Protocol

Study ID: 221853

Official Title of Study: A PHASE 1, 2-PART, OPEN-LABEL, FIXED-SEQUENCE STUDY EVALUATING THE EFFECT OF RIFAMPIN (PART 1) AND RABEPRAZOLE (PART 2) ON THE PHARMACOKINETICS OF A SINGLE DOSE OF CAMLIPIXANT (BLU-5937) 50 mg TABLET IN HEALTHY PARTICIPANTS UNDER FASTING CONDITIONS

Date of Document: 20 Jul 2023

16.1.1 Protocol and Protocol Amendments

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Study Final Protocol 1.0 dated 03-APR-2023

PROTOCOL 220254

Bellus Health study number: BUS-P1-11

A PHASE 1, 2-PART, OPEN-LABEL, FIXED-SEQUENCE STUDY EVALUATING THE EFFECT OF RIFAMPIN (PART 1) AND RABEPRAZOLE (PART 2) ON THE PHARMACOKINETICS OF A SINGLE DOSE OF CAMLIPIXANT (BLU-5937) 50 mg TABLET IN HEALTHY PARTICIPANTS UNDER FASTING CONDITIONS

Sponsor:

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Contract Research Organization:

CCI [redacted]

Protocol Version: Final

Date: 03-APR-2023

CONFIDENTIAL

Protocol Historical File

Version	Brief description/summary of changes	Date
Final	Version submitted to the Independent Ethics Committee (IEC).	03-APR-2023

Sponsor Signature Page

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PPD

2023-Apr-03 | 15:12 EDT

Dr. Denis Garceau, Ph.D.
Chief Scientific Officer

Date

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2023-Apr-03 | 14:05 EDT

Nathalie Chauret, M.Sc.
Executive Director, Head of Drug Development

Date

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2023-Apr-03 | 15:43 EDT

Sarabjit Gahir, BPharm, Ph.D.
Director of Clinical Pharmacology

Date

PPD

Investigator Signature Page

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

12-Apr-2023

Bruno Francoeur, M.D.
Executive Medical Director

Date

CCI

Facilities and Responsible Staff

Clinical Research Facilities

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

CCI

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

CCI

Biomedical Laboratory Facilities

Biomedical laboratory testing will be performed by the following laboratories:

CCI

CCI

CCI

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

CCI

CCI

CCI

CCI

CCI [redacted]

PPD

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List of Tables and Figures

List of Abbreviations

AD	atopic dermatitis
ADAM	advanced dissolution, absorption, and metabolism
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
$AUC_{0\text{-}inf}$	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
BID	*bis in die* (twice a day)
BMI	body mass index
BUN	blood urea nitrogen
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
Cl/F	apparent clearance
C_{max}	maximal observed concentration
COVID-19	coronavirus 2019
CRF	case report form
CRO	contract research organization
CTA	Clinical Trial Application
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DMP	data management plan
DNA	deoxyribonucleic acid
eCRF	electronic case report form
ECG	electrocardiogram
EFD	embryo-fetal development

ET	early termination
FDA	Food and Drug Administration
FIH	first-in-human
fm	fraction metabolized
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
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
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
LS	least squares
MAD	multiple ascending dose
Max	maximum
MDMA	3,4-methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
NERD	non erosive reflux disease
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
PEPT1	peptide transporter 1
PK	pharmacokinetic(s)
PPI	proton-pump inhibitor
PT	prothrombin time
QA	quality assurance
QC	quality control
CCI [redacted]	
QT	QT interval
QTcF	Fridericia's corrected QT interval
RBC	red blood cell
RCC	refractory and unexplained chronic cough
RNA	ribonucleic acid
SAD	single ascending dose
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
TDAE	taste disturbance adverse event
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time when the maximal concentration is observed
CCI [redacted]	[redacted]
ULN	upper limit of normal
V_z/F	apparent volume of distribution
WBC	white blood cell
WHODrug	World Health Organization Drug

Synopsis of Protocol

Project Number:	220254 BUS-P1-11
Title:	A Phase 1, 2-Part, Open-label, Fixed-sequence Study Evaluating the Effect of Rifampin (Part 1) and Rabeprazole (Part 2) on the Pharmacokinetics of a Single Dose of 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 rifampin, a cytochrome P450 (CYP) 3A4 and CCI inducer (Part 1), or rabeprazole, a proton-pump inhibitor (PPI) (Part 2), on the pharmacokinetics (PK) of a single oral dose of camlipixant (BLU-5937), administered to healthy participants. Secondary objective: • To evaluate the safety and tolerability of camlipixant when administered alone and in combination with rifampin or rabeprazole to healthy participants.
Endpoints:	Primary endpoints: • PK parameters: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} Secondary endpoints: • PK parameters: T_{max}, $T_{½\ el,}$ Residual area, K_{el}, Cl/F, and V_z/F • 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 rifampin (Part 1) or rabeprazole (Part 2) in healthy participants under fasting conditions. The start of study conduct for Part 2 is independent from Part 1 study conduct. Participants will be enrolled to either Part 1 or 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 48 hours of PK and safety assessments. Repeated oral doses of CCI mg rifampin capsules (total dose CCI mg) will be administered CCI on Days 4 to 12, with co-administration of a single oral dose of 1 x 50 mg camlipixant tablet with rifampin capsules on Day 11. Administration of camlipixant on Day 11 will occur 1 hour (± 2 minutes) after administration of rifampin, followed by 48 hours of PK and safety assessments. In Part 2, participants will receive a single oral dose of 1 x 50 mg camlipixant tablet on Day 1, followed by 48 hours of PK and safety assessments. Repeated oral doses of CCI mg rabeprazole enteric-coated tablets will be administered CCI on Days 4 to 11, with co-administration of a single oral dose of 1 x 50 mg camlipixant tablet with rabeprazole enteric-coated tablet on Day 10. Administration of camlipixant on Day 10 will occur 1 hour (± 2 minutes) after administration of rabeprazole, followed by 48 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 13 (Part 1) or Day 12 (Part 2). There will be a washout period of at least 3 days between the first dose of camlipixant on Day 1 and the first dose of rifampin (Part 1) or rabeprazole (Part 2) on Day 4. A follow-up phone call will be performed 7 ± 2 days after discharge (Day 20 ± 2 in Part 1 and Day 19 ± 2 in Part 2).
Study Population:	A total of 32 healthy participants are planned to be enrolled. Participants must be ≥ 18 and ≤ 55 years of age and non-smoker for enrollment in the study. In Part 1, a total of 16 healthy males and non-childbearing potential females will be enrolled. In Part 2, a total of 16 healthy males and females will be enrolled.
Inclusion/Exclusion Criteria:	Inclusion Criteria: 1. Male (Parts 1 and 2) or non-childbearing potential female (Part 1) or female (Part 2), 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 for males and ≥45.0 kg for females. 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 (Part 1 and Part 2) 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. Female participants of childbearing potential (Part 2 only) who are sexually active with a non-sterile male partner (sterile male partners are defined as men vasectomized for at least 3 months prior to dosing) must be willing to use one of the following acceptable contraceptive methods throughout the study and for 30 days after the last dose: a. simultaneous use of non-hormonal intrauterine device placed at least 4 weeks prior to dosing and condom for the male partner; b. simultaneous use of diaphragm or cervical cap with spermicide and condom for the male partner, started at least 21 days prior to dosing; c. tubal ligation at least 3 months prior to dosing. 5. Female participants must be willing not to donate ova for 30 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. <u>Exclusion Criteria:</u> 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, rifampin or any other rifamycins (participants in Part 1 only), rabeprazole or substituted benzimidazoles (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 recreational use of soft drugs (such as medicinal or recreational marijuana) within 1 month or hard drugs (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) within 3 months 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, hyperbilirubinemia, jaundice, or elevated liver enzymes. 12. Known Gilbert, Rotor, Crigler-Najjar, or Dubin-Johnson syndrome. 13. Medical history of ageusia/hypogeusia/dysgeusia or known presence of a dysfunction in his/her ability to taste. 14. History of clostridium difficile infection and clostridium difficile-associated diseases. 15. Participants in Part 1 only: History of liver cirrhosis, liver tuberculosis, adenocarcinoma of the liver or neoplasm of the biliary tract. 16. Participants in Part 1 only: History of coagulation disorders. 17. Participants in Part 2 only: History of osteoporosis.

