Protocol H8H-CD-LAHN (V1) (CUD-P4-001 (COL MIG-113))

A Phase I, Multicenter, Open-Label, Parallel-Group Adaptive Pharmacokinetic Single Dose Study of Oral Lasmiditan in Subjects With Normal and Impaired Renal Function

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A Phase I, Multicenter, Open-Label, Parallel-Group Adaptive Pharmacokinetic Single Dose Study of Oral Lasmiditan in Subjects with Normal and Impaired Renal Function

Protocol Number:	CUD-P4-001 (COL MIG-113)
Investigational Product:	Lasmiditan
Sponsor:	CoLucid Pharmaceuticals, Inc. 222 Third Street Suite 1320 Cambridge, MA, USA, 02142
Sponsor's contact person:	PPD Tel. Cell. PPD Email. PPD

Protocol Version		Date
1.0	**Original**	**2016/12/01**
2.0	**Amendment 01**	**2017/01/06**

COMPLIANCE

The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonisation and all applicable federal and local regulations.

CONFIDENTIALITY STATEMENT

The information provided in this document is strictly confidential and is available for review to investigator(s) and to the appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB). It may not be used, divulged, published or otherwise disclosed without the written authorization from Algorithme Pharma or the sponsor.

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STUDY SYNOPSIS

Name of Sponsor/Company:	CoLucid Pharmaceuticals, Inc.
Name of Product:	Lasmiditan
Title of Study:	A Phase I, Multicenter, Open-Label, Parallel-Group Adaptive Pharmacokinetic Single Dose Study of Oral Lasmiditan in Subjects with Normal and Impaired Renal Function
Study Development Phase:	Phase I
Objectives:	The primary objective of this study is to evaluate the pharmacokinetic (PK) profile of lasmiditan following a single oral 200 mg dose in subjects with impaired renal function relative to matched, healthy controls with normal renal function. The secondary objective of this study is to assess the safety and tolerability of a single oral 200 mg dose of lasmiditan in subjects with normal and impaired renal function.
Test Product:	Lasmiditan 200 mg tablets
Dose and Mode of Administration:	Single dose of 200 mg of lasmiditan administered orally.
Study Design:	This is a multicenter, open-label, non-randomized, parallel-group, adaptive, single dose study. This study will enroll up to 32 subjects using an adaptive design that can include up to 3 groups of subjects with different degrees of renal impairment and one group of control subjects with normal renal function. First, subjects with severe renal impairment (Group 2) and matched subjects with normal renal function (Group 1) will be enrolled. There will be 8 subjects in each group. Based on safety and PK results from subjects with severe renal impairment, Group 3 (Moderate Renal Impairment) and Group 4 (Mild Renal Impairment) will be enrolled if a substantial change in the exposure of lasmiditan is observed in subjects with severe renal impairment. There will be 8 subjects in each group. All subjects will participate in one treatment period and will receive a single dose of lasmiditan in the fasting state. Subjects will be confined to the clinic from 10 hours prior to dosing until 36 hours after drug administration.
Duration of Study:	Up to 38 days, including Screening.
Study Population:	Male and female adult subjects with normal renal function and male and female adult patients with mild, moderate, and severe renal impairment (according to the definition of the National Kidney Foundation) using the Modification of Diet in Renal Disease (MDRD) classification.

Planned Number of Subjects:	The study is planned to enroll up to 32 subjects: 8 subjects with severe renal impairment, 8 subjects with moderate renal impairment, 8 subjects with mild renal impairment, and 8 with normal renal function. Subjects with moderate and mild renal impairment will be enrolled as determined by review of safety and PK data from previous groups.
Main Criteria for Inclusion:	• Male or female aged ≥ 18 years • Body mass index ≥ 18.50 to < 42.00 kg/m^2 • Negative screening for alcohol and drugs of abuse • Non clinically significant findings on 12-lead electrocardiogram (ECG) • For females, negative result on a pregnancy test **Group 1 (Normal Renal Function)** • Presence of normal renal function (eGFR ≥ 90 mL/min/1.73m^2) • Subjects will be matched by age (±10 years), weight (±20%), and gender to the pooled mean values of subjects with the severe renal impairment. **Group 2 (Severe Renal Impairment)** • Presence of severe renal impairment (eGFR< 30 mL/min/1.73m^2) **Group 3 (Moderate Renal Impairment)** • Presence of moderate renal impairment (eGFR 30-59mL/min/1.73m^2) **Group 4 (Mild Renal Impairment)** • Presence of mild renal impairment (eGFR 60-89 mL/min/1.73m^2) Renal function for each subject will be determined at the Screening Visit, calculated using the MDRD classification.
Procedures and Assessments	Safety evaluations including vital signs (body temperature, pulse rate and blood pressure), physical exams, safety laboratory tests (general biochemistry, hematology, urinalysis, pregnancy test, drug, and alcohol screen), ECGs, adverse event (AE) collection, and concomitant medication recording will be conducted prior to and during the treatment period. PK blood samples will be collected at predose and for 36 hours after dosing on Day 1; 18 PK blood samples will be obtained from each patient/subject. PK urine samples will be collected at predose and for 36 hours after dosing on Day 1; 6 PK urine samples will be collected postdose from urine pooled during specified collection intervals.

