg), and as [CCI] ([CCI] in the morning of Day 10 (Part 2). • On Day 9 (Part 1), camlipixant will be administered 1 hour (± 2 minutes) after morning administration of gemfibrozil (Part 1). • Gemfibrozil [CCI] mg tablet administered [CCI] mg), for 7 consecutive days from Day 5 to Day 11 (Part 1). Administration will occur before [CCI] except for the morning dose on Day 9. • Dabigatran etexilate [CCI] mg capsule administered under fasting condition in the [CCI] on Day 1 and Day 10 (Part 2). • On Day 10 (Part 2), dabigatran etexilate will be co-administered at the same time with the [CCI] administration of camlipixant (Part 2). On Day 1: No food will be allowed from at least 10 hours before camlipixant (Part 1) or dabigatran etexilate (Part 2) dosing until at least 4 hours after dosing. On Day 9 (Part 1) or Day 10 (Part 2): No food will be allowed from at least 10 hours before gemfibrozil (Part 1) or camlipixant/dabigatran etexilate (Part 2) dosing until at least 4 hours after camlipixant (Part 1) or camlipixant/dabigatran etexilate (Part 2) dosing. On Days 5 to 8, evening of Day 9, and Days 10 and 11 (Part 1): Gemfibrozil will be administered approximately 30 minutes (±10 minutes) before a standard morning/evening meal. On Days 5 to 9 (Part 2): No food will be allowed from at least 2 hours before morning camlipixant dosing until 1-hour post-morning dose. A normo-caloric breakfast will be served at least 1 hour after camlipixant administration.

Study Procedures:	Blood samples for PK analysis will be collected and safety procedures will be performed at pre-defined times throughout the study as specified in Table 1.Schedule of Assessments for Part 1 and Table 2. Schedule of Assessments for Part 2. Participants will be monitored throughout the study by the clinical staff for AEs and concomitant medication use.
Statistical Analyses:	PK analysis: CCI  Concentrations for gemfibrozil (Part 1) and camlipixant (Part 2) will be tabulated. They will be presented as supportive data. Descriptive statistics on pre-morning dose concentrations of gemfibrozil in Part 1 (Days 7, 8 and 9) and camlipixant in Part 2 (Days 8, 9, and 10) will be performed to evaluate the attainment of steady-state. CCI  CCI  The sample may be also used to investigate other possible exploratory markers as deemed necessary Metabolites of camlipixant may be assayed at a later time, if deemed necessary. Safety and tolerability analysis: Safety and tolerability of camlipixant alone (Part 1 and Part 2) and in combination with gemfibrozil (Part 1) or dabigatran etexilate (Part 2) will be evaluated through the assessment of AEs, SAEs, AEMIs (i.e.,

	seriousness, severity, relationship to the study drug and the interacting drug, outcome, duration, and management), vital signs, 12-lead ECGs, clinical laboratory tests, and physical examinations. Treatment-emergent adverse events (TEAEs) will be tabulated by treatment. Safety and tolerability data will be reported using descriptive statistics.
A Summary Table of study procedures is presented in Appendix 1.	

Table 1. Schedule of Assessments for Part 1

Study Stage	Screening	Baseline	Treatment									Follow-up phone call
Day	**-28 to -1**	**-1**	**1**	**2-3**	**4**	**5**	**6-8**	**9**	**10**	**11**	**12**	**19 ± 2**
Informed consent	X											
Inclusion/exclusion criteria	X											
Demographic data	X											
Medical and medication history	X											
Confinement		X	X	X	X	X	X	X	X	X		
Discharge/ET											X[14]	
Follow-up phone call												X[15]
Study drug administration												
Camlipixant[1]			X					X				
Gemfibrozil[2]						X	X	X	X	X		
Pharmacokinetics												
Blood samples for PK analysis of camlipixant[3]			X	X	X			X	X	X	X	
Blood samples for PK analysis of gemfibrozil[4]						X	X	X				
Blood sample for pharmacogenomic analysis		X										
Safety												
Physical examination[5]	X	X					X				X	
Body measurements (height, weight, BMI)	X											
Vital signs[6]	X		X					X			X	
12-lead ECG[7]	X		X			X		X			X	
Serology tests[8]	X											
Clinical laboratory tests (biochemistry, hematology, and coagulation)[9]	X	X				X		X			X	
Urinalysis[10]	X	X				X		X			X	
FSH (for post-menopausal females)[11]	X											
Pregnancy tests[12]	X	X									X	

Study Stage	Screening	Baseline	Treatment									Follow-up phone call
Day	-28 to -1	-1	1	2-3	4	5	6-8	9	10	11	12	19 ± 2
Drug, cotinine, and alcohol screens	X	X										
COVID-19 test		X			X							
Monitoring and recording of AEs, SAEs, AEMIs, and prior/concomitant medication use[13]	←										→	

Abbreviations: AE = adverse event; AEMI =adverse event of medical interest; BMI = body mass index; CK = creatine kinase; COVID-19 = coronavirus 2019; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LFT = liver function test; PK = pharmacokinetic; SAE = serious adverse event.

1 On Day 9, camlipixant will be administered 1 hour (± 2 minutes) after CCI [redacted] administration of gemfibrozil.

2 Administration of gemfibrozil CCI [redacted], will occur at approximately the CCI [redacted] and evening from Days 5 to 11. A time window of ± 10 minutes from the scheduled dosing time will be allowed, as long as the 1-hour (± 2 minutes) time interval between gemfibrozil and camlipixant dosing on Day 9 is respected.

3 A total of 19 blood samples will be collected for PK analysis of camlipixant on Day 1 and Day 9: at pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 15, 18, 24, 48, and 72 hours post-dose. Refer to Table 3 for more details.

4 A total of 5 blood samples will be collected for PK analysis of gemfibrozil pre-morning dose on Days 5, 6, 7, 8, and 9. Refer to Table 3 for more details.

5 A complete physical examination will be performed at screening. A brief physical examination will be performed on Day -1, in the evening of Day 8, and at discharge on Day 12 (or ET).

6 Blood pressure, heart rate, respiratory rate, and oral temperature will be measured at screening and discharge on Day 12 (or ET). Blood pressure and heart rate will be measured before camlipixant dosing on Day 1 and before gemfibrozil dosing on Day 9.

7 12-lead ECG will be measured at screening, before camlipixant dosing on Day 1, before gemfibrozil dosing on Day 5 and Day 9, at approximately 1 hour post-dosing of camlipixant on Day 9, and at discharge on Day 12 (or ET).

8 Serology tests include HbsAg, HCV antibody, HIV antigen and antibody.

9 Standard biochemistry (including LFT and CK), hematology, and coagulation tests will be performed at screening, on Day -1, before gemfibrozil dosing on Day 5 and Day 9, and at discharge on Day 12 (or ET).

10 Urinalysis tests will be performed at screening, on Day -1, before gemfibrozil dosing on Day 5 and Day 9, and at discharge on Day 12 (or ET).

11 FSH levels will be measured at screening to confirm the post-menopausal status.

12 A urine pregnancy test will be performed at screening and at discharge on Day 12 (or ET), and a serum pregnancy test will be performed on Day -1. If there is a positive pregnancy result following the first study drug administration, a Pregnancy Notification form is to be completed and submitted to the Sponsor.

13 All AEs, SAEs, and AEMIs will be closely monitored and reported as indicated in safety section 8.4. Following dosing on Day 1 until the end of the study, participants who spontaneously report CCI [redacted].

Reported [redacted] will continue to be followed until resolved. Testing for COVID-19 (SARS-CoV-2) should be performed for participants reporting any ongoing or recent (within 1 week of ending) [redacted]

14 In case of ET, discharge procedures will be performed as soon as possible.

15 A safety follow-up phone call will be performed 7 ± 2 days after discharge.

Table 2. Schedule of Assessments for Part 2

Study Stage	Screening	Baseline	Treatment									Follow-up phone call
Day	**-28 to -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6-9**	**10**	**11-12**	**13**	**20 ± 2**
Informed consent	X											
Inclusion/exclusion criteria	X											
Demographic data	X											
Medical and medication history	X											
Confinement		X	X	X	X	X	X	X	X	X		
Discharge/ET											X[14]	
Follow-up phone call												X[15]
Study drug administration												
Dabigatran etexilate[1]			X						X			
Camlipixant[2]							X	X	X			
Pharmacokinetics												
Blood samples for PK analysis of dabigatran[3]			X	X	X	X			X	X	X	
Blood samples for PK analysis of camlipixant[4]							X	X	X			
Blood sample for pharmacogenomic analysis		X										
Safety												
Physical examination[5]	X	X						X			X	
Body measurements (height, weight, BMI)	X											
Vital signs[6]	X		X						X		X	
12-lead ECG[7]	X		X				X		X		X	
Serology tests[8]	X											
Clinical laboratory tests (biochemistry, hematology, and coagulation)[9]	X	X					X	X			X	
Urinalysis[10]	X	X					X	X			X	
FSH (for post-menopausal females)[11]	X											
Pregnancy tests[12]	X	X									X	

Study Stage	Screening	Baseline	Treatment									Follow-up phone call
Day	**-28 to -1**	**-1**	**1**	**2**	**3**	**4**	**5**	**6-9**	**10**	**11-12**	**13**	**20 ± 2**
Drug, cotinine, and alcohol screens	X	X										
COVID-19 test		X				X						
Monitoring and recording of AEs, SAEs, AEMIs, and prior/concomitant medication use[13]	◄											►

Abbreviations: AE = adverse event; AEMI =adverse event of medical interest; aPTT = activated partial thromboplastin time; BMI = body mass index; CK = creatine kinase; COVID-19 = coronavirus 2019; CrCl = creatinine clearance; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LFT = liver function test; PK = pharmacokinetic; PT = prothrombin time; SAE = serious adverse event.

1 On Day 10, dabigatran etexilate will be co-administered with camlipixant at the same time. Camlipixant will be swallowed first, followed immediately by dabigatran. The entire procedure should be completed within 2 minutes.

2 Administration of camlipixant CCI [redacted], will occur at approximately the same time in the CCI [redacted] and in the evening from Days 5 to 9, and in the CCI [redacted] of Day 10. A time window of ± 10 minutes from the scheduled dosing time will be allowed, as long as the co-administration of camlipixant and dabigatran etexilate at the same time on Day 10 is respected.

3 A total of 21 blood samples will be collected for PK analysis of dabigatran on Day 1 and Day 10: pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, and 72 hours post-dose. Refer to Table 4 for more details.

4 A total of 5 blood samples will be collected for PK analysis of camlipixant pre-morning dose on Days 5, 7, 8, 9 and 10. Refer to Table 4 for more details.

5 A complete physical examination will be performed at screening. A brief physical examination will be performed on Day -1, in the evening of Day 9, and at discharge on Day 13 (or ET).

6 Blood pressure, heart rate, respiratory rate, and oral temperature will be measured at screening and discharge on Day 13 (or ET). Blood pressure and heart rate will be measured before dabigatran etexilate dosing on Day 1 and before camlipixant dosing on Day 10.

7 12-lead ECG will be measured at screening, before dabigatran etexilate dosing on Day 1, before camlipixant dosing on Day 5 and Day 10, and at discharge on Day 13 (or ET).

8 Serology tests include HbsAg, HCV antibody, and HIV antigen and antibody.

9 Standard biochemistry (including LFT and CK), hematology, and coagulation tests will be performed at screening, on Day -1, before camlipixant dosing on Day 5, the day before dabigatran dosing on Day 9, and at discharge on Day 13 (or ET). All subjects should have PT, aPTT and CrCl measured. The PT and aPTT should be within the normal range and the CrCl value should be more than 60 mL/min for each subject before dabigatran dosing in order to prevent or avoid the possibility of bleeding.

10 Urinalysis will be performed at screening, on Day -1, before camlipixant dosing on Day 5, the day before dabigatran dosing on Day 9, and at discharge on Day 13 (or ET).

11 FSH levels will be measured at screening to confirm the post-menopausal status.

12 A urine pregnancy test will be performed at screening and at discharge on Day 12 (or ET), and a serum pregnancy test will be performed on Day -1. If there is a positive pregnancy result following the first study drug administration, a Pregnancy Notification form is to be completed and submitted to the Sponsor.