	18. Participants in Part 2 only: History of subacute cutaneous lupus erythematosus. 19. 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; 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). 20. 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. 21. 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. 22. 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 [redacted] on Day 1 (Part 1 and Part 2) and Day 11 (Part 1) or Day 10 (Part 2). • Rifampin [redacted] mg capsules (total dose [redacted] mg) administered [redacted], for 9 consecutive days from Day 4 to Day 12 in Part 1 only. • Rabeprazole [redacted] mg enteric-coated tablet administered [redacted], for 8 consecutive days from Day 4 to Day 11 in Part 2 only. • On Day 11 (Part 1) or Day 10 (Part 2), camlipixant will be administered 1 hour (± 2 minutes) [redacted] administration of rifampin (Part 1) or rabeprazole (Part 2).

	On Day 1: No food will be allowed from at least 10 hours before camlipixant dosing until at least 4 hours after dosing. On Day 11 (Part 1) or Day 10 (Part 2): No food will be allowed from at least 10 hours before rifampin (Part 1) or rabeprazole (Part 2) dosing until at least 4 hours after camlipixant dosing. On Days 4 to 10 and Day 12 in Part 1: No food will be allowed from at least 2 hours before rifampin dosing until 1 hour post-dose. A normo-caloric breakfast will be served at least 1 hour after rifampin administration. On Days 4 to 9 and Day 11 in Part 2: No food will be allowed from at least 2 hours before rabeprazole dosing until 1 hour post-dose. A normo-caloric breakfast will be served at least 1 hour after rabeprazole 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 [redacted] Concentrations for rifampin (Part 1) and rabeprazole (Part 2) will be tabulated. They will be presented as supportive data. Descriptive statistics on pre-dose concentrations of rifampin in Part 1 (Days 9, 10, and 11) and rabeprazole in Part 2 (Days 8, 9, and 10) will be performed to evaluate the attainment of steady-state. CCI [redacted] CCI [redacted] Other possible exploratory markers may be considered 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 and in combination with rifampin (Part 1) or rabeprazole (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**	**5-7**	**8-10**	**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												
Camlipixant[1]			X						X			
Rifampin[2]						X	X	X	X	X		
Pharmacokinetics												
Blood samples for PK analysis of Camlipixant[3]			X	X	X				X	X	X	
Blood samples for PK analysis of rifampin[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	X		X	
Urinalysis[10]	X	X				X			X		X	
FSH (for post-menopausal females)[11]	X											
Pregnancy tests[12]	X	X									X	
Drug, cotinine, and alcohol screens	X	X										

Study Stage	Screening	Baseline	Treatment									Follow-up phone call
Day	**-28 to -1**	**-1**	**1**	**2**	**3**	**4**	**5-7**	**8-10**	**11**	**12**	**13**	**20 ± 2**
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; LFT = liver function test; PK = pharmacokinetic; SAE = serious adverse event.

1 On Day 11, camlipixant will be administered 1 hour (± 2 minutes) CCI [redacted] administration of rifampin.

2 Administration of rifampin will occur at approximately CCI [redacted] from Days 4 to 12. 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 rifampin and camlipixant dosing on Day 11 is respected.

3 A total of 20 blood samples will be collected for PK analysis of camlipixant on Day 1 and Day 11: at pre-dose and 0.16, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 15, 18, 24, 36, and 48 hours post-dose. Refer to Table 3 for more details.

4 A total of 5 blood samples will be collected for PK analysis of rifampin pre-dose on Days 4, 8, 9, 10, and 11. 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 10, 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 camlipixant dosing on Day 1 and before rifampin dosing on Day 11.

7 12-lead ECG will be measured at screening, before camlipixant dosing on Day 1, before rifampin dosing on Day 4 and Day 11, and at discharge on Day 13 (or ET).

8 Serology tests include hepatitis B surface antigen (HbsAg), hepatitis C virus (HCV) antibody, and human immunodeficiency virus (HIV) antigen and antibody.

9 Standard biochemistry (including LFT and CK), hematology, and coagulation tests will be performed at screening, on Day -1, before rifampin dosing on Day 4 and Day 11, and at discharge on Day 13 (or ET). Biochemistry (including LFT and CK) will be also measured before rifampin dosing on Day 6 and Day 9.

10 Urinalysis tests will be performed at screening, on Day -1, before rifampin dosing on Day 4 and Day 11, 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 13 (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 discharge, CC [redacted]. Also, in the event of CCI [redacted], a COVID-19 test will be performed.

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**	**7-9**	**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			
Rabeprazole[2]						X	X	X	X	X		
Pharmacokinetics												
Blood samples for PK analysis of camlipixant[3]			X	X	X				X	X	X	
Blood samples for PK analysis of rabeprazole[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	7-9	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; COVID-19 = coronavirus 2019; ECG = electrocardiogram; ET = early termination; FSH = follicle-stimulating hormone; LFT = liver function test; PK = pharmacokinetic; SAE = serious adverse event.

1 On Day 10, camlipixant will be administered 1 hour (± 2 minutes) CCI administration of rabeprazole.

2 Administration of rabeprazole will occur at approximately CCI from Days 4 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 rabeprazole and camlipixant dosing on Day 10 is respected.