Criteria for Evaluation:	**Safety:** Safety will be evaluated by assessment of 12-lead safety ECGs, measurements of vital signs, physical examination and clinical laboratory tests at baseline and at various time points during the study, and by the documentation of AEs/concomitant medication. **Pharmacokinetics:** The following plasma and urine PK parameters of lasmiditan will be calculated: C_{max}, T_{max}, AUC_{0-T}, $AUC_{0-\infty}$, $AUC_{0-T/\infty}$, λ_z, T_{half}, Cl_{TOT}/F, V_D/F, Ae(0-t), fe, Cl_r.
Statistical Analyses:	Safety data will be listed by subject and summarized by renal function group using frequency of event/abnormality or descriptive statistical summaries, as appropriate. PK parameters will be listed and summarized by group using descriptive statistics. Mean and individual plasma concentration-time profiles will be presented graphically. A regression analysis in which the estimated renal function and the pharmacokinetic parameters are treated as continuous variables will be used to evaluate the relationship between renal function and the estimated pharmacokinetic parameters of lasmiditan. If the slope is found to be significantly different from zero ($p < 0.05$), and if more than one group of subjects with impaired renal function are enrolled, an analysis of variance will be performed to assess the difference in the PK parameter between the control and each group of subjects with impaired renal function. The 90% confidence interval of the difference will be calculated for each comparison.

LIST OF ABBREVIATIONS

Term	Definition
AE	Adverse event
ANOVA	Analysis of variance
AUC	Area under the curve
BLQ	Below the limit of quantification
C_{max}	Maximum observed concentration
CNS	Central Nervous System
CL	Clearance
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of variation
EOI	End of infusion
GeoCV%	Percent geometric coefficient of variation
GeoMean	Geometric mean
λ_Z	Apparent terminal elimination rate constant
IV	Intravenous
LLOQ	Lower limit of quantification
MDRD	Modification of Diet in Renal Disease
MRT_{∞}	Mean residence time extrapolated to infinity
MTD	Maximum tolerated dose
Min	Minimum
Max	Maximum
n	Number of Observations
NCA	Noncompartmental analysis
PD	Pharmacodynamic
PK	Pharmacokinetic
QA	Quality assurance
QC	Quality control
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SOP	Standard Operating Procedure
T_{half}	Apparent terminal elimination half-life
T_{max}	Time to peak concentration
U.S.	United States

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PROTOCOL APPROVAL

RESEARCH PROTOCOL NUMBER: CUD-P1-001

Sponsor Project No COL MIG-113

TITLE: A PHASE I, MULTICENTER, OPEN-LABEL, PARALLEL-GROUP ADAPTIVE PHARMACOKINETIC SINGLE DOSE STUDY OF ORAL LASMIDITAN IN SUBJECTS WITH NORMAL AND IMPAIRED RENAL FUNCTION

We have read this study protocol and agree that it contains all necessary information required to conduct this study. We agree to conduct the study according to this protocol and in accordance with Good Clinical Practices and the applicable regulatory requirements:

PPD

2017/01/11

Date (yyyy/mm/dd)

PPD

Date (yyyy/mm/dd)

PPD

PPD

2017/01/12

Date (yyyy/mm/dd)

Altasciences
CLINICAL RESEARCH
ALGORITHME PHARMA

PROTOCOL APPROVAL

RESEARCH PROTOCOL NUMBER: CUD-P1-001

Sponsor Project No COL MIG-113

TITLE: A PHASE I, MULTICENTER, OPEN-LABEL, PARALLEL-GROUP ADAPTIVE PHARMACOKINETIC SINGLE DOSE STUDY OF ORAL LASMIDITAN IN SUBJECTS WITH NORMAL AND IMPAIRED RENAL FUNCTION

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PPD

Date (yyyy/mm/dd)

PPD

2017/02/02

Date (yyyy/mm/dd)

PPD

PPD

Date (yyyy/mm/dd)

PROTOCOL APPROVAL

RESEARCH PROTOCOL NUMBER: CUD-P1-001

Sponsor Project No COL MIG-113

TITLE: A PHASE I, MULTICENTER, OPEN-LABEL, PARALLEL-GROUP ADAPTIVE PHARMACOKINETIC SINGLE DOSE STUDY OF ORAL LASMIDITAN IN SUBJECTS WITH NORMAL AND IMPAIRED RENAL FUNCTION

On behalf of the sponsor, I am aware of, and agree to comply with, all of the procedures contained within this protocol:

PPD

_____

Date (yyyy/mm/dd)

1. INTRODUCTION

1.1. Background

CoLucid Pharmaceuticals, Inc. (CoLucid) is developing lasmiditan (COL-144), a small molecule 5-HT_{1F} receptor agonist. The chemical name of lasmiditan (COL-144) is 2,4,6-trifluoro-N-[6-(1-methylpiperidine-4-carbonyl)pyridine-2-yl]benzamide hemisuccinate.