13 All AEs, SAEs, and AEMIs will be closely monitored and reported as indicated in safety section 8.4. Following dosing on Day 5 until the end of the study, participants who spontaneously report taste disturbance as an AE will be asked to provide additional characterization of their taste disturbance. CCI [redacted] CCI [redacted]

14 In case of ET, discharge procedures will be performed as soon as possible.

15 A safety follow-up phone call will be performed 7 ± 2 days after discharge.

1. Introduction

1.1 Background Information

Camlipixant (previously identified as BLU-5937) is a small molecule of the [redacted] that is developed for the treatment of refractory (or unexplained) chronic cough (RCC). It has been shown to be a potent, selective, and non-competitive P2X3 homotrimeric receptor antagonist. P2X3 receptors are adenosine triphosphate (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 refractory RCC. Camlipixant was shown to reduce significantly cough frequency in patients with baseline awake cough frequency [redacted] coughs/hour in a Phase 2b clinical study [redacted] Of note, the high selectivity of camlipixant for the P2X3 homotrimeric receptor versus P2X2/3 heterotrimeric receptor should reduce the taste disturbance AEs that have been associated to P2X2/3 and observed with other less selective P2X3 antagonists.

1.2 Nonclinical

[redacted]

The toxicology of camlipixant has been studied in several preclinical species. Selected findings are presented below. Please refer to the Investigator's Brochure (IB) for a complete description and summary. Regarding the male reproductive system, camlipixant was shown to have effects in the testis with decreased sperm in the epididymis upon long-term administration in animal toxicity studies (26 weeks in rat and 39 weeks in dog). These findings were fully reversible and were not observed with shorter-term dosing (28 days toxicity study, and a fertility study where male rats were administered camlipixant up to 60 days). However, it is not known whether the effects seen in animals will also occur in men dosed with camlipixant. Since only the long-term preclinical studies have resulted in testicular toxicity and that this has been observed to be

reversible, it is considered that the risks to healthy male adults receiving single doses, and with a suitable washout period between doses, is minimal.

Lens and corneal opacities have been observed upon chronic 26- and 39-week administration in rats and dogs, respectively. These were minor in terms of severity and were considered non-adverse as they are not expected to affect the vision. These were not observed with short-term dosing and the risks to healthy participants receiving single doses is considered minimal.

1.3 Clinical

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To date, approximately 560 participants have been exposed to camlipixant at doses ranging from 12.5 mg to 1200 mg as single or multiple BID doses for up to 4 weeks in Phase 1 and Phase 2 studies. Camlipixant was found to be generally well tolerated in healthy adult participants, participants with RCC, and participants with chronic pruritis associated with atopic dermatitis. Overall, 210 healthy participants have been exposed to camlipixant at doses ranging from 12.5 mg to 1200 mg as single or multiple doses in Phase 1 studies. There were no deaths or SAEs reported during these studies. The most common TEAEs (camlipixant/placebo) following administration were headache (10.0% / 3.2%), somnolence (9.5% [possibly all related to CCI in a DDI study]) / 0.0%), dysgeusia (9.0% / 1.6%), constipation (6.2% / 0.0%), dizziness (5.2% / 0.0%), nausea (4.3% / 4.8%), hypoesthesia (3.8% / 0.0%), diarrhea (3.3% / 0.0%), dyspepsia (2.4% / 1.6%), and abdominal pain (0.0% / 3.2%). There were no significant changes in vital signs or ECG parameters at any dose level. There were no significant changes in laboratory parameters, except for two isolated cases of mild elevations in liver enzymes (ALT and/or AST), 1 case at 400 mg BID in the FIH and one case at 200 mg BID in a DDI study (BUS-P1-02). In both cases, these elevations in liver enzymes were not associated with a concomitant increase in bilirubin or with clinical symptoms of liver injury. There was a slight trend of increased bilirubin in the FIH study (especially at 400 mg BID) and 1 case with 200 mg BID in a DDI study (BUS-P1-02; both representing a supra-therapeutic dose), which were not associated with any concomitant increases in liver enzymes. The mild elevation in bilirubin in the absence of increased liver enzyme levels is likely due to the drug's interference in bilirubin disposition through OATP inhibition and is likely to represent a benign process. Overall, 3 participants were discontinued from the Phase 1 clinical studies due to TEAEs, all from the DDI (BUS-P1-02) study at the 200 mg BID dose: 2 participants had mild rash (camlipixant) and one of these participants had increased AST and ALT levels (sulfasalazine alone)CCI

CCI

Refer to the IB v.5 and the IB addendum for detailed background information on camlipixantCCI

1.4 Background Information on Gemfibrozil

Gemfibrozil is an antihyperlipidemic agent indicated as an adjunct to diet and other therapeutic measures for: 1) treatment of adult patients with very high serum triglyceride levels, Fredrickson classification Type [redacted]. The maximum recommended daily dose is 1500 mg. AEs associated with gemfibrozil are listed in the Product Monograph.[5]

Gemfibrozil is a lipid regulating agent which decreases serum triglycerides and total cholesterol, and increases high density lipoprotein cholesterol. The mechanism of action has not been definitely established. In man, gemfibrozil has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. Gemfibrozil also inhibits the synthesis and increases clearance of very low density lipoprotein (VLDL) carrier apolipoprotein B, leading to a decrease in VLDL.[5]

Gemfibrozil is completely absorbed after oral administration. Peak plasma levels occur in 1 to 2 hours following single doses. Plasma levels appear proportional to dose and do not demonstrate accumulation across time following multiple doses. Gemfibrozil PK is affected by the timing of meals relative to time of dosing. In one study, both the rate and extent of absorption of the drug were significantly increased when administered 0.5 hours before meals. Average area under the concentration-time curve (AUC) was reduced by 14 to 44% when gemfibrozil was administered after meals compared to 0.5 hour before meals. In a subsequent study, rate of absorption of gemfibrozil was maximum when administered 0.5 hour before meals with the C_{max} 50-60% greater than when given either with meals or fasting. In this study, there were no significant effects on AUC of timing of dose relative to meals.[5]

Three metabolic pathways have been identified. The first metabolic pathway is that of conjugation of gemfibrozil and its metabolites. The second, and presumably the principal route, involves hydroxylation of the meta-methyl group of gemfibrozil, yielding a benzyl alcohol (Metabolite II) that undergoes rapid oxidation to a benzoic acid metabolite (Metabolite III, the major metabolite). The third pathway involves hydroxylation of the aromatic ring to a phenol (Metabolite I) which is further converted to a compound (Metabolite IV) with no intact carboxylic acid function, but which is phenolic in nature. In human subjects, approximately 70% of a given dose is excreted in the urine, primarily as the glucuronide conjugate, with less than 2% excreted as unchanged gemfibrozil; 6% of the dose is accounted for in the feces. The mean half-life was approximately 1.5 hours following single doses and 1.3 hours following multiple doses.[5]

Gemfibrozil inhibits CYP 2C8 isoenzyme. This irreversible inactivation of CYP2C8 is mediated by Gemfibrozil-1-O-beta-glucuronide (GEM-1-O-gluc), a metabolite of gemfibrozil. Gemfibrozil is also known to potently inhibit CYP2C9 activity. Although gemfibrozil also acts as an OATP1B1 inhibitor, a transporter involved in disposition of endogenous compounds such as bilirubin, this pathway is not believed to be important for camlipixant metabolism. Gemfibrozil is highly bound to plasma proteins and there is potential for displacement interactions with other drugs.[5]

1.5 Background Information on Dabigatran Etexilate

Dabigatran etexilate is a direct thrombin inhibitor, indicated for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement (THR) or total knee replacement (TKR) surgery, treatment of venous thromboembolism events (deep vein thrombosis [DVT], pulmonary embolism [PE]) and prevention of recurrent DVT and PE, and prevention of stroke and systemic embolism in patients with atrial fibrillation. In most indications, for patients with creatinine clearance (CrCl) >30 mL/min, the recommended dose of dabigatran etexilate is 150 mg taken orally, BID, with food or on an empty stomach. Dosage may be individualized according to the patient's age and medical condition. AEs associated with dabigatran etexilate are listed in the Product Monograph.[6]

Dabigatran etexilate is a prodrug which does not exhibit anticoagulant activity itself. Following oral administration, dabigatran etexilate is rapidly absorbed and converted to dabigatran by esterase-catalysed hydrolysis in plasma and in the liver. Dabigatran is a competitive, reversible direct thrombin inhibitor and is the main active principle in plasma. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation.[6]

After oral administration, dabigatran etexilate is rapidly and completely converted to dabigatran. The PK profile of dabigatran in plasma is characterized by a rapid increase in plasma concentrations with C_{max} attained 0.5 to 2.0 hours post-administration. The absolute bioavailability of dabigatran following oral administration of dabigatran etexilate was approximately 6.5 %. The oral bioavailability may be increased by 75% (about 1.8 -fold) compared to the reference capsule formulation when the pellets are taken without the hydroxypropylmethylcellulose (HPMC) capsule shell. Hence, the integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of dabigatran etexilate. As such, dabigatran etexilate should be taken orally with the entire capsule to be swallowed whole. The capsule should not be chewed, broken, or opened. Food does not affect the bioavailability of dabigatran but delays the time-to-peak plasma concentrations by 2 hours.[6]

The cleavage of the prodrug dabigatran etexilate by esterase-catalysed hydrolysis to the active principle dabigatran is the predominant metabolic reaction. Dabigatran is metabolised in the liver by conjugation with activated glucuronic acid forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounting for <10% of total dabigatran in plasma. Cytochrome P450 metabolic enzymes are not involved in dabigatran metabolism.[6]

After C_{max}, plasma concentrations of dabigatran showed a biexponential decline with a mean terminal half-life of approximately 11 hours in healthy elderly subjects. Following administration of multiple doses, a terminal half-life of about 12 to 14 hours was observed, with the half-life independent of dose. C_{max} and AUC were dose-proportional. After an intravenous dose, the dabigatran-derived radioactivity was eliminated primarily in the urine (85%). Faecal excretion accounted for 6% of the administered dose. Hepatic elimination via the bile represents a minor elimination pathway (approximately 20% of the administered dose). Dabigatran is eliminated

primarily in the unchanged form in the urine, at a rate of approximately 100 mL/min corresponding to the glomerular filtration rate.[6]

1.6 Study Rationale

Part 1:

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Metabolic inhibition may result in increased plasma concentrations of drugs and/or their active metabolite(s). These increased plasma concentrations may lead to toxicity associated with these drugs.

Therefore, the purpose of Part 1 is to assess, *in vivo*, the potential of camlipixant to be a victim of DDIs precipitated by inhibition of the CYP2C8 enzyme believed to be involved in the biotransformation of camlipixant. In accordance with the recommendations provided in the FDA *Guidance for Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (2020)*,[7] multiple doses of the CYP inhibitor gemfibrozil[8] will be administered to evaluate the effect on the PK of single dose camlipixant. Gemfibrozil is a clinically validated, strong inhibitor for CYP2C8.[8] Its use in the current clinical DDI study will allow to potentially corroborate the findings related to CYP2C8 inhibition from the previously conducted PBPK study.

Part 2:

Based on PBPK modeling predicting camlipixant as a perpetrator in DDIs, a weak interaction may be seen with the P-gp substrate dabigatran while no other interactions are anticipated with substrates of CYP or transporters. PBPK simulations performed using the Ki for P-gp inhibition showed no significant interaction with digoxin and dabigatran. Using a 15-x reduced P-gp Ki, a small increase in C_{max} (28%) and no significant increase in AUC were predicted for digoxin while a 56% and 44% increase in C_{max} and AUC was predicted for dabigatran CCI

Therefore, the purpose of Part 2 is to assess, *in vivo*, the potential of camlipixant to act as a perpetrator in DDIs through inhibition of the P-gp transporter. In accordance with the recommendations provided in the FDA *Guidance for Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (2020)*,[7] a single dose of dabigatran etexilate, a clinically validated substrate of P-gp,[8] will be administered alone and in combination with camlipixant, in order to evaluate the impact of camlipixant on P-gp efflux. The choice of dabigatran etexilate will allow to verify clinically the observations on P-gp from the PBPK study.