3 A total of 20 blood samples will be collected for PK analysis of camlipixant on Day 1 and Day 10: at pre-dose and 0.16, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 15, 18, 24, 36, and 48 hours post-dose. Refer to Table 4 for more details.

4 A total of 5 blood samples will be collected for PK analysis of rabeprazole pre-dose on Days 4, 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 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 rabeprazole dosing on Day 10.

7 12-lead ECG will be measured at screening, before camlipixant dosing on Day 1, before rabeprazole dosing on Day 4 and Day 10, and at discharge on Day 12 (or ET).

8 Serology tests include hepatitis B surface antigen (HbsAg), hepatitis C virus (HCV) antibody, and human immunodeficiency virus (HIV) antigen and antibody.

9 Standard biochemistry (including LFT and CK), hematology, and coagulation tests will be performed at screening, on Day -1, before rabeprazole dosing on Day 4 and Day 10, and at discharge on Day 12 (or ET).

10 Urinalysis will be performed at screening, on Day -1, before rabeprazole dosing on Day 4 and Day 10, 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, CCI Also, in the event of a CCI, a COVID-19 test will be performed.

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.[1] [redacted] [2,3] 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]

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).[1] 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]

1.3 Clinical

CCI

[redacted]

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 serious adverse events (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 [redacted] 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 (alanine aminotransferase [ALT] and/or aspartate aminotransferase [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).[1]

[redacted].

Refer to the IB v.5 and the IB addendum for detailed background information on camlipixant.[1]

1.4 Background Information on Rifampin

Rifampin is indicated for the treatment of pulmonary tuberculosis, as well as prophylaxis for meningococcal infection. The recommended dosage should not exceed a once daily dose of

600 mg for the treatment of tuberculosis and 600 mg twice daily for treatment of meningococcal infection. It is recommended that rifampin be administered once daily on an empty stomach (1 hour before a meal) to ensure optimum absorption. AEs associated with rifampin are listed in the Product Monograph.[5]

Rifampin may be bacteriostatic or bactericidal in action, depending on the concentration of the drug attained at the site of infection and the susceptibility of the infecting organism. Rifampin suppresses initiation of chain formation for ribonucleic acid (RNA) synthesis in susceptible bacteria by inhibiting deoxyribonucleic acid (DNA)-depending RNA polymerase.[5]

Rifampin is well absorbed from the gastrointestinal tract. Time to peak plasma concentration is 1.5 to 4 hours after oral administration; peak concentration may be decreased and delayed following administration with food. Its elimination half-life is initially 3 to 5 hours; with repeated administration half-life decreasing to 2 to 3 hours.[5]

Both in the laboratory animal and man, the administration of rifampin has been associated with evidence of induction of drug metabolizing enzyme systems of the liver,[5] especially the CYP family including CCI [redacted]

1.5 Background Information on Rabeprazole

Rabeprazole is a substituted benzimidazole PPI. It is indicated for the treatment of conditions where a reduction of gastric acid secretion is required, such as erosive or ulcerative gastroesophageal reflux disease (GERD), symptomatic GERD (also known as non-erosive reflux disease [NERD]), duodenal and gastric ulcers, and hypersecretory conditions such as Zollinger-Ellison syndrome. In combination with antibiotics, it is also used to eradicate *Helicobacter pylori* associated with duodenal ulcer disease. The recommended daily dosage ranges from 10 to 60 mg, depending on the disease being treated, with 10 to 20 mg once daily being the most frequently recommended dosing regimen. Doses up to 100 mg CCI [redacted] and 60 mg twice daily (BID) have been administered as well. AEs associated with rabeprazole are listed in the Product Monograph.[7]

Rabeprazole sodium is an antisecretory compound that suppresses gastric acid secretion by inhibiting the gastric H+, K+- ATPase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric PPI.[7]

Following oral administration, rabeprazole is rapidly absorbed and can be detected in plasma as early as 0.5 hours. After oral administration of CCI [redacted] mg rabeprazole, peak plasma concentrations (C_{max}) are reached at an average of 1.6 to 5.0 hours. Bioavailability is 52%. The rabeprazole C_{max} and AUC are linear with doses from 10 mg to 40 mg. Rabeprazole does not accumulate and its PK are not altered by multiple dosing. Rabeprazole is 96.3% bound to human plasma proteins.[7]

Taking rabeprazole tablets with food does not alter C_{max} or AUC relative to the fasting state; the T_{max} is increased by 1.7 hours. Administration of rabeprazole with a high fat meal may delay its absorption by approximately 4 hours or longer; however, the C_{max} and AUC are not altered.[7]

The plasma half-life is approximately 1 hour.[7]

1.6 Study Rationale

Part 1:

In vitro studies indicate that CCI play a role in the oxidative metabolism of camlipixant.[CCI][1]

Metabolic induction may result in decreased plasma concentrations of drugs and/or their active metabolite(s). These decreased plasma concentrations may diminish the therapeutic effects of 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 inducers CYP enzymes (CCI believed to be important 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)*,[8] multiple doses of the CYP inducer, rifampin,[9] will be administered to evaluate the effect on the PK of single dose camlipixant. Rifampin was judged to be the optimal choice among CYP inducers for this study, given its ability to induce both CCI It is a clinically validated, strong inducer for CCI and one of the only clinically validated inducers of CYP2C8.[9] Additionally, rifampin does not require an initial up-titration phase, allowing for an overall shorter exposure time to the perpetrator drug and reduces study duration for healthy participants. Therefore, in terms of participant safety, the selection of this clinical index inducer represents an advantageous risk mitigation strategy, because, with appropriate dosing duration, it allows to achieve sufficient CYP3A induction while limiting exposure. Moreover, the use of rifampin to induce both CCI and CCI represents the worst-case scenario and will enable the Sponsor to validate and refine an existing PBPK model and delineate the relative contributions of the two metabolic pathways in clearance of camlipixant. Therefore, rifampin is the most optimal inducer to achieve these objectives and characterize the DDI profile of camlipixant.