Triptans, which are 5-$HT_{1B/1D}$ receptor agonists, are well established as an acute therapy for migraine, though they are not effective in all patients or attacks. Triptans were developed as cerebral vasoconstrictors, mediated via their affinity for 5-HT_{1B} receptors located on vascular smooth muscle. Inherent in this mechanism of action is a liability for coronary vasoconstriction, and therefore, triptans are contraindicated in patients with cardiovascular disease.

1.2. Nonclinical Studies

Unlike triptans, lasmiditan is a highly selective and potent agonist at the 5-HT_{1F} receptor with >470-fold higher affinity for the 5-HT_{1F} receptor than for 5-$HT_{1B/1D}$ receptors. In preclinical models (rodent) of relevance to migraine, agonists selective for 5-HT_{1F} receptors inhibited trigeminal nociceptive processing without affecting blood vessel tone. Unlike triptans, lasmiditan did not constrict rabbit saphenous vein, an assay predictive of human coronary artery constriction. Lasmiditan is under development as a neurally acting treatment for migraine without the vasoconstrictor liability of triptans.

Safety pharmacology studies (central nervous system [CNS] respiratory, cardiovascular, and renal) employing single intravenous (IV) administration of lasmiditan indicated that administration of lasmiditan at the intended clinically effective exposure levels is unlikely to produce adverse effects on cardiovascular, respiratory or renal function. Based on observations in mice, the neural mechanism of action of lasmiditan may, with exposure to high doses, produce CNS effects such as increased sensitivity to auditory stimuli, analgesia, reduced activity, hypothermia, and anticonvulsant activity. However, there have been no comparable observations in clinical studies, apart from alleviation of headache pain.

1.3. Pharmacokinetics

C_{max} and AUC for subjects dosed orally (200 mg) were also measured in a fed/fasted study (COL MIG-104). During fed conditions (394.7 ng/mL and 2244 ng*h/mL, respectively) PK parameters were slightly increased compared to the fasted condition (322.8 ng/mL and 1892 ng*h/mL, respectively). Hence, food had a minor effect on the PK of lasmiditan.

The plasma clearance (~59 L/h IV and 160 L/h oral), and the high total volume of distribution (~300 L for IV and 1016 L for oral), indicated extensive distribution. There were no significant effects of gender or body weight on PK parameters.

In vitro and in vivo metabolism studies have shown that the metabolic pathways of lasmiditan include N-oxidation, N-dealkylation, carbonyl oxidation, desaturation of the piperidine moiety, ketoreduction, or a combination of each. Up to 12 metabolites have been detected in human hepatocytes, of which none were unique to human. When examined in vivo using LC-MS/MS

analysis of human plasma samples from subjects receiving oral lasmiditan, three major metabolites (M7, M8, and (S,R)-M18) were detected. The relative proportions of metabolites to intact lasmiditan remained reasonably constant throughout the oral dose range studied and their PK were approximately linear.

The half-life of the metabolites fell into two categories; the non-reduced metabolites with a half-life similar to or only slightly longer than intact lasmiditan (~4.5 h), and the reduced metabolites with a half-life distinctly longer (>12 h) than that of lasmiditan.

1.4. Clinical Information

Five Phase 1 studies of lasmiditan have been completed in Europe using IV, sublingual, and oral formulations of lasmiditan in 213 healthy subjects. Two European Phase 2 studies have been completed with lasmiditan in the acute treatment of migraine. COL MIG-301 (SAMURAI) the first of two, Phase 3 randomized, double-blind, placebo controlled trials has completed in the United States. The second confirmatory study, COL MIG-302 (SPARTAN), is ongoing in the US, UK and Germany along with COL MIG-305, the open-label year long dosing study.

Further information on the lasmiditan formulation, animal studies, and human studies can be found in the current Investigator's Brochure.