1.6.1 Analytes to Measure

The analytes to be measured will include the investigational drug camlipixant (Parts 1 and 2), as well as gemfibrozil (Part 1) and dabigatran (Part 2).

Metabolites of camlipixant may be assayed at a later time, if deemed necessary.

Dabigatran etexilate is a prodrug and, after oral administration, it is rapidly and completely converted to dabigatran, which is the active form in plasma after oral administration. The analyte of interest will be dabigatran. Both free dabigatran (non-conjugated) and total dabigatran will be analyzed. Results for the free form will be used as supportive data.

In this clinical study, perpetrator drugs (gemfibrozil in Part 1 and camlipixant in Part 2) will be administered in a controlled setting i.e., within a clinical research unit with directly observed dosing. Thus, it is not relevant to measure extensively gemfibrozil in Part 1 or camlipixant in Part 2 blood levels. Accordingly, as participants will be confined to the clinical unit the full duration of the study, only sparse samples for gemfibrozil in Part 1 and camlipixant in Part 2 will be collected to provide information on attainment of steady-state, or to help explain any aberrant results.

1.6.2 Rationale for the Dose and Dosing Regimen

Camlipixant is a film-coated, immediate release tablet, available in different strengths from 12.5 to 100 mg.[1] In Part 1, one tablet of 50 mg camlipixant will be administered as a single dose on Day 1 and Day 9. According to the FDA guidance, single dose administration of the substrate drug is acceptable if the substrate does not show time-dependent-PK, and, if the substrate drug has dose-proportional PK, any dose in the linear range may be used.[7] The 50 mg dose of camlipixant was chosen because it is the highest clinically relevant dose currently being tested in Phase 3 studies. In addition, since the PK are linear, the drug interaction at a 50 mg dose is anticipated to be representative of the interactions across the clinically relevant range. In Part 2, camlipixant will be administered at 50 mg BID from Days 5 through 9, and in the morning of Day 10. According to the FDA guidance,[7] the dose of the perpetrator drug used in DDI studies should maximize the possibility of identifying a DDI, by using the maximum approved dose and shortest dosing interval. In a population PK model, exposure response modeling confirmed that the camlipixant 50 mg BID dose should provide near maximal or maximal participant benefit with the highest level of confidence. Doses higher than 50 mg BID (62.5, 75, and 200 mg BID) did not provide a substantial increase in the maximum effect. Accordingly, the highest proposed dose and dosing regimen of camlipixant for Phase 3 clinical trials is 50 mg BID. Considering the half-life of camlipixant is 4 to 9 hours[8] a 5-day lead-in period with camlipixant ensures attainment of steady-state before co-administration with dabigatran etexilate on the 6th day (Day 10) of dosing.

For gemfibrozil, the [CCI]) 30 minutes before the [CCI] and [CCI] meal.[5] Therefore, in line with FDA guidance[7] and commonly used dose in the literature,[9,10] a [CCI] mg dose of gemfibrozil will be administered [CCI] A 4-day lead-in period from Days 5 to 8 before co-administration with camlipixant on the 5th day (Day 9) ensures attainment of steady-state and inhibition of

CYP2C8 by the day of co-administration. The last gemfibrozil dose will be administrated on the evening of Day 11, before-last PK sampling timepoint of camlipixant, to maintain inhibition. Other than the morning dose that will be co-administered with camlipixant on Day 9, all other gemfibrozil administrations will occur 30 minutes (±10 minutes) before a standard morning/evening meal.

The recommended dose of dabigatran etexilate is CCI mg taken orally, CCI, with food or on an empty stomach.[6] Following recommendations from the FDA guidance,[7] one capsule of CCI mg of CCI CCI will be administered alone as a single dose on Day 1 and co-administered with camlipixant on Day 10. This dose is commonly used in the literature.[11]

1.6.3 Pharmacogenomic Testing

One blood sample for pharmacogenomic testing will be taken on Day -1 CCI [redacted]. The sample may be also used to investigate other possible exploratory markers as deemed necessary.

1.6.4 Rationale for the Study Population

A healthy volunteer population has been selected for the study because healthy participants with no concomitant diseases and using no concomitant medications represent a homogenous population allowing for proper evaluation of the PK, safety, and tolerability of a drug without confounding factors.

To date, approximately 560 participants have been exposed to camlipixant at doses ranging from 12.5 mg to 1200 mg as single or multiple BID doses for up to 4 weeks in Phase 1 and Phase 2 studies. Camlipixant was found to be generally well tolerated in healthy adult participants as outlined in Section 1.3. Embryo-fetal development (EFD) and female and male fertility studies on camlipixant in rats and rabbits did not identify any findings of concern for humans, including teratogenicity, at the proposed clinical doses (safety margins >20 at the 50 mg single dose proposed in this current study). The no observed adverse effect levels (NOAEL) for EFD toxicity in pregnant rats was 100 mg/kg/day with lower maternal body weights, lower fetal body weights, and increased incidence of fetal tail abnormalities and skeletal variations observed at the highest dose tested (250 mg/kg/day). No test article-related effects on maternal survival, clinical findings, ovarian and uterine parameters or gross macroscopic findings were observed at any camlipixant dose level evaluated. The NOAEL for fertility and reproductive effects and early embryonic development in female rats was 150 mg/kg/day due to adverse lower fertility and fecundity indices, lower number of implantation sites, and post implantation loss observed at 450 mg/kg/day. In the EFD study in pregnant rabbits, based upon the maternal clinical signs and lower body weight gain and food consumption at 450 mg/kg/day, the NOAEL for maternal toxicity was considered to be 200 mg/kg/day while the NOAEL for EFD toxicity is considered to be 450 mg/kg/day. In the male fertility study, the no observed effect level (NOEL) for paternal toxicity and male mating, fertility, sperm parameters, and reproductive outcome is considered to be 450 mg/kg/day. There have been no clinical studies of camlipixant conducted in pregnant women.

At oral doses of approximately 95 and 325 mg/kg/day in male and female rats, gemfibrozil produced a dose-related suppression of fertility but had no effect on length of gestation, duration of parturition, litter size, or embryonic or fetal wastage. Treated males were responsible for the reduced fertility rate, probably because of the marked suppression of weight gain they experienced. In pregnant rats and rabbits at doses of 81 and 281 mg/kg, examination of fetuses removed from treated rats and rabbits one day before expected parturition disclosed no significant effects on either litter or fetal characteristics, nor were significant malformations found among almost 400 offspring from 36 litters of treated rats or 100 fetuses from 22 litters of treated rabbits. Among women, gemfibrozil is to be discontinued several months prior to conception. Because of the potential for tumorgenicity shown in rats, a decision should be made whether to discontinue nursing or discontinue the drug for nursing mothers.[5]

In teratology studies of dabigatran in rats and rabbits, a slight effect on the morphogenesis of foetuses was observed in rats at 200 mg/kg (free base equivalent). In a fertility study in rats, a slight decrease in corpora lutea and an increase in pre-implantation loss led to a decrease in the mean number of implantations in the 200 mg/kg (free base equivalent) dose group. Dabigatran decreased the number of implantations when male and female rats were treated at dosages about 2.6 to 3.0x the human exposure at maximum recommended human dose (MRHD) prior to mating and up to implantation. Treatment of pregnant rats after implantation at the same dose increased the number of dead offspring and caused excess vaginal/uterine bleeding close to parturition. Although dabigatran increased the incidence of delayed or irregular ossification of fetal skull bones and vertebrae in the rat, it did not induce major malformations in rats or rabbits. There are no studies of dabigatran etexilate in pregnant women and therefore, the potential risk in these patients is unknown. There are no clinical data available on the excretion of dabigatran into breast milk.[6]

In light of these data, only male and non-pregnant, non-lactating female participants will be enrolled in this study. Sexually active female subjects of childbearing potential and non-surgically sterile male participants with female partners of childbearing potential will be required to use a double contraceptive method. Pregnancy tests will also be performed at different times over the course of the study for female participants. Additional pregnancy reporting information is provided in section 8.4.7.

Additionally, most older subjects demonstrate an increase in dabigatran exposure; especially in those patients with age-related decline of renal function. Elderly subjects showed an increase of 40 to 60% (1.4 to 1.6-fold) in the AUC and about 25% (1.3-fold) in C_{max}, compared to young subjects.[6] Therefore, the population in this study will include healthy individuals between the ages of 18 and 55 years.

Finally, for patients of low body weight (< 50 kg), dabigatran etexilate is to be used with caution since limited data are available in these patients. As such, a lower limit of 50 kg will be applied to participants in this study .

1.7 Benefit/Risk Assessment

The inclusion and exclusion criteria have been chosen to select participants who are known to be free from any significant illness, history of autoimmune diseases, and from any condition that

could impact their safety or interfere with meeting the study objectives. The proposed safety screening and monitoring assessments are deemed to be sufficient to monitor potential risks of camlipixant administration alone and in combination with gemfibrozil or dabigatran etexilate. There is no anticipated therapeutic benefit for the healthy participants in this study.

2. Objectives

Primary objectives:

- To assess the effect of repeated oral doses of gemfibrozil, a CYP2C8 inhibitor, on the PK of a single oral dose of camlipixant (Part 1) administered to healthy participants.
- To assess the effect of repeated oral doses of camlipixant on the PK of a single oral dose of dabigatran etexilate, a P-gp substrate (Part 2), administered to healthy participants.

Secondary objective:

- To evaluate the safety and tolerability of camlipixant when administered alone and in combination with gemfibrozil or dabigatran etexilate to healthy participants.

3. Endpoints

Primary endpoints:

- PK parameters: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} of camlipixant (Part 1) and dabigatran (Part 2*)

Secondary endpoints:

- PK parameters: T_{max}, $T_{½\,el}$, Residual area, K_{el}, Cl/F, and V_z/F of camlipixant (Part 1) and dabigatran (Part 2*)

  *For Part 2, both total and free dabigatran will be assayed, and their PK parameters generated.

- Safety evaluation:
  - AEs, SAEs, AEMIs, vital signs measurements (blood pressure, heart rate, respiratory rate, and oral temperature), 12-lead ECG recordings, physical examinations, and clinical laboratory test results, including hematology, biochemistry, coagulation, and urinalysis.

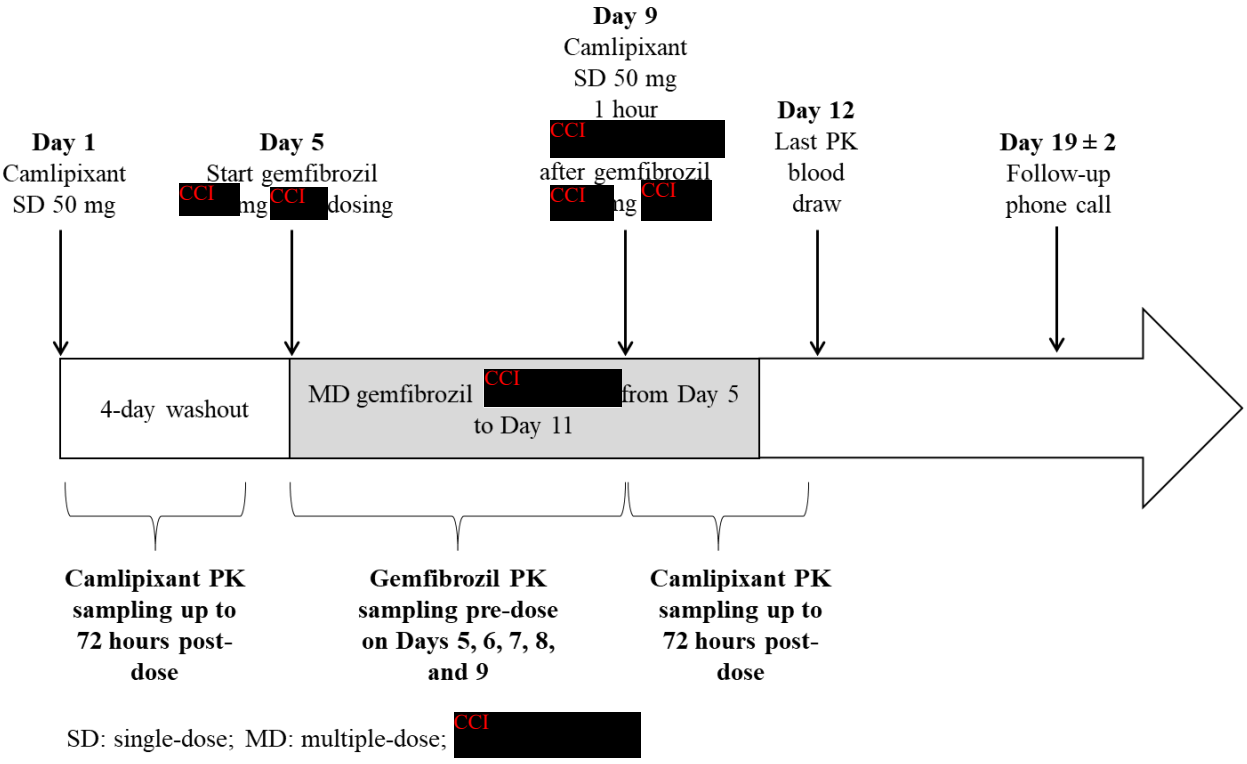
4. Study Design

This is a single-center, 2-part, Phase 1, open-label, fixed-sequence, DDI study designed to compare the PK of camlipixant when administered with and without gemfibrozil (Part 1) or to compare the PK of dabigatran when administered with and without camlipixant (Part 2) in healthy participants under fasting conditions. Participants will be enrolled to either Part 1 or Part 2. In each part, participants will receive the assigned treatment. The start of study conduct for Part 2 is independent from Part 1 study conduct.