Part 2:

Solubility of camlipixant in simulated biological fluids and in buffers at different pH was assessed at 37°C.[CCI][1] Based on the FDA *Guidance for Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing agents: Study Design, Data Analysis, and Clinical Implications (2020)*, most drugs that have demonstrated pH-dependent DDIs are weak bases with low intrinsic aqueous solubility compared to the solubility needed to dissolve the clinical dose (i.e., dose divided by 250 mL water).[10] In other words, the potential for an interaction with pH modifying agents is low when the solubility of a drug is higher than the dose divided by 250 mL.[CCI]

Accordingly, the purpose of Part 2 is to assess, *in vivo*, the potential of camlipixant to be a victim of DDIs related to reduction in gastric pH. Among acid-reducing agents, PPIs are listed in the FDA *Guidance for Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing agents: Study Design, Data Analysis, and Clinical Implications (2020)* as producing long lasting effects on gastric pH. In this study, multiple doses of the PPI rabeprazole, mentioned in the FDA's guidance,[9] will be administered to evaluate the effect on the PK of single-dose camlipixant. Considering that a range of cytochromes (CYPs) are involved in the metabolism of camlipixant, rabeprazole is an appropriate choice of PPI as it has a low affinity for a range of CYP isoenzymes.[11]

1.6.1 Analytes to Measure

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

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

In this clinical study, rifampin (Part 1) and rabeprazole (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 rifampin or rabeprazole blood levels. Accordingly, as participants will be confined to the clinical unit the full duration of the study, only sparse samples for rifampin (Part 1) and rabeprazole (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

According to the FDA guidance,[8] 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. For inducers, such as rifampin, multiple doses are used to ensure the maximal induction of a specific pathway. Except for prophylaxis of meningococcal infection, the maximal dose and dosing regimen of rifampin in the clinical setting is CCI mg CCI.[5] According to the literature, CCI mg was the most commonly used dose in DDI studies using rifampin as a perpetrator drug. The duration of rifampin dosing varies between studies. Dosing for 7 days is expected to achieve near maximal induction.[12] In the interest of not exposing healthy participants to more than the minimum required lead-in period of rifampin, and, considering that 7 days of dosing is common practice in the literature, co-administration of rifampin with the investigational drug will occur on the 8th day of rifampin dosing in this study. This approach has

been judged to be sufficient to achieve adequate CCI induction, while minimizing unnecessary exposure and safety risks. Following co-administration with camlipixant, rifampin will continue to be administered for 1 day, in order to maintain CCI induction during the collection period for PK sampling of camlipixant. Therefore, a CCI mg dose of rifampin given CCI as oral capsules for 9 consecutive days, with administration of rifampin 1 hour before camlipixant dosing on the 8th day of rifampin administration, has been selected for Part 1.

Based on the FDA DDI guidance on acid-reducing agents, pre-treatment with PPIs for several days (e.g., 4 to 5 days) is needed to reach the pharmacodynamic steady-state of PPIs before administering the investigational drug. It is preferable to select a dose that is expected to provide a near maximum effect on pH elevation.[10] In this study, attainment of maximal effect on pH will be ensured by a lead-in period of 6 days with rabeprazole before co-administration of camlipixant on the 7th day of rabeprazole dosing. A dose of CCI of rabeprazole represents the highest recommended dose for most indications,[7] and is in line with the dose listed in the FDA guidance.[10] The effect of PPIs on gastric pH is long lasting, and thus staggered administration of an investigational drug with a PPI is not expected to mitigate the DDI risk.[10] A 1-hour time interval between rabeprazole and camlipixant dosing will be kept for the day of co-administration as standardization with other previously performed DDI studies with camlipixant, without minimizing the possible effect on pH. Following co-administration with camlipixant, rabeprazole will continue to be administered for 1 day, as a conservative approach. Therefore, a CCI mg dose of rabeprazole given CCI as an oral tablet for 8 consecutive days, with administration of rabeprazole 1 hour before camlipixant dosing on the 7th day of rabeprazole administration, has been selected for Part 2.

1.6.3 Pharmacogenomic Testing

One blood sample for pharmacogenomic testing will be taken on Day -1. CCI 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.

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.[1] There have been no clinical studies of camlipixant conducted in pregnant women.

Rifampin has been demonstrated to cross the placental barrier and is teratogenic in rodents when given orally. In rat studies, a greater number of reabsorbed fetuses and a dose-related decrease in fetal weights were observed in the group receiving 200 mg/kg. Treatment with 200 mg/kg of rifampin caused an incidence of fusion of the palatine bones, two cases of general malformations (monstrosity), one case of bone malformation which consisted of bone centers of the sternum divided or missing entirely and fusion of vertebral bodies. In rabbits treated with 200 mg/kg rifampin, the number of reabsorbed fetuses were higher and the number of live fetuses lower. This was a dose-related effect. The progeny of rabbits treated with 200 mg/kg rifampin showed evidence of fissure of the second bone of the sternum, along with hydrocephalus. Also in this group, an incidence of 11.9% of spina bifida was observed. In mice, doses of 150-200 mg/kg caused dose-dependent toxic effects on the embryos and malformations (particularly cleft palate and spina bifida) in 5-10% of the pregnant mice. It is recommended that pregnant women with tuberculosis be treated for a minimum of 9 months with multi-drug therapy, including rifampin. It has rarely caused postnatal hemorrhages in the mother and infant when administered during the last few weeks of pregnancy; vitamin K may be indicated. Neonates should be carefully observed for evidence of adverse effects.[5] While there are no well controlled studies in pregnant women, cases of fetal malformation have been reported when used during pregnancy.[13] Thus, women of childbearing potential will not be recruited into Part 1; only male and non-childbearing potential female participants will be included into this part of the study. Sexually active non-surgically-sterile male participants with female partners of childbearing potential will be required to use a double contraceptive method.

For rabeprazole, at maternally toxic doses (25 and 50 mg/kg) in the rat EFD study, incomplete ossification of the parietal and/or occipital bones was observed. There were no other effects on viability, weight or morphology. At maternally toxic doses (30 mg/kg) in the rabbit EFD study, decreased fetal weight and delayed ossification of the proximal tibial epiphysis was observed. There were no other effects on fetal viability or morphology. Adequate absorption of rabeprazole was demonstrated in the rabbit during the organogenesis period. No effects on fetal development, parturition, lactation, postnatal growth and offspring development, or offspring reproductive performance were observed in this study. The safety of rabeprazole treatment in pregnancy has not been established. Rabeprazole tablets should not be administered to pregnant women unless the expected benefits outweigh the potential risks to the fetus.[7] In light of these data, only male and non-pregnant, non-lactating female participants will be included in Part 2. Sexually active female participants of childbearing potential and non-surgically-sterile male participants with female partners of childbearing potential will be required to use a double contraceptive method.

In order to avoid any potential DDIs associated with hormonal contraceptives in this study, hormonal methods of contraception will not be allowed for female participants.

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, caution in dosage of rifampin is recommended in elderly persons.[5] Furthermore, in 20 healthy elderly participants given a CCI mg rabeprazole dose CCI for seven days, the AUC doubled and the C_{max} increased by 60% compared to measurements in a parallel younger control group. Also, several published observational studies suggest that PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. In the geriatric population, benefits of use of PPIs should be weighed against the increased risk of fractures as patients in this category may already be at high risk of osteoporosis-related fractures.[7] Therefore, the population in this study will include healthy individuals between the ages of 18 and 55 years.