1.5. Study Rationale

Lasmiditan is excreted through the kidneys. This study was designed to evaluate the effects of impaired renal function on lasmiditan PK parameters, and on its safety. This study will employ a targeted, reduced PK study design in which subjects enrolled will have severe renal impairment with a screening estimated eGFR < 30 mL/min/1.73m^2. Data from these subjects will be compared to matched subjects with normal renal function (eGFR ≥ 90 mL/min/1.73m^2). This approach is consistent with recommendations in the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function-Study Design, Data Analysis, and Impact on Dosing and Labeling". Should substantial changes in exposure be observed, additional groups including subjects with lesser degrees of renal impairment will be enrolled.

Results of this study may inform on lasmiditan dosing recommendation in patients with renal impairment.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to evaluate the pharmacokinetic profile of lasmiditan following a single oral 200 mg dose in subjects with impaired renal function relative to matched, healthy controls with normal renal function.

2.2. Secondary Objectives

The secondary objective of this study is to assess the safety and tolerability of a single oral 200 mg dose of lasmiditan in subjects with normal and impaired renal function.

3. STUDY DESIGN

3.1. General Study Design

This is a multi-center, open-label, non-randomized, parallel-group, adaptive, single dose study.

This study will enroll up to 32 subjects using an adaptive design that can include up to 3 groups of 8 subjects with different degree of renal impairment and one group of 8 control subjects with normal renal function.

Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered in the study.

First, approximately 16 subjects will be enrolled with severe renal impairment and matched subjects with normal renal function. There will be 8 subjects in each of the following groups based on renal function at screening:

- Group 1: Healthy subjects with normal renal function (eGFR ≥ 90 mL/min/1.73m^2)
- Group 2: Severe renal impairment subjects (eGFR < 30 mL/min/1.73m^2)

Based on safety and PK results from subjects with severe renal impairment (Group 2), Group 3 (Moderate Renal Impairment) and Group 4 (Mild Renal Impairment) will be enrolled if substantial change in the exposure of lasmiditan is observed in subjects with severe renal impairment. There will be 8 subjects in each of the following groups based on renal function at screening:

- Group 3: Moderate renal impairment subjects (eGFR 30-59 mL/min/1.73m^2)
- Group 4: Mild renal impairment subjects (eGFR 60-89 mL/min/1.73m^2)

All subjects will participate in one treatment period and will receive a single dose of lasmiditan in the fasting state.

Subjects will be confined to the clinic from 10 hours prior to dosing until 36 hours after drug administration.

The total duration of each subject's participation in the study will be 3 days (Day –1 through the last PK sample taken on Day 2), not including the screening and follow-up phone call.

3.2. Number of Centers and Subjects

The study is planned to enroll up to 32 subjects in 2 centers. Eight subjects will be enrolled in each group. Subjects who withdraw from the study may be replaced. Replacement subjects will be not enrolled for subjects who discontinue the study due to treatment-related AEs.

An effort will be made to include subjects with high BMI, moreover, an effort will be made to enroll more females than males (for an approximate ratio of 60%/40%) or at least 50%/50%.

3.3. Schedule of Drug Administration

The following treatment regimen will be used:

- Experimental treatment: Lasmiditan 200 mg

The total duration of the study is expected to be 35 days, including the screening.

The study may be stopped or interrupted at any time for safety, PK, or administrative reasons.

4. SUBJECT SELECTION

4.1. Study Population

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be eligible for participation in this study. A signed copy of the informed consent form will be provided to each subject.

4.2. Inclusion Criteria

All subjects:

1. Availability for the entire study period
2. Motivated volunteer and absence of intellectual problems likely to limit the validity of consent to participate in the study or the compliance with protocol requirements; ability to cooperate adequately; ability to understand and observe the instructions of the physician or designee
3. Male or female volunteer
4. A female volunteer must meet one of the following criteria:
   - If of childbearing potential – agrees to use one of the accepted contraceptive regimens from at least 28 days prior to the drug administration, during the study and for at least 60 days after the dose. An acceptable method of contraception includes one of the following:
     - Abstinence from heterosexual intercourse
     - Systemic contraceptives (birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch)
     - Intrauterine device (with or without hormones)
     - Condom with spermicide or condom with intra-vaginally applied spermicide
   - If of non-childbearing potential – should be surgically sterile (i.e. has undergone complete hysterectomy, bilateral oophorectomy, or tubal ligation) or in a menopausal state (at least one year without menses)
5. A male volunteer with sexual partners who are pregnant, possibly pregnant, or who could become pregnant must meet the following criteria:

- Participant is unable to procreate, defined as surgically sterile (i.e. has undergone a vasectomy within at least the last 6 months)
- Participant is apt to procreate and agrees to use one of the accepted contraceptive regimens from first drug administration until 3 months after the drug administration. An acceptable method of contraception includes one of the following:
  - Abstinence from heterosexual intercourse.
  - Condom with spermicide or condom with intra-vaginally applied spermicide