A total of 36 participants will be enrolled in Part 1 or Part 2 (16 participants in Part 1 and 20 participants in Part 2). In each part, participants will receive the assigned treatment.

In Part 1, participants will receive a single oral dose of 1 x 50 mg camlipixant tablet on Day 1, followed by 72 hours of PK and safety assessments. Repeated oral doses of [redacted] mg gemfibrozil tablet will be administered [redacted] mg) on Days 5 to 11, with co-administration of a single oral dose of 1 x 50 mg camlipixant tablet with the morning dose of gemfibrozil on Day 9. Administration of camlipixant on Day 9 will occur 1 hour (± 2 minutes) after administration of gemfibrozil, followed by 72 hours of PK and safety assessments. The study design is presented in Figure 1.

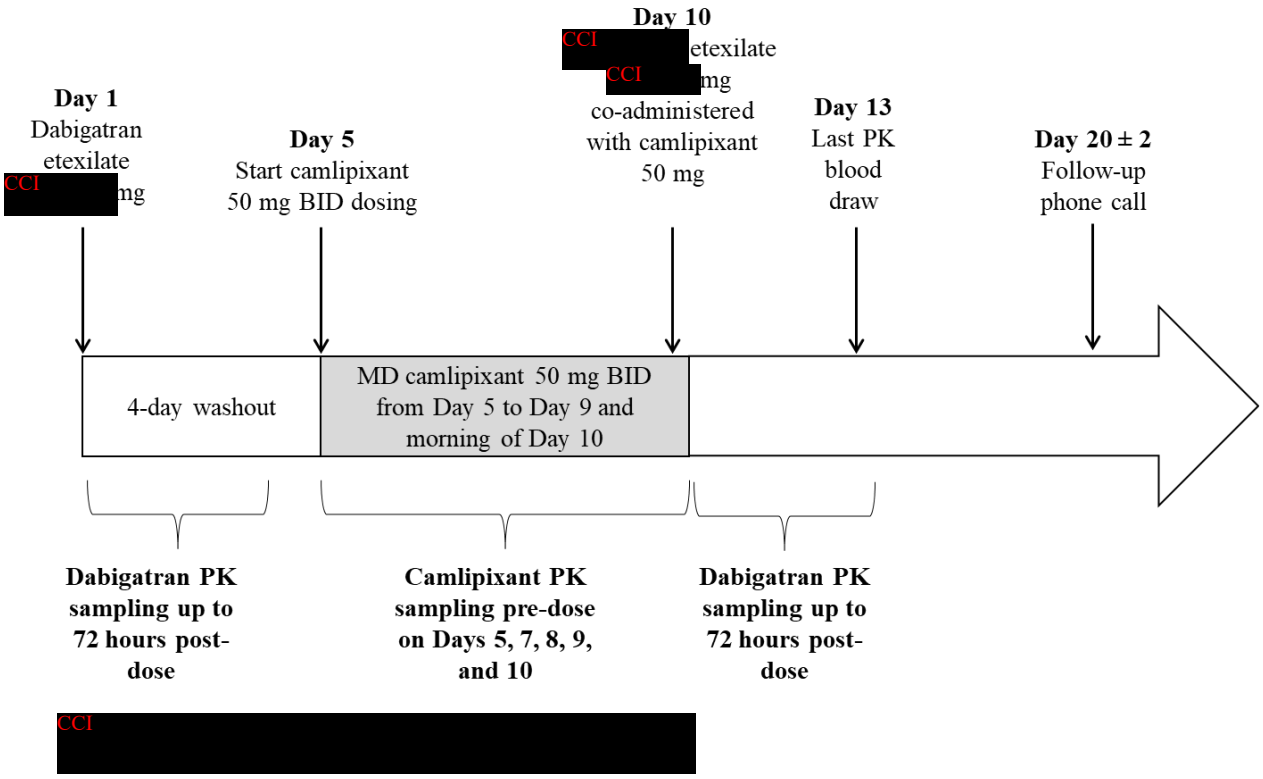
Figure 1. Study Design Diagram for Part 1



SD: single-dose; MD: multiple-dose; [redacted]

In Part 2, participants will receive a single oral dose of [CCI] mg dabigatran etexilate capsule on Day 1, followed by 72 hours of PK and safety assessments. Repeated oral doses of 1 x 50 mg camlipixant tablet will be administered on Days 5 to 10 ([CCI] mg, on Days 5 to 9), with same time co-administration of a single oral dose of [CCI] mg dabigatran etexilate capsule and the dose of camlipixant in the morning of Day 10. This will be followed by 72 hours of PK and safety assessments. The study design is presented in Figure 2.

Figure 2. Study Design Diagram for Part 2



The study will include a screening visit from Day -28 to Day -1. In each part of the study, eligible participants will be admitted to the clinical site on Day -1 and will be confined until completion of the assessments on Day 12 (Part 1) or Day 13 (Part 2). There will be a washout period of at least 4 days between the first dose of camlipixant on Day 1 and the first dose of gemfibrozil on Day 5 (Part 1), and a washout period of at least 4 days between the first dose of dabigatran etexilate on Day 1 and the first dose of camlipixant on Day 5 (Part 2). A follow-up phone call will be performed 7 ± 2 days after discharge (Day 19 ± 2 in Part 1 and Day 20 ± 2 in Part 2).

Outings may be permitted during confinement. If permitted, outings will be supervised at all times by the clinical site staff to ensure compliance with the protocol and will be limited to the grounds surrounding the clinic.

The total duration of study participation for each participant from screening through the follow-up phone call is anticipated to be approximately 7 weeks for both study parts.

Each study part is intended to dose in one group; if, for any reason, the study is dosed in more than one group, all groups will be dosed at the same clinical site and the same protocol requirements and procedures will be followed within each group.

5. Study Population

5.1 Number of Participants

It is planned to enroll up to 16 participants in Part 1 and up to 20 participants in Part 2 for participation in this study (total of 36 participants) in order to have an adequate number of participants to characterize PK in both Part 1 and Part 2. No formal sample size calculation has been made. Based on experience from previous similar studies, a total of 36 participants (16 in Part 1 and 20 in Part 2) is considered sufficient to adequately characterize the potential for a clinical DDI.

5.2 Inclusion Criteria

Participants must meet all of the following criteria to be included in the study:

1. Male or female, non-smoker (no use of tobacco or nicotine products within 3 months prior to screening), ≥18 and ≤55 years of age, with BMI >18.5 and <30.0 kg/m^2 and body weight ≥50.0 kg.
2. Healthy as defined by:
   a. the absence of clinically significant illness and surgery within 4 weeks prior to dosing.
   b. the absence of clinically significant history of neurological, endocrine, cardiovascular, respiratory, hematological, immunological, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease.
3. Female participants of non-childbearing potential must be:
   a. post-menopausal (spontaneous amenorrhea for at least 12 months prior to dosing) with confirmation by documented FSH levels ≥40 mIU/mL; or
   b. surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy) at least 3 months prior to dosing.
4. Females of childbearing potential who are sexually active with a non-sterile male partner (sterile male partners are defined as men vasectomized since at least 3 months) must be willing to use one of the following acceptable contraceptive methods throughout the study and for 90 days after the last study drug administration:
   a. simultaneous use of intra-uterine contraceptive device without hormone release system placed at least 4 weeks prior to study drug administration, and condom for the male partner;
   b. simultaneous use of diaphragm or cervical cap with intravaginally applied spermicide and male condom for the male partner, started at least 21 days prior to study drug administration.

c. tubal ligation at least 3 months prior to dosing.

5. Female participants must be willing not to donate ova for 90 days after the last dose.
6. Male participants who are not vasectomized for at least 3 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 the first dose and for 90 days after the last dose:
   a. simultaneous use of condom and hormonal contraceptive (e.g., oral, patch, depot injection, implant, vaginal ring, intrauterine device) or non-hormonal intrauterine device used for at least 4 weeks prior to sexual intercourse for the female partner;
   b. simultaneous use of condom and a diaphragm or cervical cap with spermicide for the female partner.
7. Male participants (including men who have had a vasectomy) with a pregnant partner must agree to use a condom from the first dose and for 90 days after the last dose.
8. Male participants must be willing not to donate sperm for 90 days after the last dose.
9. Able to understand the study procedures and provide signed informed consent to participate in the study.

5.3 Exclusion Criteria

Participants to whom any of the following applies will be excluded from the study:

1. Any clinically significant abnormal finding at physical examination at screening.
2. Clinically significant abnormal laboratory test results or positive serology test results for HBsAg, HCV antibody, or HIV antigen and antibody, at screening.
3. Any of the following laboratory parameters above the ULN values at screening or baseline (Day -1): AST, ALT, direct bilirubin, indirect bilirubin, and total bilirubin. Only abnormal values up to 1.5x ULN may be repeated once for confirmation to below ULN.
4. Positive pregnancy test or lactating female participant.
5. Positive urine drug screen, urine cotinine test, or alcohol breath test.
6. Positive test for COVID-19 at admission.
7. Known allergic reactions or hypersensitivity to camlipixant, gemfibrozil (participants in Part 1 only), dabigatran etexilate or dabigatran (participants in Part 2 only), or other related drugs, or to any excipient in the formulation.
8. Clinically significant ECG abnormalities (for example, QTcF > 450 ms) or vital signs abnormalities (systolic blood pressure lower than 90 or over 140 mmHg, diastolic blood pressure lower than 50 or over 90 mmHg, or heart rate less than 50 or over 100 bpm) at screening.
9. History of drug abuse within 1 year prior to screening or use of drugs (such as cocaine, PCP, crack, opioid derivatives including heroin, and amphetamine derivatives) within 3 months

prior to screening, except for cannabis, hashish, or any products containing either, which are not allowed within 1 month prior to screening.