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 rifampin or rabeprazole. 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 rifampin, a [CCI] and [CCI] inducer (Part 1), or rabeprazole, a PPI (Part 2), on the PK of a single oral dose of camlipixant (BLU-5937), administered to healthy participants.

Secondary objective:

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

3. Endpoints

Primary endpoints:

- PK parameters: $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max}

Secondary endpoints:

- PK parameters: T_{max}, $T_{½\ el}$, Residual area, K_{el}, Cl/F, and V_z/F
- 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.

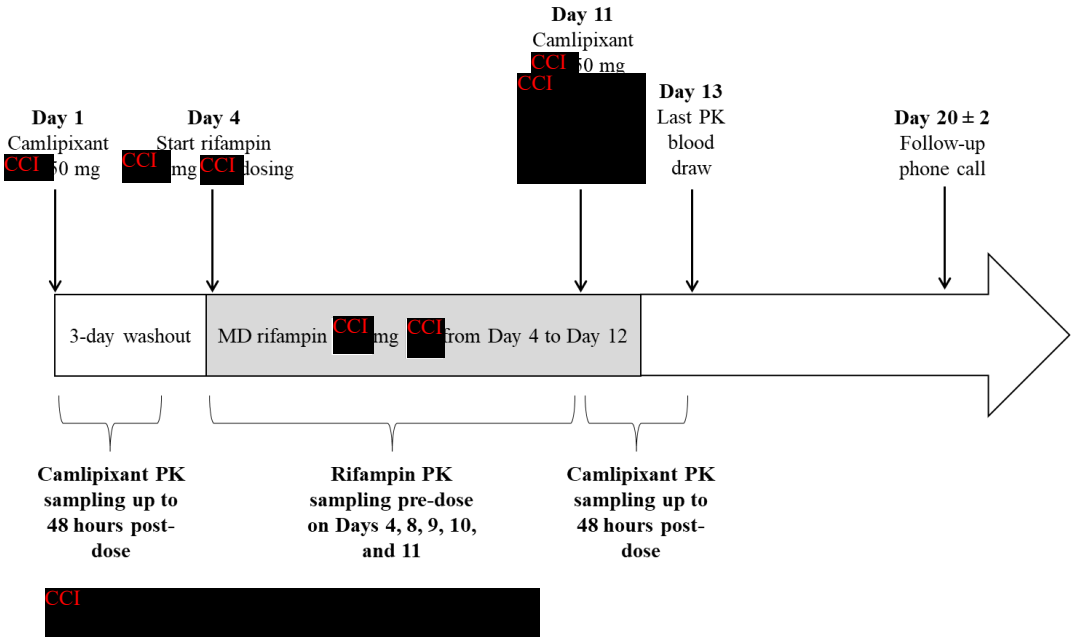
4. Study Design

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 rifampin (Part 1) or rabeprazole (Part 2) in healthy participants under fasting conditions. The start of study conduct for Part 2 is independent from Part 1 study conduct.

A total of 32 participants will be enrolled to either Part 1 or Part 2 (16 participants in each part). In each part, participants will receive the assigned treatment.

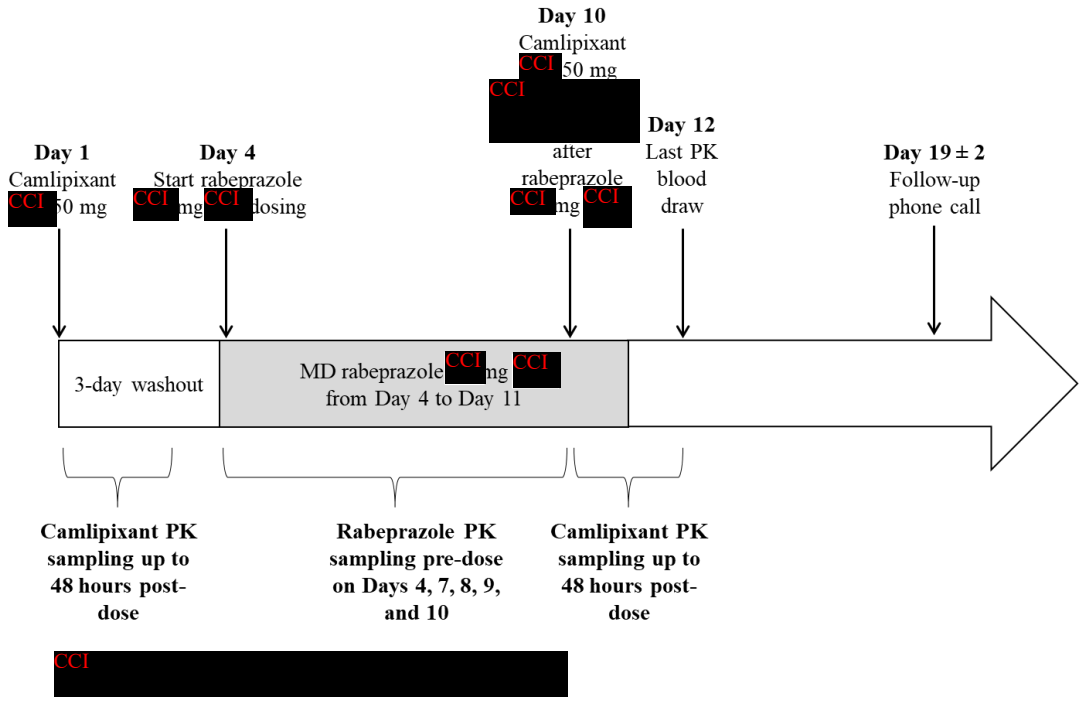
In Part 1, participants will receive a single oral dose of 1 x 50 mg camlipixant tablet on Day 1, followed by 48 hours of PK and safety assessments. Repeated oral doses of CCI mg rifampin capsules (total dose CCI mg) will be administered CCI on Days 4 to 12, with co-administration of a CCI mg camlipixant tablet with rifampin capsules on Day 11. Administration of camlipixant on Day 11 will occur 1 hour (± 2 minutes) after administration of rifampin, followed by 48 hours of PK and safety assessments. The study design is presented in Figure 1.

Figure 1. Study Design Diagram for Part 1



In Part 2, participants will receive a single oral dose of 1 x 50 mg camlipixant tablet on Day 1, followed by 48 hours of PK and safety assessments. Repeated oral doses of CCI mg rabeprazole enteric-coated tablets will be administered CCI on Days 4 to 11, with co-administration of a single oral dose of 1 x 50 mg camlipixant tablet with rabeprazole enteric-coated tablet on Day 10. Administration of camlipixant on Day 10 will occur 1 hour (± 2 minutes) after administration of rabeprazole, followed by 48 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 13 (Part 1) or Day 12 (Part 2). There will be a washout period of at least 3 days between the first dose of camlipixant on Day 1 and the first dose of rifampin (Part 1) or rabeprazole (Part 2) on Day 4. A follow-up phone call will be performed 7 ± 2 days after discharge (Day 20 ± 2 in Part 1 and Day 19 ± 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 Part 1 and 7 weeks for Part 2.