6. A male volunteer agrees to refrain from sperm donation from drug administration until 3 months after the drug administration
7. Volunteer aged of at least 18 years
8. Volunteer with a body mass index (BMI) ≥18.50 kg/m^2 and < 42.00 kg/m^2
9. Light-, non- or ex-smokers. A light smoker is defined as someone smoking 10 cigarettes or less per day for at least 3 months before Day 1 of this study. An ex-smoker is defined as someone who completely stopped smoking for at least 6 months before Day 1 of this study
10. Willingness to adhere to the protocol requirements as evidenced by the informed consent form (ICF) duly read, signed and dated by the volunteer

Subjects with Normal Renal Function:

11. Clinical laboratory values within the laboratory's stated normal range; if not within this range, these must be without any clinical significance
12. Have no clinically significant diseases captured in the medical history or evidence of clinically significant findings on physical examination and/or clinical laboratory evaluations (hematology, general biochemistry, electrocardiogram [ECG], and urinalysis)
13. For each gender, have to match by age (± 10 years) and weight (± 20%) to the pooled mean values of subjects with severe renal impairment
14. Have an eGFR ≥ 90 mL/min/1.73m^2 calculated using MDRD equation at screening

Renal Impaired Subjects:

15. Considered clinically stable in the opinion of the Investigator
16. Presence of mild renal impairment (eGFR 60-89 mL/min/1.73m^2), moderate renal impairment (eGFR 30-59 mL/min/1.73m^2), or severe renal impairment (eGFR < 30 mL/min/1.73m^2) calculated using MDRD equation at screening

4.3. Exclusion Criteria

All Subjects:

1. Females who are pregnant or are lactating

2. History of significant hypersensitivity to lasmiditan or any related products (including excipients of the formulations) as well as severe hypersensitivity reactions (like angioedema) to any drugs
3. Suicidal tendency, history of or disposition to seizures, state of confusion, clinically relevant psychiatric diseases
4. Subject is at imminent risk of suicide (positive response to question 4 or 5 on the C-SSRS) or had a suicide attempt within 6 months prior to the screening visit
5. Presence or history of any disorder (including Parkinson disease) that could interfere with completion of the study based on the opinion of the Principal Investigator
6. Any history of tuberculosis and/or prophylaxis for tuberculosis
7. Positive results to HIV Ag/Ab Combo, Hepatitis B surface Antigen (HBsAG (B) (hepatitis B)) or Hepatitis C Virus (HCV (C)) tests
8. Maintenance therapy with any drug or significant history of drug dependency or alcohol abuse (> 3 units of alcohol per day, intake of excessive alcohol, acute or chronic)
9. Use of any enzyme-modifying drugs, including strong inhibitors of cytochrome P450 (CYP) enzymes (such as cimetidine, fluoxetine, quinidine, erythromycin, ciprofloxacin, fluconazole, ketoconazole, diltiazem and HIV antivirals) and strong inducers of CYP enzymes (such as barbiturates, carbamazepine, glucocorticoids, phenytoin, rifampin and St John's Wort), in the previous 28 days before Day 1 of this study
10. Females who are pregnant according to a positive pregnancy test
11. Volunteers who took lasmiditan in the previous 28 days before Day 1 of this study
12. Volunteers who took an Investigational Product (in another clinical trial) in the previous 28 days before Day 1 of this study
13. Volunteers who have already participated in this clinical study
14. Volunteers who donated 50 mL or more of blood in the previous 28 days before Day 1 of this study
15. Donation of 500 mL or more of blood (Canadian Blood Services, Hema-Quebec, clinical studies, etc.) in the previous 56 days before Day 1 of this study

Subjects with Normal Renal Function:

16. Seated pulse rate less than or equal 40 Beats per Minute (bpm) or more than 100 bpm at screening
17. Seated blood pressure below 90/60 mmHg or higher than 140/90 mmHg at screening
18. Presence of significant gastrointestinal, liver, or kidney disease, or any other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs or known to potentiate or predispose to undesired effects

19. History of significant gastrointestinal, liver or kidney disease that may affect drug bioavailability, including but not limited to cholecystectomy
20. Presence of significant cardiovascular, pulmonary, hematologic, neurological, psychiatric, endocrine, immunologic or dermatologic disease
21. Presence of out-of-range cardiac interval (PR < 110 msec, PR > 220 msec, QRS < 60 msec, QRS >119 msec and QTc > 450 msec for males and > 460 msec for females) on the screening ECG or other clinically significant ECG abnormalities
22. Positive screening of alcohol and/or drugs of abuse
23. Any clinically significant illness in the previous 28 days before Day 1 of this study

Renal Impaired Subjects:

24. Seated pulse rate less than 50 bpm or more than 110 bpm at screening
25. Seated blood pressure below 90/50 mmHg or higher than 180/110 mmHg at screening
26. Currently undergoing any method of dialysis
27. History of renal transplant
28. History or presence, in the opinion of the Investigator, of significant clinically unstable respiratory, cardiovascular, pulmonary, hepatic, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or psychiatric disease,
29. Have poorly controlled Type 1 or Type 2 diabetes as defined by Hemoglobin A1c > 10%
30. Require immunosuppressive medications for treatment of immune-mediated renal disease or kidney transplant recipients
31. Evidence of renal carcinoma present at the time of screening
32. Have relevant clinical laboratory abnormalities, including any elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), or bilirubin at screening. If the investigator concludes that there is no safety risk for subjects with isolated laboratory abnormalities (eg, those that do not reflect end-organ dysfunction; for example, elevated bilirubin in Gilbert's subjects) to participate in the study, such cases need to be discussed and approved by the sponsor's medical monitor prior to study enrollment
33. Presence of clinically significant physical, laboratory, or ECG finding that, in the opinion of the Investigator and/or sponsor, may interfere with any aspect of study conduct or interpretation of results
34. Subjects with acute, unstable, or untreated significant medical conditions. Subjects requiring treatment for renal impairment or other chronic disease (eg, well-controlled diabetes, hypertension) must be on a stable treatment plan (medicines, doses, and regimens) for at least 2 weeks (except insulin) prior to Day 1 and during the entire study. Small adjustments in the dosages of some concomitant medications may be permitted during the study, and will be discussed on a case-by-case basis. In all cases, the subjects'

treatment history must be reviewed and their enrollment must be agreed to by both the investigator and the sponsor's medical monitor

35. Positive screening of alcohol and/or drugs of abuse unless results can be explained by a prescription medication
36. Concurrent use of medications known to affect the elimination of serum creatinine (eg, trimethoprim/sulfamethoxazole [Bactrim®] or cimetidine [Tagamet®]) and competitors of renal tubular secretion (eg, probenecid) within 30 days prior to the first dose of study drug or anticipated need for these therapies through the last PK sample

4.4. Withdrawal Criteria

Subjects may voluntarily withdraw from the study, or be removed from the study at the discretion of the Investigator or sponsor at any time. The Investigator may withdraw a subject at any time if it is determined that continuing the study would result in a significant safety risk to the subject.

If such withdrawal occurs, or if the subject fails to return for visits, the Investigator should determine the primary reason for a subject's premature withdrawal from the study and record the reason in the respective subject's study documents. Attempts should be made to have the subject complete the Post-Study tests or Early Termination study procedures.

Premature withdrawal may occur for any of the following reasons:

- A subject who experiences emesis within 5 hours following drug administration will be removed from the study period.
- Noncompliance with the protocol requirements
- Difficulties with blood collection
- Pregnancy
- AE
- Subject request
- Investigator request
- Sponsor request
- Unanticipated event that could result in an inadequately characterized pharmacokinetic profile, such as a missed blood draw, an AE, meal deviations or concomitant medications.
- Subjects who are prematurely withdrawn from the study for reasons other than safety may be replaced by an equal number of newly enrolled subjects at the sponsor's discretion.

5. STUDY TREATMENTS

5.1. Description and Handling of Study Treatments

5.1.1. Formulation of Test Product

Lasmiditan is a new formulation of CCI, which are 5-HT_{1F} receptor agonists, developed by CoLucid Pharmaceuticals, Inc. for oral administration of the acute treatment of migraine. Oral doses of lasmiditan 50 mg, 100 mg and 200 mg are being investigated in Phase 3 clinical trials. Lasmiditan is available in a 200 mg tablets. The Test product used in this study will be provided by the sponsor. See Table 1 for the formulation of lasmiditan.

Table 1: Formulation of Lasmiditan, 200 mg Tablets

Component	Function	Amount 200mg Tablet
Intragranular Components		
Lasmiditan hemisuccinate [a, b]	Active Ingredient	231.28 mg
Microcrystalline cellulose PH102 [b]	Filler	123.47 mg
Starch 1500	Binder	30.0 mg
Croscarmellose sodium	Disintegrant	22.5 mg
Sodium lauryl sulfate	Wetting Agent	2.25 mg
Purified water [c]	Granulating Medium	Qs
Extragranular Components		
Croscarmellose sodium	Disintegrant	31.5 mg
Magnesium stearate (Non-bovine)	Lubricant	9.0 mg
Totals		**450 mg**
Film Coating Materials		
Opadry II White (85F18422) [d]	Film Coat	11.25 mg
Purified water [e]	Suspending Agent	(45.00 mg)

[a] A salt correction factor for the hemisuccinate is assigned as 0.865

[b] Note that the amount of lasmiditan hemisuccinate may be adjusted for purity and moisture content. An adjustment will be made to the amount of microcrystalline cellulose used to maintain tablet weight.