10. History of alcohol abuse within 1 year prior to screening or regular use of alcohol within 6 months prior to screening that exceeds 10 units for women or 15 units for men of alcohol per week (1 unit = 340 mL of beer 5%, 140 mL of wine 12%, or 45 mL of distilled alcohol 40%).
11. History of gastrointestinal disorders, such as stomach ulcers, IBS, ulcerative or pseudomembranous colitis, intestinal obstruction, previous liver disease or hepatic dysfunction (including primary biliary cirrhosis), hyperbilirubinemia, jaundice, or elevated liver enzymes.
12. Known Gilbert, Rotor, Crigler-Najjar, or Dubin-Johnson syndrome.
13. CCI [redacted].
14. History of gallbladder disease, including cholelithiasis.
15. History of renal dysfunction and those with estimated CrCl less than 60 mL/min.
16. Participants in Part 1 only: History of myoglobinuria, myopathy, myalgia, myositis or rhabdomyolysis.
17. Participants in Part 1 only: History of Type I hyperlipoproteinemia.
18. Participants in Part 2 only: Participants with haemorrhagic manifestations, clinically significant active bleeding, including gastrointestinal bleeding, bleeding diathesis, spontaneous or pharmacological impairment of haemostasis.
19. Participants in Part 2 only: Participants with lesions, diseases, or procedures at risk of clinically significant bleeding/haemorrhagic risks, such as congenital or acquired coagulations disorders, thrombocytopenia or functional platelet defects, recent cerebral infarction (haemorrhagic or ischemic) within the last 6 months, active ulcerative gastrointestinal disease (including peptic ulcer) with recent gastrointestinal bleeding, bacterial endocarditis, recent biopsy or major trauma, brain, spinal or ophthalmic surgery, prosthetic heart valves, or hemodynamically significant rheumatic heart disease.
20. Participants in Part 2 only: History of antiphospholipid disease.
21. Participants in Part 2 only: Participants having undergone any major surgery within 6 months prior to the start of the study, unless deemed otherwise by the Investigator.
22. Participants in Part 2 only: Any of the following laboratory parameters outside the normal ranges at screening or baseline (Day -1): PT and aPTT.
23. Use of medications for the timeframes specified below, with the exception of medications exempted by the Investigator on a case-by-case basis because they are judged unlikely to affect the PK profile of the study drug or participant safety (e.g., topical drug products without significant systemic absorption):
    a. depot injection or implant within 3 months prior to dosing;

b. any drug known to induce or inhibit hepatic drug metabolism, including St. John's wort, within 30 days prior to dosing or 10 half-lives, whichever is longer;

c. prescription medications within 14 days prior to dosing;

d. any vaccine, including COVID-19 vaccine, within 14 days prior to dosing;

e. OTC medications and natural health products (including herbal remedies, homeopathic and traditional medicines, probiotics, food supplements such as vitamins, minerals, amino acids, essential fatty acids, and protein supplements used in sports) within 7 days prior to dosing, with the exception of the occasional use of acetaminophen (up to 2 g daily).

24. Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days prior to dosing, administration of a biological product in the context of a clinical research study within 90 days prior to dosing, or concomitant participation in an investigational study involving no drug or device administration.
25. Donation of plasma within 7 days prior to dosing or donation or loss of 500 mL or more of whole blood within 8 weeks prior to dosing.
26. Any reason which, in the opinion of the Investigator, would prevent the participant from participating in the study.

5.4 Participant Withdrawal and Replacement

Participants will be advised that they are free to withdraw from the study at any time. Over the course of the study, the Sponsor and the Investigator or designee may withdraw any participant from the study for one of the reasons described below; participant withdrawal will be done in accordance with the clinical site's SOP:

- Safety reason;
- Non-compliance with protocol requirements;
- Significant protocol deviation;
- Positive pregnancy test, drug screen, cotinine test, or alcohol breath test.

Participants who withdraw or are withdrawn from the study after dosing will not be replaced. However, in the event that the number of drop-outs exceeds initial expectations, participants who withdraw or are withdrawn might be replaced at the discretion of the Sponsor. Such replacement resulting in dosing more participants than planned in this protocol would be documented in a protocol amendment.

Participants who withdraw or are withdrawn will be asked to remain at the clinic until the Investigator or designee agrees that the participant is safe and can be discharged. As soon as participant withdrawal is confirmed, blood sampling will be stopped. A PK blood sample may be collected at the time of withdrawal if deemed required by the Investigator. Discharge/ET procedures will be performed at the time of withdrawal from the study or as soon as possible thereafter.

6. Study Treatments

6.1 Drug Supplies and Accountability

It is the responsibility of the Sponsor to ensure that study drug provided for this study are manufactured under Good Manufacturing Practice (GMP) and are suitable for human use. The Sponsor is responsible to ship a sufficient amount of dosage units to allow the clinical site to maintain an appropriate sampling for the study.

The clinical site will be responsible for sourcing gemfibrozil and dabigatran etexilate from the Canadian market.

The study drugs will be stored at the clinical site pharmacy as per applicable requirements in a locked, environmentally-controlled medication room with restricted access. Container(s) will be labeled according to applicable regulations.

Individual doses for each participant will be dispensed at the clinical site pharmacy, as per appropriate SOP and according to the fixed-sequence, in appropriate containers indicated with at least the project number and the participant number/spare number.

All study drugs received at the site will be inventoried and accounted for throughout the study and the result recorded in the drug accountability record according to the clinical site appropriate SOP.

6.2 Identification of Treatments

Parts 1 and 2: CCI [redacted].

Part 1: CCI [redacted] mg tablet of gemfibrozil (Sourced from the Canadian market) administered CCI [redacted] mg) for 7 consecutive days from Day 5 to Day 11. Administration will occur before the CCI [redacted], except for the morning dose on Day 9.

Part 2: CCI [redacted] mg CCI [redacted] of dabigatran etexilate (Sourced from the Canadian market) administered under CCI [redacted] in the morning on Day 1 and Day 10.

6.3 Randomization and Blinding

This study will be an open-label study due to the objective nature of the data. Thus, no randomization and blinding measures will be applied. Participants will be administered each treatment according to the fixed-sequence scheme.

6.4 Study Drug Administration

Part 1:

On Day 1 and Day 9, camlipixant will be administered to each participant with 240 mL of water. On Day 9, camlipixant will be administered 1 hour after administration of gemfibrozil dosing, with a time-tolerance window of ± 2 minutes. The time of administration of both camlipixant and gemfibrozil will be recorded, and the time interval between the 2 administrations must not fall outside of the scheduled acceptable range.

Gemfibrozil will be administered to each participant as 1 tablet CCI for 7 consecutive days, from Day 5 to Day 11. The tablet will be administered to each participant with 240 mL of water. Administration of gemfibrozil will be performed at approximately the same time on Days 5 to 11. A time window of ± 10 minutes from the scheduled gemfibrozil dosing time will be allowed, as long as the 1-hour (± 2 minutes) time interval between gemfibrozil and camlipixant dosing on Day 9 is respected.

A hand and mouth check will be performed to ensure consumption of the medication.

On Day 1, no food will be allowed from at least 10 hours before camlipixant dosing until at least 4 hours post-dose.

On Day 9, no food will be allowed from at least 10 hours before gemfibrozil dosing until at least 4 hours after camlipixant dosing.

On Days 5 to 8, evening of Day 9, and Days 10 and 11, gemfibrozil will be administered approximately 30 minutes (±10 minutes) before a standard morning/evening meal.

On Day 1, except for water given with camlipixant, no fluids will be allowed for 1 hour before dosing until 1 hour post-dose. On Day 9, except for water given with camlipixant and gemfibrozil dosing, no fluids will be allowed for 1 hour before gemfibrozil dosing until 1 hour post-dose of camlipixant. On Days 5 to 8, 10, and 11, except for water given with gemfibrozil dosing and meals, no fluids will be allowed for 1 hour before dosing until 30 minutes post-dose. Water will be provided *ad libitum* at all other times.

Meals will be standardized throughout the study.

Part 2:

On Day 1 and Day 10, dabigatran etexilate will be administered to each participant with 240 mL of water. The capsule should be swallowed whole, and must not be chewed, broken, or opened. On Day 10, dabigatran etexilate will be co-administered at the same time with camlipixant. The time of administration of both camlipixant and dabigatran etexilate will be recorded. Camlipixant will be swallowed first, followed immediately by dabigatran. The entire procedure should be completed within 2 minutes.

Camlipixant will be administered to each participant as 1 tablet for 6 consecutive days, from Day 5 to Day 9 as CCI, and as CCI in the morning of Day 10. The camlipixant tablet will be administered to each participant with 240 mL of water. Administration of camlipixant will be performed at approximately the same time on Days 5 to 10. A time window

of ± 10 minutes from the scheduled camlipixant dosing times will be allowed, as long as the dabigatran etexilate will be co-administered at the same time with camlipixant.

A hand and mouth check will be performed to ensure consumption of the medication.

On Day 1, no food will be allowed from at least 10 hours before dabigatran etexilate dosing until at least 4 hours post-dose.

On Day 10, no food will be allowed from at least 10 hours before camlipixant/dabigatran etexilate dosing until at least 4 hours after camlipixant/dabigatran etexilate dosing.

On Days 5 to 9: No food will be allowed from at least 2 hours before morning camlipixant dosing until 1-hour post-morning dose. A normo-caloric breakfast will be served at least 1 hour after camlipixant administration.

On Day 1, except for water given with the dabigatran etexilate, no fluids will be allowed for 1 hour before dosing until 1 hour post-dose. On Day 10, except for water given with camlipixant/dabigatran etexilate dosing, no fluids will be allowed for 1 hour before until 1-hour post-dose of camlipixant/dabigatran etexilate. On Days 5 to 9, except for water given with camlipixant dosing, no fluids will be allowed for 1 hour before dosing until 1-hour post-dose. Water will be provided *ad libitum* at all other times.

Meals will be standardized throughout the study.

7. Study Restrictions

7.1 Concomitant Medications

Participants will be required to avoid receiving any vaccination (including COVID-19 vaccine) and using prescription medications, OTC medications, and natural health products (including herbal remedies, homeopathic and traditional medicines, probiotics, food supplements such as vitamins, minerals, amino acids, essential fatty acids, and protein supplements used in sports) for the period of time specified in exclusion criterion no. 23 and throughout the study.

Hormonal contraception and hormone replacement therapy for female participants will not be allowed.

No concomitant medications will be allowed during the study, with the exception of medications required for the medical management of an AE/SAE, and medications exempted by the Investigator on a case-by-case basis that are judged unlikely to affect the PK profile of the study drug or participant safety (e.g., topical drug products without significant systemic absorption).

If vaccination is required for any reason, it must first be discussed with and exempted by the Investigator on a case-by-case basis to ensure that it does not compromise the PK profile of the study drug or the participant safety.

Medications taken by participants before dosing will be documented as prior medications and medications taken by participants after dosing up to follow-up phone call will be documented as concomitant medications. Any prior or concomitant medication use, other than the allowed

medications stated above, will be reviewed and evaluated on a case-by-case basis by the Investigator to determine if they affect a participant's eligibility or continued participation in the study, or for potential impact on the study results.

7.2 Drugs, Nicotine and Alcohol

Participants will be required to abstain from:

- Drugs of abuse from screening and throughout the study;
- Any nicotine product from screening and throughout the study;
- Alcohol-based products from 24 hours prior to admission until after the last PK blood sample collection of the study.

7.3 Diet

Participants will be required to abstain from:

- Food or beverages containing grapefruit, Seville orange, starfruit, pomegranate, pineapple, or pomelo from 7 days prior to first dosing until after the last PK blood sample collection of the study;
- Food or beverages containing xanthine derivatives or xanthine-related compounds (coffee, black/green tea, chocolate) or energy drinks from 48 hours prior to first dosing until after the last PK blood sample collection of the study;
- Food containing poppy seeds from 24 hours prior to admission.

7.4 Posture and Physical Activity

Part 1:

Participants will be allowed to engage in normal activity but will avoid lying down or sleeping for 4 hours after camlipixant administration on Day 1. On Day 9, participants will be allowed to engage in normal activity but will avoid lying down or sleeping for 5 hours after gemfibrozil morning administration. On Days 5 to 8 and Days 10 and 11, participants will be allowed to engage in normal activity but will avoid lying down or sleeping for 4 hours after each morning gemfibrozil administration. On Days 5 to 11, participants will be allowed to engage in normal activity but will avoid lying down or sleeping for 2 hours after each evening gemfibrozil administration.

Participants will be required to refrain from strenuous exercise at least 3 days before admission and throughout the study.