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 16 participants in Part 2 for participation in this study (total of 32 participants) in order to have at least 12 evaluable participants for PK analysis in each part of the study. No formal sample size calculation has been made. Based on experience from previous similar studies, a total of 32 participants (16 in each study part) was considered sufficient to adequately characterize the PK 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 (Parts 1 and 2) or non-childbearing potential female (Part 1) or female (Part 2), 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 for males and ≥45.0 kg for females.
2. Healthy as defined by:
    c. the absence of clinically significant illness and surgery within 4 weeks prior to dosing.
    d. 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 (Part 1 and Part 2) 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. Female participants of childbearing potential (Part 2 only) who are sexually active with a non-sterile male partner (sterile male partners are defined as men vasectomized for at least 3 months prior to dosing) must be willing to use one of the following acceptable contraceptive methods throughout the study and for 30 days after the last dose:
    a. simultaneous use of non-hormonal intrauterine device placed at least 4 weeks prior to dosing and condom for the male partner;
    b. simultaneous use of diaphragm or cervical cap with spermicide and condom for the male partner, started at least 21 days prior to dosing;
    c. tubal ligation at least 3 months prior to dosing.

5. Female participants must be willing not to donate ova for 30 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 coronavirus 2019 (COVID-19) at admission.
7. Known allergic reactions or hypersensitivity to camlipixant, rifampin or any other rifamycins (participants in Part 1 only), rabeprazole or substituted benzimidazoles (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 recreational use of soft drugs (such as medicinal or recreational marijuana) within 1 month or hard drugs (such as cocaine, phencyclidine [PCP], crack, opioid derivatives including heroin, and amphetamine derivatives) within 3 months 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, hyperbilirubinemia, jaundice, or elevated liver enzymes.
12. Known Gilbert, Rotor, Crigler-Najjar, or Dubin-Johnson syndrome.
13. Medical history of ageusia/hypogeusia/dysgeusia or known presence of a dysfunction in his/her ability to taste.
14. History of clostridium difficile infection and clostridium difficile-associated diseases.
15. Participants in Part 1 only: History of liver cirrhosis, liver tuberculosis, adenocarcinoma of the liver or neoplasm of the biliary tract.
16. Participants in Part 1 only: History of coagulation disorders.
17. Participants in Part 2 only: History of osteoporosis.
18. Participants in Part 2 only: History of subacute cutaneous lupus erythematosus.
19. 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;
    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).
20. 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.
21. 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.
22. 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 fine 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 rifampin from the Canadian or US market and rabeprazole 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: [redacted]

Part 1: [redacted] mg capsules of rifampin, total dose [redacted] mg (Sourced from the Canadian or US market) administered [redacted], for 9 consecutive days from Day 4 to Day 12 in Part 1 only.

Part 2: [redacted] mg of rabeprazole enteric-coated tablet (Sourced from the Canadian market) administered [redacted], for 8 consecutive days from Day 4 to Day 11 in Part 2 only.

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 11, camlipixant will be administered to each participant with 240 mL of water. On Day 11, camlipixant will be administered 1 hour after administration of rifampin dosing, with a time-tolerance window of ± 2 minutes. The time of administration of both camlipixant and rifampin will be recorded, and the time interval between the 2 administrations must not fall outside of the scheduled acceptable range.

Rifampin will be administered to each participant as [redacted] capsules [redacted] for 9 consecutive days, from Day 4 to Day 12. The rifampin capsules will be administered to each participant with 240 mL of water. In the event that participants cannot swallow all capsules with 240 mL of water, additional water may be allowed up to a maximum total volume of 400 mL. Administration of rifampin will be performed at approximately the same time on Days 4 to 12. A time window of ± 10 minutes from the scheduled rifampin dosing time will be allowed, as long as the 1-hour (± 2 minutes) time interval between rifampin and camlipixant dosing on Day 11 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 11, no food will be allowed from at least 10 hours before rifampin dosing until at least 4 hours after camlipixant dosing.

On Days 4 to 10 and Day 12: No food will be allowed from at least 2 hours before rifampin dosing until 1 hour post-dose. A normo-caloric breakfast will be served at least 1 hour after rifampin administration.

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 11, except for water given with camlipixant and rifampin dosing, no fluids will be allowed for 1 hour before rifampin dosing until 1 hour post-dose of camlipixant. On Days 4, 5, 6, 7, 8, 9, 10, and 12, except for water given with rifampin 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.

Part 2:

On Day 1 and Day 10, camlipixant will be administered to each participant with 240 mL of water. On Day 10, camlipixant will be administered 1 hour after administration of rabeprazole dosing, with a time-tolerance window of ± 2 minutes. The time of administration of both camlipixant and rabeprazole will be recorded, and the time interval between the 2 administrations must not fall outside of the scheduled acceptable range.

Rabeprazole will be administered to each participant as CCI tablet CCI [redacted] for 8 consecutive days, from Day 4 to Day 11. The rabeprazole tablet will be administered to each participant with 240 mL of water. Administration of rabeprazole will be performed at approximately the same time on Days 4 to 11. A time window of ± 10 minutes from the scheduled rabeprazole dosing time will be allowed, as long as the 1-hour (± 2 minutes) time interval between rabeprazole and camlipixant dosing on Day 10 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 10, no food will be allowed from at least 10 hours before rabeprazole dosing until at least 4 hours after camlipixant dosing.

On Days 4 to 9 and Day 11: No food will be allowed from at least 2 hours before rabeprazole dosing until 1 hour post-dose. A normo-caloric breakfast will be served at least 1 hour after rabeprazole administration.

On Day 1, except for water given with the camlipixant, no fluids will be allowed for 1 hour before dosing until 1 hour post-dose. On Day 10, except for water given with camlipixant and rabeprazole dosing, no fluids will be allowed for 1 hour before rabeprazole dosing until 1 hour post-dose of camlipixant. On Days 4, 5, 6, 7, 8, 9, and 11, except for water given with rabeprazole 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. 19 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:

- Soft or hard drugs 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 11, participants will be allowed to engage in normal activity but will avoid lying down or sleeping for 5 hours after rifampin administration. On Days 4 to 10 and Day 12, participants will be allowed to engage in normal activity but will avoid lying down or sleeping for 4 hours after each rifampin 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 camlipixant administration on Day 1. On Day 4, participants will be required to remain seated or semi-reclined and will avoid lying down or sleeping for 4 hours after rabeprazole administration. On Day 10, participants will be required to remain seated or semi-reclined and will avoid lying down or sleeping for 5 hours after rabeprazole administration. On Days 5 to 9 and Day 11, participants will be allowed to engage in normal activity but will avoid lying down or sleeping for 4 hours after each rabeprazole 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 (rifampin)	Time window
1 and 11	Pre-dose	Pre-dose (Day 11)	Within 30 minutes
	0.16, 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 12	24 and 36 hours	-	±5 minutes
3 and 13	48 hours	-	±10 minutes
4, 8, 9, and 10	Not applicable	Pre-dose	Within 30 minutes