[c] Water for granulation is removed upon drying of the wet mass.

[d] Opadry II White (85F18422) is prepared as a suspension at 20% w/w in Sterile Water for Injection and applied to a target of 2.5% weight gain.

[e] The amount of water may be adjusted to facilitate suspension of the coating agent. This water is removed during processing and does not appear in the final product.

5.1.2. Packaging and Labeling

The sponsor will be responsible for ensuring that the treatment is manufactured in accordance with applicable Good Manufacturing Practice regulations and requirements. All labels for study

drugs will meet applicable requirements of the protocol and the Canadian Health Products and Food Branch.

5.1.3. Storage and Handling

Lasmiditan tablets should be stored by the study site at controlled room temperature of 25°C (77°F); excursions are permitted to 15°C (59°F).

Measures that minimize drug contact with the body should always be considered during handling, preparation, and disposal procedures.

5.2. Method of Assigning Subjects to Treatment Groups

No randomization will be performed for this study. Instead subjects will be categorized into either the control group of healthy volunteers with normal renal function, or into one of the three groups of subjects with varying degrees of renal impairment.

Once a subject number has been assigned to a subject, it will not be reassigned to another subject. Subjects who withdraw from the study may be replaced. Replacement subjects will not be enrolled for subjects who discontinue the study due to treatment-related toxicity. A new unique subject number will be assigned to the replacement subject.

5.3. Blinding

No unblinding procedure is required, as this is an open-label study.

5.4. Dosing and Administration

5.4.1. Dispensing

Designated site staff will dispense study drug in tablet form.

Study drugs will be administered to the subjects under supervision of the study center personnel.

5.4.2. Administration Instructions

Study drug will be administered orally in the morning.

Dosing will be performed by trained personnel and supervised by the Principal Investigator or physician in charge. Adequate time intervals between subjects will be observed to ensure timely blood sampling.

Subjects will be asked to fast overnight (no food or drink, except water) prior to each dosing, for a minimum of 10 hours, at Day -1. Fasting will continue for at least 4 hours following drug administration, after which a standardized lunch will be served. A supper, a light snack and other meals will also be served at appropriate times thereafter, but not before 9 hours after dosing.

Fluid intake other than water will be controlled for housing period and for all subjects. Water will be provided ad libitum until 1 hour pre-dose. The drug will be given with about 240 mL (8 oz.) of water at room temperature. Water will be allowed ad libitum beginning 1 hour after the administration of the drug.

The tablet must be swallowed whole and must not be chewed or broken.

Study medications will be administered to each subject consecutively for the purpose of accurate sampling time. The date and time of each dose must be recorded.

The physician in charge will remain at the clinical site for at least the first 4 hours following drug administration, and will remain available at all times during the study.

5.4.3. Treatment Compliance

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of the Investigator (or designee).
- A mouth and hand check of all subjects will be carried out to ensure that all tablets have been swallowed.

5.4.4. Study Drug Accountability

Complete and accurate records of all study drugs must be kept. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), subject dispensing records, and returned or destroyed study product.

At the conclusion of the study, all unused investigational products and all medication containers will be returned to the sponsor unless the sponsor has approved other arrangements. Drug accountability will be performed at the completion of the trial.

5.5. Prior and Concomitant Medication

Renal-impaired subjects will be permitted to continue taking any prescription or OTC medication necessary for the management of their renal disease or other concurrent illness. The dosing schedules must be stable for 2 weeks (except insulin) before Day 1 of the study and maintained throughout the study. Minor dose changes consistent with treatment practices may be permitted at the discretion of the Investigator. All medications taken during the 14 days prior to dosing will be recorded in the subject's CRF and reviewed by the Investigator. When concomitant medications are administered, the indication, name, dose, route, and frequency will be recorded in each subject's CRF.

For healthy subjects, beside enzyme-modifying drugs that are not allowed for 28 days (refer to exclusion criteria), subjects will be requested to abstain from taking any prescription medications used with the intention to treat a condition for 28 days prior to the first dosing and during the study, unless judged differently by the Principal Investigator or designee. Systemic contraceptives and hormone replacement therapy will be permitted. Subjects will also be requested to abstain from taking any over-the-counter (OTC) products for 7 days prior to the first dosing and during the study. They will be specifically reminded that this includes cold preparations (containing ASA), acetylsalicylic acid (ASA), vitamins and natural products used for therapeutic benefits and antacid preparations. Vitamins used as nutritional supplements in non-therapeutic doses (as judged by the Principal Investigator or designee) may be accepted, but they must be stopped at least 48 hours prior to the first dosing and during the study.