Part 2:

Participants will be allowed to engage in normal activity but will avoid lying down or sleeping for 4 hours after dabigatran etexilate administration on Day 1. On Day 10, participants will be

allowed to engage in normal activity but will avoid lying down or sleeping for 4 hours after camlipixant/dabigatran etexilate morning administration. On Days 5 to 9, participants will be allowed to engage in normal activity but will avoid lying down or sleeping for 4 hours after each morning camlipixant administration. On Days 5 to 9, participants will be allowed to engage in normal activity but will avoid lying down or sleeping for 2 hours after each evening camlipixant administration.

Participants will be required to refrain from strenuous exercise at least 3 days before admission and throughout the study.

8. Study Procedures

Participants must provide written informed consent prior to initiation of any study procedures.

Unless otherwise specified, study procedures will be conducted in accordance with clinical site SOPs. From screening through the follow-up phone call, participants will undergo study procedures at pre-defined times as specified in Table 1. Schedule of Assessments for Part 1 and Table 2. Schedule of Assessments for Part 2 and as described in sections 8.1, 8.2, and 8.3.

Every effort will be made to schedule and perform the procedures as close to the nominal time as possible, giving considerations to appropriate posture conditions, practical restrictions, and other procedures to be performed at the same time point.

PK blood sample collection will be performed closest to the nominal time. When vital signs measurement or ECG recording coincide with a blood collection, they should preferably be performed before the blood collection, whenever possible. Sample collections done outside the pre-defined time windows will not be considered as protocol deviations since actual post-dose sampling times will be used for PK and statistical analyses.

8.1 Pharmacokinetic Assessments

8.1.1 Pharmacokinetic Blood Sample Collection and Processing

Blood samples for PK analysis will be collected via an intravenous catheter or by direct venipuncture at the time points indicated in Table 1. Schedule of Assessments for Part 1 and Table 2. Schedule of Assessments for Part 2. Applicable time windows for PK blood samples are defined in the tables below.

Table 3. Time Windows for PK Blood Samples for Part 1

Day	Time point (camlipixant)	Time point (gemfibrozil)	Time window
1 and 9	Pre-dose	Pre-dose (Day 9)*	Within 30 minutes
	0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, and 6 hours	-	±1 minute
	8, 10, 12, 15, and 18 hours	-	±3 minutes

2 and 10	24 hours	-	±5 minutes
3, 4, 11, and 12	48 and 72 hours	-	±10 minutes
5, 6, 7, and 8	Not applicable	Pre-dose*	Within 30 minutes

*morning dose only.

Table 4. Time Windows for PK Blood Samples for Part 2

Day	Time point (dabigatran)	Time point (camlipixant)	Time window
1 and 10	Pre-dose	Pre-dose (Day 10)*	Within 30 minutes
	0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, and 6 hours	-	±1 minute
	8, 10, 12, and 16	-	±3 minutes
2 and 11	24 and 36 hours	-	±5 minutes
3, 4, 12, and 13	48, 60, and 72 hours	-	±10 minutes
5, 7, 8, and 9	Not applicable	Pre-dose*	Within 30 minutes

*morning dose only.

The planned volume of blood to be collected for this study, including that collected for eligibility and safety purposes, should not exceed 250 mL in Part 1 and 300 mL in Part 2. Additional tests or blood draws could be performed, if deemed required by the Investigator or study staff.

Procedures for collection and processing of PK blood samples will be detailed in a separate document.

Plasma concentrations of the study drug will be determined using a validated analytical method. Details of the analytical method will be provided in a separate document.

8.2 Pharmacogenomic Assessments

One blood sample for pharmacogenomic analysis will be collected upon admission on Day -1 in both Part 1 and Part 2.

8.3 Safety and Tolerability Assessments

Part 1:

Participants will be monitored throughout the study by the clinical staff for AEs/SAEs. On Day 1, the Investigator or designee will be on site for camlipixant administration and until 4 hours post-dose. On Day 5, the Investigator or designee will be on site for gemfibrozil morning administration and until 4 hours post-dose. On Day 9, the Investigator or designee will be on site for gemfibrozil morning administration and camlipixant administration and until 4 hours post-dose of camlipixant. The Investigator or designee will be available on call for the remainder of the study.

Part 2:

Participants will be monitored throughout the study by the clinical staff for AEs/SAEs. On Day 1, the Investigator or designee will be on site for dabigatran etexilate administration and until 4 hours post-dose. On Day 5, the Investigator or designee will be on site for camlipixant morning administration and until 4 hours post-dose. On Day 10, the Investigator or designee will be on site for camlipixant/dabigatran etexilate morning administration and until 4 hours post-dose. The Investigator or designee will be available on call for the remainder of the study.

Parts 1 and 2:

If necessary, the Investigator or designee at the clinical site or a healthcare professional in a nearby hospital will administer treatment for any AEs/SAEs. A crash cart or emergency bag containing the necessary rescue material and appropriate medications will be available in the clinic to allow rapid intervention in case of emergency.

Safety parameters (ECG, vital signs, and clinical laboratory results) will be assessed by the Investigator or designee, using the clinical site acceptance ranges as suggested guidelines in making the medical assessment.

For eligibility purposes, abnormal vital signs measurements or clinical laboratory test results may be repeated once if an abnormal result is observed at the initial reading. Only abnormal values up to 1.5x ULN may be repeated once for confirmation to below ULN for AST, ALT, direct bilirubin, indirect bilirubin, and total bilirubin at screening and baseline (Day -1). Moreover, abnormalities found in the ECG may need to be confirmed by repeated measurements. In the event that the participation of a participant in the study is delayed and some screening procedures had been performed outside of the prescribed screening window, outdated screening procedures can be repeated.

Safety assessments scheduled during the study will be repeated according to the clinical site SOPs or upon request from the Investigator or designee. Any abnormal repeated measurement will be evaluated and repeated, if judged necessary. Further action may be taken upon the Investigator or designee's request.

8.3.1 Physical Examination

Physical examinations will be performed at the times specified in Table 1. Schedule of Assessments for Part 1 and Table 2. Schedule of Assessments for Part 2.

A complete physical examination will include assessments of the following: head, eyes, ears, nose, throat (HEENT), neck, chest, lungs, abdomen, musculoskeletal, dermatological, cardiovascular/peripheral vascular, and general neurological examination.

A brief physical examination will include assessments of the following: HEENT, chest, lungs, abdomen, dermatological, cardiovascular/peripheral vascular, and areas of note elicited from the participant.

8.3.2 Body Measurements

Body measurements will be performed at screening and will include body weight and height measurements, as well as BMI calculation.

8.3.3 Vital Signs

Blood pressure, heart rate, respiratory rate, and oral temperature will be measured after the participants have been resting for at least 5 minutes in a sitting position at the times specified in Table 1. Schedule of Assessments for Part 1 and Table 2. Schedule of Assessments for Part 2.

8.3.4 12-lead ECG

Standard 12-lead ECG will be recorded after the participants have been resting for at least 5 minutes in a semi-recumbent or supine position at the times specified in Table 1. Schedule of Assessments for Part 1 and Table 2. Schedule of Assessments for Part 2.

8.3.5 Laboratory Assessments

Blood and urine samples for clinical laboratory assessments will be collected according to the clinical site SOPs at the times specified in Table 1. Schedule of Assessments for Part 1 and Table 2. Schedule of Assessments for Part 2. The clinical laboratory assessments to be performed are listed in the table below. Clinical laboratory test results may be repeated once for eligibility purposes as described per Section 8.3. In case of abnormal results during the conduct of the study, additional testing may be performed at the discretion of the Investigator.

Table 5. Clinical Laboratory Assessments

Biochemistry	Hematology	Urinalysis
Albumin Alkaline phosphatase ALT AST Calcium Chloride Creatine kinase Creatinine GGT Glucose Phosphorus Potassium Sodium Total, direct and indirect bilirubin[1] Total protein Urea (BUN) Uric acid	Hematocrit Hemoglobin Platelet count RBC count WBC count and differential: • Basophils • Eosinophils • Lymphocytes • Monocytes • Neutrophils **Coagulation[2]**	Bilirubin Blood (occult) Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (in the event of abnormal findings)

Creatinine clearance (estimated with serum creatinine values using the Cockcroft-Gault)	aPTT PT INR	
Serology	**Drug, cotinine, and alcohol screens**	**Hormone panel - females only**
HBsAg HCV antibody HIV antigen/antibody	Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine MDMA Methadone Opiates PCP THC Urine cotinine test Alcohol breath test	FSH (post-menopausal females only) Serum pregnancy test Urine pregnancy test

Abbreviations: ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; LFT = liver function test; MDMA = 3,4- methylenedioxymethamphetamine; PCP = phencyclidine; PT = prothrombin time; RBC = red blood cell; THC = tetrahydrocannabinol; WBC = white blood cell.

1 Considering that indirect bilirubin is calculated from total and direct bilirubin values, indirect bilirubin result would not be available in case of total or direct bilirubin below the limit of quantification.

2 If the coagulation tests results come back normal but the LFTs results are still abnormal after the repeat, the coagulation tests may be repeated upon Investigator's judgement.

8.3.6 Follow-up Phone Call

A follow-up phone call will be performed at the times specified in Table 1.Schedule of Assessments for Part 1 and Table 2. Schedule of Assessments for Part 2, to ensure the ongoing wellbeing of participants after discharge.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definition of Adverse Event

An AE is defined as any untoward medical occurrence in a participant who is administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

8.4.2 Definition of Adverse Events of Medical Interest

AEMIs are AEs of scientific interest specific to the drug class. They are required to be monitored closely and reported by the Investigator to the Sponsor promptly, regardless of relationship, severity, expectedness, and seriousness.

AEMIs for this study include the following, but not limited to:

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

The incidence of AEMIs from Day 1 to Day 5 pre-dose of gemfibrozil (Part 1) will act as a baseline. In Part 2, AEs occurring before camlipixant dosing on Day 5 should not be reported/treated as AEMIs.

AEMIs appearing following gemfibrozil administration alone from Day 5 to Day 9 pre-dose of camlipixant (Part 1) will be accounted for causality based on their onset date/time with respect to camlipixant and gemfibrozil dosing and the known safety profiles of the drugs administered in respective treatment periods.

AEMIs appearing following camlipixant administration alone from Day 5 to Day 10 pre-dose of dabigatran (Part 2) will be accounted for causality based on their onset date/time with respect to camlipixant and dabigatran dosing and the known safety profiles of the drugs administered in the respective treatment periods.

AEMIs appearing following camlipixant co-administration with gemfibrozil on Day 9 (Part 1) or dabigatran on Day 10 (Part 2) until the end of the study will be accounted for causality based on their onset date/time, baseline reference, and known safety profiles of the drugs administered.

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8.4.3 Definition of Serious Adverse Event

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

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect, or;
- Is otherwise considered to be an important medical event (IME) that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Medical and scientific judgement should be exercised in deciding whether an event should be considered as an IME.

The Sponsor can upgrade an event at any time; downgrade is not permitted at any time.

If a SAE occurs to a participant on this study, contact the Sponsor personnel listed in Section 8.4.6.

8.4.4 Assessment of Severity

The severity will be described and documented using the following definitions:

Table 6. Severity Scale

Severity	Description
Mild	Awareness of signs and symptoms but are easily tolerated; are of minor irritant type; causing no limitations of usual activities. Signs or symptoms may require minor action.
Moderate	Discomfort severe enough to cause some limitations of usual activities and may require action.
Severe	Incapacitating with inability to carry out usual activities or significantly affects clinical status, and requires specific action and/or medical attention.

8.4.5 Assessment of Relationship to Study Drug

Each AE/SAE must be classified based on medical judgement and according to the following relationship categories: definite, probable, possible, unlikely, and not related. Causality assessments will need to be applied to the study drug and interacting drug the participant has been administered. The definitions for the relationship categories are as follows:

Table 7. Relationship Categories

Assessment	Definition
Definite	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically using a satisfactory re-challenge (the drug is re-administered to determine if the same reaction occurs) procedure if necessary.
Probable	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to the drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide plausible explanations.
Not related	Any event that does not meet the above criteria; there is sufficient information that aetiology of the event is in no relation to the study drug.

8.4.6 Event Reporting

All safety events will be recorded and evaluated for their seriousness, severity, and relationship to the study drug and the interacting drug. Safety events will be collected and documented starting from the time of signing the informed consent form (ICF), throughout the study, and until the follow-up phone call.