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

Day	Time point (camlipixant)	Time point (rabeprazole)	Time window
1 and 10	Pre-dose	Pre-dose (Day 10)	Within 30 minutes
	0.16, 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 11	24 and 36 hours	-	±5 minutes
3 and 12	48 hours	-	±10 minutes
4, 7, 8, and 9	Not applicable	Pre-dose	Within 30 minutes

The planned volume of blood to be collected for this study, including that collected for eligibility and safety purposes, should not exceed 200 mL in Part 1 and 200 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 4, the Investigator or designee will be on site for rifampin administration and until 4 hours post-dose. On Day 11, the Investigator or designee will be on site for rifampin 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 camlipixant administration and until 4 hours post-dose. On Day 4, the Investigator or designee will be on site for rabeprazole administration and until 4 hours post-dose. On Day 10, the Investigator or designee will be on site for rabeprazole 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.

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 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. 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. In case of abnormal results, additional testing may be conducted 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	Bilirubin Blood (occult) Color and appearance Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (in the event of abnormal findings)
	Coagulation[2]	
	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; 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 unfavorable 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]

The incidence of AEMIs of camlipixant alone from Day 1 to Day 4 pre-dose of rifampin (Part 1) or rabeprazole (Part 2) will act as a baseline.

AEMIs appearing following rifampin administration alone from Day 4 to Day 11 pre-dose of camlipixant (Part 1) and rabeprazole administration alone from Day 4 to Day 10 pre-dose of camlipixant (Part 2) will be accounted for causality based on their onset date/time.

CCI [redacted]

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 judgment 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:

PPD

Drug Safety and Pharmacovigilance

PPD

And to:

PPD

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 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

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 11 (Part 1)/Day 10 (Part 2) and have at least one reportable concentration.

9.1.3 Pharmacokinetic Parameter Population

The PK parameter population will include all participants for whom the Day 1 and Day 11 (Part 1) or Day 10 (Part 2) PK profiles of the victim drug camlipixant can be adequately characterized, specifically, when administered alone and in combination with rifampin (Part 1) or rabeprazole (Part 2).

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 camlipixant treatment, compliance with rifampin (Part 1) or rabeprazole (Part 2) treatment impacting camlipixant PK (number of doses received equal to 9 [Part 1] or 8 [Part 2]), 1-hour time interval between rifampin and camlipixant dosing on Day 11 of Part 1 or 1-hour time interval between rabeprazole and camlipixant dosing on Day 10 of 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:

- $AUC_{0\text{-}t}$: 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 rifampin (Part 1): pre-dose concentrations on the morning of Days 4, 8, 9, 10, and 11.

The following information will be presented for rabeprazole (Part 2): pre-dose concentrations on the morning of Days 4, 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], CV%, minimum [Min], maximum [Max], and median) of the plasma concentrations versus time will be presented as well for the PK parameters.

CCI [redacted]

Concentrations for rifampin (Part 1) and rabeprazole (Part 2) will be tabulated. They will be presented as supportive data. Descriptive statistics on pre-dose concentrations of rifampin in Part 1 (Days 9, 10, and 11) and rabeprazole in Part 2 (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

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 and in combination with rifampin (Part 1) or rabeprazole (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

CCI [redacted] Other possible exploratory markers may be considered 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 electronic case report form (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

1 BLU-5937. Investigator's Brochure. Bellus Health Inc. 5th Edition (version dated April 22nd, 2022) and Addendum Version 5.0 (dated April 19th, 2022).

2 Bellus Health Inc. A 24-Week Study of the Efficacy and Safety of BLU-5937 in Adults With Refractory Chronic Cough (CALM-2). ClinicalTrials.gov identifier: NCT05600777. Updated: March 6, 2023. https://clinicaltrials.gov/ct2/show/NCT05600777?term=5937&cond=refractory+chronic+cough&draw=2&rank=3

3 Bellus Health Inc. A 52-Week Study of the Efficacy and Safety of BLU-5937 in Adults With Refractory Chronic Cough (CALM-1). ClinicalTrials.gov identifier: NCT05599191. Updated: March 6, 2023. https://clinicaltrials.gov/ct2/show/NCT05599191?term=5937&cond=refractory+chronic+cough&draw=2&rank=2

4 A Phase I, Double-Blind, Randomized, Adaptive-designed Study to Assess the Pharmacokinetics and Safety of BLU-5937 in Healthy Adult Japanese and Caucasian Subjects Following Single and Multiple Oral Doses. BUS-P1-07/C20042. Clinical Study Report. Bellus Health. 11 November 2022.

5 ROFACT®, Product Monograph. Version revised on June 28, 2019. Drug Product Database, Health Canada. Available online at: health-products.canada.ca/dpd-bdpp/index-eng.jsp

6 Rifampin Capsules USP, Drug Label Information. Version revised: April 2022. Available online at: dailymed.nlm.nih.gov/dailymed/index.cfm

7 PARIET®, Product Monograph. Version revised on August 8, 2022. Drug Product Database, Health Canada. Available online at: health-products.canada.ca/dpd-bdpp/index-eng.jsp

8 Center for Drug Evaluation and Research (CDER), FDA. Guidance for Industry: Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions. January 2020.

9 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.

10 Center for Drug Evaluation and Research (CDER), FDA. Evaluation of Gastric pH-Dependent Drug Interactions With Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications. November 2020.

11 Wedemeyer RS, Blume H. Pharmacokinetic drug interaction profiles of proton pump inhibitors: an update. Drug Saf. 2014;37(4):201-211.

12 Kapetas AJ, Sorich MJ, Rodrigues AD, Rowland A. Guidance for Rifampin and Midazolam Dosing Protocols To Study Intestinal and Hepatic Cytochrome P450 (CYP) 3A4 Induction and De-induction. AAPS J. 2019;21(5):78. Published 2019 Jun 19.

13 Kalayci T, Erener-Ercan T, Buyukkale G, Cetinkaya M. Limb deformity in a newborn. Is rifampicin just an innocent bystander?. Eur Rev Med Pharmacol Sci. 2015;19(3):517-519.