After the initial AE/SAE report, the Investigator is required to proactively follow up with each participant at all subsequent visits or contact. All events will be followed up until the resolution, stabilization, the event is otherwise explained, or the participant refuses to provide additional information (documented as lost to follow-up).

At any point after completion of the study, if a participant experiences an SAE that is considered by the Investigator to be either Definite, Probable, or Possible to study drug, this needs to be submitted to the Sponsor as described within.

Safety events will be reported within 24 hours of learning of the event, using the appropriate reporting forms (SAE Form or Pregnancy Form). The notification must be directed to:

IQVIA Safety Operations:
PHV_EarlyPhaseSafety_SO@iqvia.com

PPD

PPD

And to:

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Blank copies of the forms are included in the study Investigator's file. It is not acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor company or its representative in lieu of completion of the appropriate AE electronic case report form (eCRF) page or SAE Report Form. However, there may be instances when copies of medical records for certain cases are requested by the Sponsor or its representative. In this instance, all participant identifiers will be blinded on the copies of the medical records before submission to the Sponsor or its representative.

If the Investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before completing and sending the form.

Follow-up reports (as many as required) should be completed and faxed/e-mailed following the same procedure above. The Investigator should follow the participant with the event until resolution or stabilization of the condition.

The Investigator must keep a copy of all documentation related to the event in the clinical site files.

8.4.6.1 Suspected Unexpected Serious Adverse Event Reporting to the IEC and Regulatory Agency(ies)

It is the responsibility of the clinical site to report suspected, unexpected, serious adverse reactions (SUSARs) to the IEC responsible for the study per their policies. Report of fatal or life-threatening SUSARs must be made as soon as possible, but no later than 7 calendar days after first knowledge of the event. Report of SUSARs that are neither fatal nor life-threatening must be made as soon as possible, but no later than 15 calendar days after first knowledge of the event.

The Sponsor (or representative) is responsible for notifying the regulatory agency(ies) of SUSARs observed during the study conduct per their regulations, as soon as possible but no later than 7 calendar days after becoming aware of the information when fatal or life-threatening, or 15 calendar days when neither fatal nor life-threatening. The Sponsor (or representative) is responsible to comply with any other applicable regulatory requirement(s) related to the reporting of SAE to other regulatory authority(ies).

8.4.7 Pregnancy Reporting

In the event a dosed female participant or the female partner of a dosed male participant (i.e., has received at least one dose of the investigational product) becomes pregnant during or up to 30 days after the last dose, this pregnancy will be reported to the Sponsor (or representative) within 24 hours of first knowledge of the event as described in Section 8.4.6. The applicable Pregnancy Notification and Outcome forms will be used.

Any participant who becomes pregnant during the study will be immediately withdrawn. Follow-up information regarding the course and outcome of the pregnancy will be documented (after obtaining the consent of the female partner) as per site's SOP.

If at any time during the pregnancy or the outcome of the pregnancy, the participant and/or baby experiences an AE that meets the criteria of an SAE and/or reportable event, reporting of the event to the IEC responsible for the study and/or to applicable regulatory agency(ies) will be performed as per site's SOP and country-specific reporting requirement.

8.4.8 Overdose Reporting

Although unlikely to occur as study drug is administered as a single dose under direct supervision, should a participant experience an overdose (with or without an AE/SAE), protocol deviation will need to be documented and reported promptly to the Sponsor.

8.5 Premature Termination of the Study

The study may be prematurely terminated by the Investigator following consultation with the Sponsor, by the Sponsor or by the regulatory authorities. Following a decision to discontinue the trial, the Investigator will promptly inform the active study participants and the IEC responsible for this trial, stating the reasons for discontinuation of the study. It is the responsibility of the Sponsor (or representative) to report the premature termination of the study to the regulatory authority(ies), when required by the applicable regulatory requirement(s).

9. Statistical Analyses

A complete description of the statistical analyses to be performed on PK as well as safety and tolerability data will be presented in a statistical analysis plan (SAP).

9.1 Analysis Populations

9.1.1 Safety Population

The safety population is defined as all participants who receive at least one dose of the study drug.

9.1.2 Pharmacokinetic Concentration Population

Part 1:

The pharmacokinetic concentration (PC) population for camlipixant will include all participants who received at least one dose of camlipixant drug at Day 1 or Day 9 and have at least one reportable concentration.

Part 2:

The PC population for dabigatran etexilate will include all participants who received at least one dose of dabigatran etexilate drug at Day 1 or Day 10 and have at least one reportable concentration.

9.1.3 Pharmacokinetic Parameter Population

Part 1:

The PK parameter population will include all participants for whom the Day 1 and Day 9 PK profiles of the victim drug camlipixant can be adequately characterized, specifically, when administered alone and in combination with gemfibrozil.

Part 2:

The PK parameter population will include all participants for whom the Day 1 and Day 10 PK profiles of the victim drug dabigatran can be adequately characterized, specifically, when administered alone and in combination with camlipixant.

Any participant who experienced emesis during the sampling interval will be evaluated on a case-by-case basis in order to determine whether the participant will be excluded from the descriptive statistics and statistical analysis.

Here are some aspects to be considered (but not to be limited to) when determining data availability for the PK population: inclusion and exclusion criteria, acceptable times for visit dates and measurements, compliance with the dosing timing and number of camlipixant and gemfibrozil treatments (Part 1), dabigatran etexilate and camlipixant treatments (Part 2), the nature and quality of the data, withdrawal, and any protocol deviation. The final responsibility of deciding which participants are to be included or excluded lies with the Investigator and/or the Sponsor.

9.1.4 Pharmacogenomic Population

The pharmacogenomic population is defined as all participants in the safety population who had at least one pharmacogenomic measurement data available.

9.2 Pharmacokinetic Parameters

The following PK parameters will be calculated based on the PK population by standard non-compartmental methods for camlipixant (Part 1) and dabigatran (free and total) (Part 2):

- $AUC_{0\text{-}t}$: Area under the concentration-time curve from time zero until the last observed concentration
- $AUC_{0\text{-}inf}$: Area under the concentration-time curve from time zero to infinity (extrapolated)
- Residual area: Percentage of $AUC_{0\text{-}inf}$ due to extrapolation from the time of the last observed concentration to infinity, calculated as $[1 – (AUC_{0\text{-}t}/AUC_{0\text{-}inf})] \times 100$
- C_{max}: Maximal observed concentration
- T_{max}: Time when the maximal concentration is observed
- $T_{½\ el}$: Terminal elimination half-life
- K_{el}: Terminal elimination rate constant
- Cl/F: Apparent clearance
- V_z/F: Apparent volume of distribution

The following information will be presented for gemfibrozil (Part 1): pre-dose concentrations on the morning of Days 5, 6, 7, 8, and 9.

The following information will be presented for camlipixant (Part 2): pre-dose concentrations on the morning of Days 5, 7, 8, 9, and 10.

Additional PK parameters may be calculated.

9.3 Pharmacokinetic Statistical Analysis

Statistical analysis described in this section will be based on the PK parameter population.

Individual and mean plasma concentration versus time curves will be presented for both linear and semi-log scales. Descriptive statistics (arithmetic and geometric means, standard deviation [SD], coefficient of variation (CV%), minimum [Min], maximum [Max], and median) of the plasma concentrations versus time will be presented as well for the PK parameters.

Part 1:

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Concentrations for gemfibrozil will be tabulated. They will be presented as supportive data. Descriptive statistics on pre-morning dose concentrations of gemfibrozil (Days 7, 8 and 9) will be performed to evaluate the attainment of steady-state.

Part 2:

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PK parameters for free dabigatran will also be calculated as above, and presented as supportive data.

Concentrations for camlipixant will be tabulated. They will be presented as supportive data. Descriptive statistics on pre-morning dose concentrations of camlipixant (Days 8, 9, and 10) will be performed to evaluate the attainment of steady-state.

Additional PK statistical analysis may be performed.

A SAP will be prepared after completion of the final protocol and prior to database lock.

9.4 Criteria for No Drug-Drug Interaction for Camlipixant

Part 1:

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Part 2:

CCI [redacted]

9.5 Safety and Tolerability Analysis

Demographic parameters will be summarized descriptively.

Safety and tolerability analysis will be performed for all participants in the safety population. No inferential statistical analysis of safety data is planned.

Safety and tolerability of camlipixant alone (Part 1 and Part 2) and in combination with gemfibrozil (Part 1) or dabigatran etexilate (Part 2) will be evaluated through the assessment of AEs, SAEs, AEMIs (i.e., seriousness, severity, relationship to the study drug and the interacting drug, outcome, duration, and management), vital signs, 12-lead ECGs, clinical laboratory tests, and physical examinations. AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

Concomitant medications will be coded using the most current version of World Health Organization drug (WHODrug) dictionary available.

Note that both MedDRA and WHODrug dictionaries are updated twice annually.

TEAEs will be tabulated by treatment. Changes from baseline values in vital signs, 12-lead ECGs, and clinical laboratory tests will be evaluated. Safety and tolerability data will be reported using descriptive statistics.

9.6 Pharmacogenomic Evaluation

One blood sample for pharmacogenomic testing will be taken on Day -1. CCI [redacted]. The sample may be also used to investigate other possible exploratory markers as deemed necessary

10. Data Collection

The source data will be collected mainly on paper as per site SOPs. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Source documents will be maintained in order to maintain data integrity. The Investigator and/or the clinical staff have the responsibility of ensuring the accuracy, completeness, legibility, and timeliness of the source data.

Source data will be transcribed by the clinical site in the RAVE electronic data capture system eCRF designed to capture study protocol required data. Vendor data will be received

electronically and will be reconciled with eCRF data. Details on the data management process will be described in a data management plan (DMP).

11. Regulatory Considerations and Quality Assurance

11.1 IEC Approval of Protocol and Other Study Documents

The Investigator(s) agree to provide the IEC with all appropriate documents, including a copy of the protocol/amendments, ICFs, advertising text (if any), Investigator's Brochure (if any), and any other written information provided to study participants. The trial will not begin until the Investigators have obtained the IEC favourable written approvals for the above-mentioned study documents. A properly executed written ICF shall be read, signed, and dated by each participant prior to entering the trial or prior to performing any study procedure. The original signed and dated ICF will be kept at the clinical site and a copy will be given to the participant.

In the event that the protocol is amended, the revised protocol must be approved by the IEC prior to its implementation, unless the changes involve only logistical or administrative aspects of the trial. If a revised ICF is introduced during the study, each participant's further consent must be obtained. The new version of the ICF must be approved by the IEC, prior to subsequently obtaining each participant's consent.

The Investigator and the Sponsor's representative must sign the protocol and its amendments (if any) before initiating the study.

It is the Sponsor's responsibility to submit the protocol and its amendments (if any), and the ICFs to regulatory authorities when necessary. This task has been delegated to the contract research organization (CRO).

11.2 Compliance

This study will be conducted in compliance with the protocol, GCP ICH E6 (R2), all applicable regulations, including the Federal Food, Drug and Cosmetic Act, U.S. applicable Code of Federal Regulations (title 21), and any IEC requirements relative to clinical studies. The study will also be conducted in compliance with the recommendations laid down in the most recent version of the Declaration of Helsinki, with the exception that registration of such Phase 1 trials in a publicly accessible database is not mandatory. As required by the Canadian regulatory agency, a Clinical Trial Application (CTA) will be submitted before the beginning of the study and a No Objection Letter (NOL) must be received prior to dosing.

11.3 Quality Assurance and Monitoring

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data. When applicable, quality assurance procedures will be performed according to the site SOPs.

The study will be monitored according to the Sponsor monitoring plan and SOP to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements. The Sponsor is entitled to access information about the status of the study and to review the original documents of the study.

The Sponsor may arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, SOPs, GCP, and all applicable regulatory requirements. In such case, audits will be independent of and separate from the routine monitoring and quality control functions.

11.4 Confidentiality and Retention of Study Records

This document contains trade secrets and commercial information that is confidential and may not be disclosed to third parties. Persons to whom this study protocol is disclosed must be informed that all the information herein is confidential and may not be further divulged. These restrictions will apply as well to all future communications if deemed privileged or confidential. Publication of the study results may only be allowed with written permission from the Sponsor.

All information on a participant obtained during the conduct of the study will be kept confidential. Participants will be identified by an anonymized identifier on all samples and study records provided to the Sponsor or designee. In compliance with ICH GCP, the Sponsor's authorized representatives, monitor(s), auditor(s), IEC, and regulatory authority(ies) will be granted direct access to the participant's original trial-related records for verification of clinical trial procedures and/or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations. Consent from the participant for disclosure of such information will be obtained in writing in the ICF. In addition, should a participant require medical care or hospitalization during the course of the study, the clinical site may contact the treating physician with the participant's consent, except that consent may not be requested if there is an emergency situation. If the results of the study are published, the participant's identity will remain confidential.

The clinical site will maintain adequate study records for 25 years after completion or termination of study. The Sponsor will be notified prior to the destruction of study records.

12. References

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8 Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Content current as of 08/24/2022. Accessed on: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table4-2.

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10 Itkonen MK, Tornio A, Neuvonen M, Neuvonen PJ, Niemi M, Backman JT. Clopidogrel and Gemfibrozil Strongly Inhibit the CYP2C8-Dependent Formation of 3-Hydroxydesloratadine and Increase Desloratadine Exposure In Humans. Drug Metab Dispos. 2019;47(4):377-385.

11 Härtter S, Sennewald R, Nehmiz G, Reilly P. Oral bioavailability of dabigatran etexilate (Pradaxa®) after co-medication with verapamil in healthy subjects. Br J Clin Pharmacol. 2013;75(4):1053-1062.

13. Appendix 1

Summary Table for Part 1

	Procedures
Screening	• Informed consent • Inclusion/exclusion criteria • Demographic data • Medical and medication history • Complete physical examination • Body measurements (height, weight, BMI) • Vital signs (blood pressure, heart rate, respiratory rate, and oral temperature) • 12-lead ECG • Serology (HBsAg, HCV antibody, and HIV antigen and antibody) • Biochemistry (including LFT and CK), hematology, coagulation, urinalysis • Drug, cotinine, and alcohol screens • Urine pregnancy test • FSH levels to confirm post-menopausal status • Monitoring of AE/SAE/AEMI
D -1	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Start of confinement • Blood sample for pharmacogenomic analysis • Brief physical exam • Biochemistry (including LFT and CK), hematology, coagulation, urinalysis • Drug, cotinine, and alcohol screens • COVID-19 test • Serum pregnancy test
D1	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Single dose administration of camlipixant 50 mg tablet • Blood samples for PK analysis of camlipixant • Blood pressure and heart rate: before dosing • 12-lead ECG: before dosing
D2	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Blood samples for PK analysis of camlipixant
D3	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Blood samples for PK analysis of camlipixant
D4	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • COVID-19 test • Blood samples for PK analysis of camlipixant
D5	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Multiple dose administration of gemfibrozil CCI mg tablet CCI • Blood sample for PK analysis of gemfibrozil • 12-lead ECG: pre-dose of gemfibrozil administration • Biochemistry (including LFT and CK), hematology, coagulation, and urinalysis: before dosing
D6	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Multiple dose administration of gemfibrozil CCI mg tablet CCI

	• Blood sample for PK analysis of gemfibrozil
D7	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Multiple dose administration of gemfibrozil [CCI] mg tablet [CCI] • Blood sample for PK analysis of gemfibrozil
D8	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Multiple dose administration of gemfibrozil [CCI] mg tablet [CCI] • Blood sample for PK analysis of gemfibrozil • Brief physical exam in the evening
D9	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Multiple dose administration of gemfibrozil [CCI] mg tablet [CCI] • Single dose administration of camlipixant 50 mg tablet 1 hour (± 2 minutes) after gemfibrozil morning administration • Blood samples for PK analysis of camlipixant • Blood sample for PK analysis of gemfibrozil • Blood pressure and heart rate: before gemfibrozil dosing • 12-lead ECG: before gemfibrozil dosing and approximately 1 hour post-dosing of camlipixant • Biochemistry (including LFT and CK), hematology, coagulation and urinalysis before gemfibrozil dosing
D10	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Multiple dose administration of gemfibrozil [CCI] mg tablet [CCI] • Blood samples for PK analysis of camlipixant
D11	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Multiple dose administration of gemfibrozil [CCI] mg tablet [CCI] • Blood samples for PK analysis of camlipixant
D12 Discharge or ET	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Brief physical exam • Vital signs (blood pressure, heart rate, respiratory rate, and oral temperature) • 12-lead ECG • Biochemistry (including LFT and CK), hematology, coagulation, urinalysis • Urine pregnancy test • Blood samples for PK analysis of camlipixant • Discharge
D19 ± 2	• Follow-up phone call • Monitoring of AEs/SAEs/AEMIs and concomitant medications

Abbreviations: AE = adverse event; AEMI = adverse event of medical interest; [CCI]; BMI = body mass index; CK = creatine kinase; COVID-19 = coronavirus 2019; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LFT = liver function test; PK = pharmacokinetic, SAE = serious adverse event.

Summary Table for Part 2

	Procedures
Screening	• Informed consent • Inclusion/exclusion criteria • Demographic data • Medical and medication history • Complete physical examination • Body measurements (height, weight, BMI) • Vital signs (blood pressure, heart rate, respiratory rate, and oral temperature) • 12-lead ECG • Serology (HBsAg, HCV antibody, and HIV antigen and antibody) • Biochemistry (including LFT and CK), hematology, coagulation, urinalysis • Drug, cotinine, and alcohol screens • Urine pregnancy test • FSH levels to confirm post-menopausal status • Monitoring of AEs/SAEs/AEMIs
D -1	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Start of confinement • Blood sample for pharmacogenomic analysis • Brief physical exam • Biochemistry (including LFT and CK), hematology, coagulation, urinalysis • Drug, cotinine, and alcohol screens • COVID-19 test • Serum pregnancy test
D1	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Single dose administration of dabigatran etexilate CCI mg capsule • Blood samples for PK analysis of dabigatran • Blood pressure and heart rate: before dosing • 12-lead ECG: before dosing
D2	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Blood samples for PK analysis of dabigatran
D3	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Blood samples for PK analysis of dabigatran
D4	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • COVID-19 test • Blood samples for PK analysis of dabigatran
D5	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Multiple dose administration of camlipixant 50 mg tablet CCI • Blood sample for PK analysis of camlipixant • 12-lead ECG: pre-dose • Biochemistry (including LFT and CK), hematology, coagulation, and urinalysis: before dosing
D6	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Multiple dose administration of camlipixant 50 mg tablet CCI
D7	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement

	• Multiple dose administration of camlipixant 50 mg tablet CCI • Blood sample for PK analysis of camlipixant
D8	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Multiple dose administration of camlipixant 50 mg tablet CCI • Blood sample for PK analysis of camlipixant
D9	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Multiple dose administration of camlipixant 50 mg tablet CCI • Blood sample for PK analysis of camlipixant • Brief physical exam in the evening • Biochemistry (including LFT and CK), hematology, coagulation and urinalysis
D10	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Morning dose administration of camlipixant 50 mg tablet • Single dose administration of dabigatran etexilate CCI mg capsule 1 hour (± 2 minutes) after camlipixant administration • Blood samples for PK analysis of dabigatran • Blood sample for PK analysis of camlipixant • Blood pressure and heart rate: before camlipixant dosing • 12-lead ECG: before camlipixant dosing
D11	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Blood samples for PK analysis of dabigatran
D12	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Blood samples for PK analysis of dabigatran
D13 Discharge or ET	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Blood samples for PK analysis of dabigatran • Brief physical exam • Vital signs (blood pressure, heart rate, respiratory rate, and oral temperature) • 12-lead ECG • Biochemistry (including LFT and CK), hematology, coagulation, urinalysis • Urine pregnancy test • Discharge
D20 ± 2	• Follow-up phone call • Monitoring of AEs/SAEs/AEMIs and concomitant medications

Abbreviations: AE = adverse event; AEMI = adverse event of medical interest; CCI ; BMI = body mass index; CK = creatine kinase; COVID-19 = coronavirus 2019; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; LFT = liver function test; PK = pharmacokinetic, SAE = serious adverse event.

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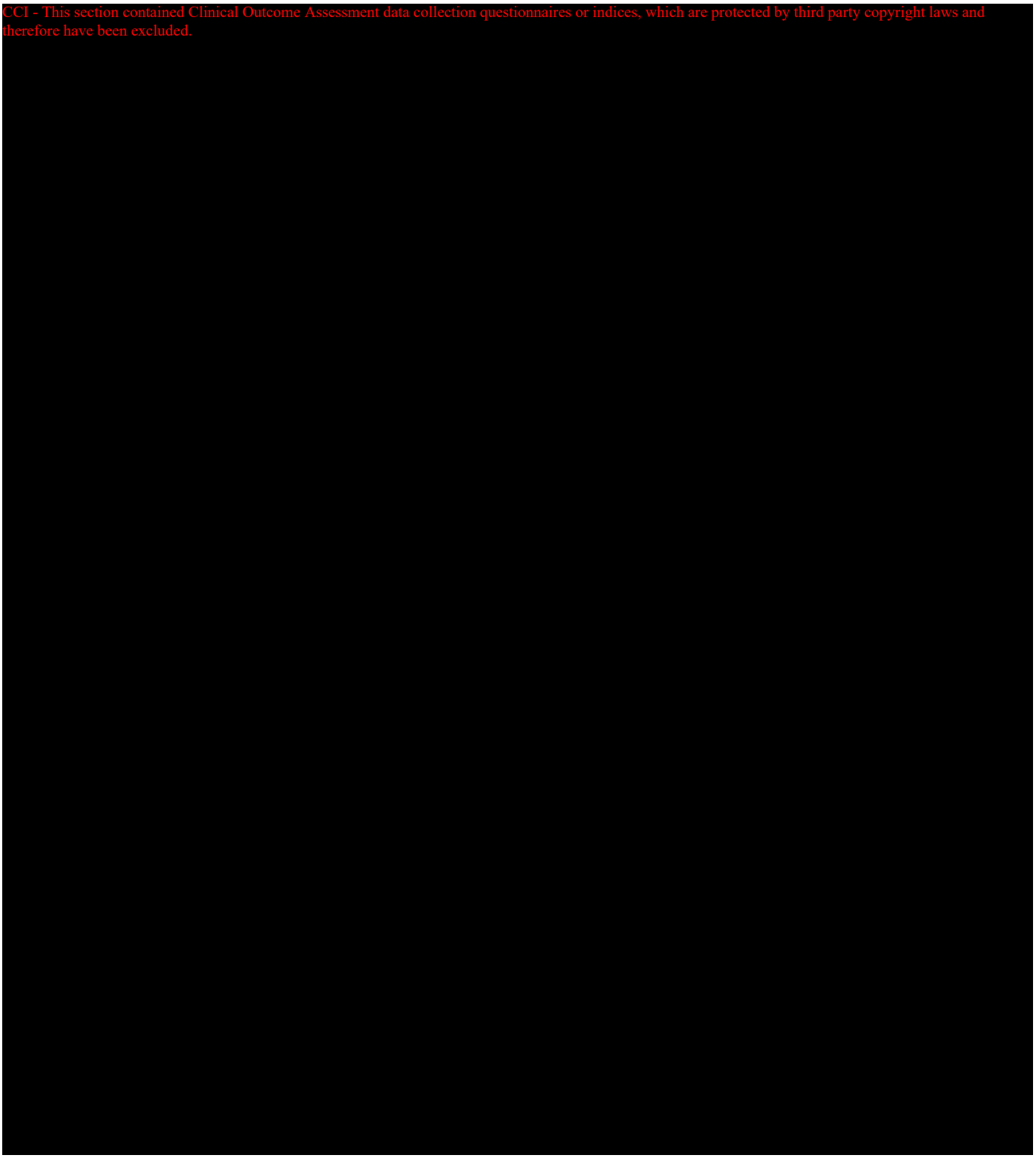


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