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 • COVID-19 test • Blood samples for PK analysis of camlipixant
D4	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • CCI dose morning administration of CCI capsules of rifampin CCI mg CCI • Blood sample for PK analysis of rifampin • 12-lead ECG: pre-dose of rifampin administration • Biochemistry (including LFT and CK), hematology, coagulation, and urinalysis: before dosing
D5	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • CCI dose morning administration of 2 capsules of rifampin CCI mg CCI
D6	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • CCI dose morning administration of CCI capsules of rifampin CCI mg CCI

	• Biochemistry (including LFT and CK) before dosing
D7	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • CCI dose morning administration of CCI capsules of rifampin CCI mg CCI
D8	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • CCI dose morning administration of CCI capsules of rifampin CCI mg CCI • Blood sample for PK analysis of rifampin
D9	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Multiple dose morning administration of CCI capsules of rifampin CCI mg CCI • Blood sample for PK analysis of rifampin • Biochemistry (including LFT and CK) before dosing
D10	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Multiple dose morning administration of CCI capsules of rifampin CCI mg CCI • Blood sample for PK analysis of rifampin • Brief physical exam in the evening
D11	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • Multiple dose morning administration of CCI capsules of rifampin CCI mg CCI • Single dose administration of camlipixant 50 mg tablet 1 hour (± 2 minutes) after rifampin administration • Blood samples for PK analysis of camlipixant • Blood sample for PK analysis of rifampin • Blood pressure and heart rate: before rifampin dosing • 12-lead ECG: before rifampin dosing • Biochemistry (including LFT and CK), hematology, coagulation and urinalysis before rifampin dosing
D12	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • CCI dose morning administration of CCI capsules of rifampin CCI mg CCI • Blood samples for PK analysis of camlipixant
D13 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
D20 ± 2	• Follow-up phone call • Monitoring of AEs/SAEs/AEMIs and concomitant medications

Abbreviations: AE = adverse event; AEMI = adverse event of medical interest; 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, CCI; 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 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 • COVID-19 test • Blood samples for PK analysis of camlipixant
D4	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • CCI [redacted] dose CCI [redacted] administration of rabeprazole CCI mg enteric-coated tabled CCI • Blood sample for PK analysis of rabeprazole • 12-lead ECG: pre-dose • Biochemistry (including LFT and CK), hematology, coagulation, and urinalysis: before dosing
D5	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • CCI [redacted] dose morning administration of rabeprazole CCI mg enteric-coated tabled CCI
D6	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • CCI [redacted] dose morning administration of rabeprazole CCI mg enteric-coated tabled CCI
D7	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement

	• [redacted] dose [redacted] administration of rabeprazole [redacted] mg enteric-coated tabled [redacted] • Blood sample for PK analysis of rabeprazole
D8	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • [redacted] dose [redacted] administration of rabeprazole [redacted] mg enteric-coated tabled [redacted] • Blood sample for PK analysis of rabeprazole
D9	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • [redacted] dose [redacted] administration of rabeprazole [redacted] mg enteric-coated tabled [redacted] • Blood sample for PK analysis of rabeprazole • Brief physical exam in the evening
D10	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • [redacted] dose [redacted] administration of rabeprazole [redacted] mg enteric-coated tabled [redacted] • Single dose administration of camlipixant [redacted] mg tablet 1 hour (± 2 minutes) after rabeprazole administration • Blood samples for PK analysis of camlipixant • Blood sample for PK analysis of rabeprazole • Blood pressure and heart rate: before rabeprazole dosing • 12-lead ECG: before rabeprazole dosing • Biochemistry (including LFT and CK), hematology, coagulation and urinalysis before rabeprazole dosing
D11	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Continued confinement • [redacted] dose [redacted] administration of rabeprazole [redacted] mg enteric-coated tabled [redacted] • Blood samples for PK analysis of camlipixant
D12 Discharge or ET	• Monitoring and recording of AEs/SAEs/AEMIs and concomitant medication use • Blood samples for PK analysis of camlipixant • 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
D19 ± 2	• Follow-up phone call • Monitoring of AEs/SAEs/AEMIs and concomitant medications

Abbreviations: AE = adverse event; AEMI = adverse event of medical interest; 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, [redacted] SAE = serious adverse event.

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

CCI [redacted]

Protocol Administrative Letter dated 13-JUN-2023

CCI	**Protocol Administrative Letter for Early Phase Studies**

Project: 220254 (Sponsor code: BUS-P1-11)	Sponsor: Bellus Health
CC: *Final Protocol dated 03-APR-2023*	Date: 13-JUN-2023
Study Title: A Phase 1, 2-Part, Open-label, Fixed-sequence Study Evaluating the Effect of Rifampin (Part 1) and Rabeprazole (Part 2) on the Pharmacokinetics of a Single Dose of Camlipixant (BLU-5937) 50 mg Tablet in Healthy Participants under Fasting Conditions	

This Protocol administrative letter intends to bring the following change to the above-mentioned final protocol.

It should be clarified that safety events must be reported CCI responsible for pharmacovigilance and case processing, using an additional e-mail address. Therefore, the information on pages 52-53, under section 8.4.6 Event Reporting, has been modified as follows:

From:

PPD
Drug Safety and Pharmacovigilance
PPD

And to:

PPD

To:

PPD

Bellus Health:
PPD
Drug Safety and Pharmacovigilance
PPD

And to:

PPD

Created by:		
PPD , Clinical Research Scientist II	PPD	Jun 13, 2023
Printed Name, Title	Signature	Date (dd-MMM-YYYY)

Protocol Administrative Letter dated 20-JUL-2023

CCI [redacted]	**Protocol Administrative Letter for Early Phase Studies**

Project: 220254 (Sponsor code: BUS-P1-11)	Sponsor: Bellus Health
CC: *Final Protocol dated 03-APR-2023*	Date: 20-JUL-2023
Study Title: A Phase 1, 2-Part, Open-label, Fixed-sequence Study Evaluating the Effect of Rifampin (Part 1) and Rabeprazole (Part 2) on the Pharmacokinetics of a Single Dose of Camlipixant (BLU-5937) 50 mg Tablet in Healthy Participants under Fasting Conditions	

This Protocol administrative letter intends to bring the following change to the above-mentioned final protocol.

On page 50, under section 8.4.2 Definition of Adverse Events of Medical Interest, it is stated that adverse events of medical interest (AEMIs) occurring until the end of the study discharge will require CCI [redacted]. This may be misinterpreted as the time of discharge from the clinic. However, as AEMIs are part of the secondary safety endpoints, they need to be reported and documented from camlipixant first dosing until the end of the study (i.e. until the follow-up phone call or early termination [if applicable]), just as any other adverse event. Therefore, AEMIs occurring up until the end of the study, and not only until discharge from the clinic, will require CCI [redacted].

The following sentence:

CCI [redacted]

Should read as:

CCI [redacted]

Created by: PPD [redacted], Senior Clinical Research Scientist	PPD [redacted]	Jul 20, 2023
Printed Name, Title	Signature	Date (dd-MMM-YYYY)