If a medication (including OTC) other than those specified in the protocol is used after the first drug administration or at any time before the end of the study, the Principal Investigator or designee and/or the sponsor will decide whether the subject will be permitted to remain in the study, depending on the drug used, the time of drug intake, etc. The drug and dose will be noted.

5.6. Study-Specific Restrictions

- Subjects will be requested to abstain from alcohol for 48 hours prior to dosing and during study period. Throughout the study (including the return visits), in case of any doubt about alcohol consumption, a test for alcohol may be performed to confirm the physician's judgment.
- During the study, subjects who are light-smokers should not smoke more than 10 cigarettes per day. They will also be instructed to abstain from smoking for 2 hours prior to and until 4 hours after drug administration at study period.
- Subjects will be requested to avoid food or beverages containing xanthines (i.e. tea, coffee, cola drinks, energy drinks or chocolate) for 48 hours prior to dosing and during study period.
- Subjects will be instructed to avoid food or beverages containing grapefruit and/or pomelo for 7 days prior to dosing and during study period.
- Subjects will remain seated for the first 4 hours following drug administration, avoiding both vigorous exertion and complete rest. However, should AEs occur at any time, subjects may be placed in an appropriate position. Subjects will not engage in strenuous activity at any time during the confinement.
- Female volunteers of childbearing potential will have to take appropriate measures to prevent pregnancy for at least 28 days prior to the administration of the study drug, during the study and for at least 60 days after the drug administration, as described in Section 4.2.
- Male subjects who are apt to procreate will be expected to use an acceptable contraceptive regimen from Day 1 of this study, throughout the duration of the entire study, and until at least 3 months after the drug administration, as described in Section 4.2. Condoms with spermicide will be provided to subjects upon departure from the clinical site. In addition to the use of condoms with spermicide, subjects will be informed that it is strongly recommended that their female partner uses one of the two methods listed below:
  - Systemic contraceptives (birth control pills, injectable/ implantable/ insertable hormonal birth control products, transdermal patch).
  - Intrauterine device.
- Male subjects must refrain from sperm donation from the screening and until at least 3 months after the drug administration.

6. STUDY PROCEDURES AND GUIDELINES

Unless otherwise stated in this protocol, clinical site standard operating procedures (SOPs), which are available for all activities relevant to the quality of the study, will be followed during this study. The different parts of this study are summarized in Table 2 and explained in the following sections. The list of assessments for each study parts are indicated with an "X" when

the assessments have to be performed. Any deviation from protocol procedures should be noted in the CRFs and the sponsor should be notified.

Table 2. Schedule of Assessments for all subjects

Examination	Screening	Days			Post-Study Tests or ET[a]	End of Study
	Day 28 to – 1	-1	1	2	2	7 (±3)
Review Inc/Exclusion Criteria & Medical History	X					
Informed Consent	X					
Check-in		X				
Dosing			X			
Clinic Confinement		X	X	X		
Discharge				X		
Demographics	X					
C-SSRS questionnaire	X				X	
Concomitant Medication	X	X	X	X	X	X
Physical Examination	X				X	
Vital Signs	X		X[b]		X	
Height, Weight, and BMI	X					
12-lead ECG	X	X[c]	X[c]		X	
HIV Ag/Ab Combo, HBsAg (B) (Hepatitis B) and HCV (C) Tests	X					
Drug and Alcohol Screen	X	X				
Pregnancy test (females)	X	X			X	
Clinical Laboratory Evaluations	X	X[d]			X	
PK Blood Samples[e]			X	X		
Urine PK Collection[e]			X	X		
Follow-up Call						X
AEs Recording	X	X	X	X	X	

[a] Early Termination (ET).
[b] Vital signs will be measured prior to dosing and approximately 2 and 4 hours after study drug administration.
[c] 12-lead ECG will be performed prior to dosing and approximately 2 hours after study drug administration.
[d] Clinical laboratory tests (hematology, biochemistry, and urinalysis) will be performed in the evening prior to drug administration.
[e] PK blood and urine samples will be collected according to schedule of PK assessments in Table 4.

Table 3. Schedule of Pharmacokinetic Assessments

PK Blood Sampling	Urine PK Collection Intervals
Prior to dosing	Prior to dosing
0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 12, 16, 24 and 36 hours postdose	0-2, 2-4, 4-8, 8-12, 12-24 and 24-36 hours postdose

Time of PK sampling and dosing must be recorded.

6.1. Study Procedures

Safety assessments will include physical examination, vital signs (blood pressure, heart rate, and body temperature), 12-lead ECG, laboratory tests (hematology, biochemistry, and urinalysis), and continuous AE monitoring. Body weight and height will be measured at Screening.

Clinically significant physical examination findings prior to the administration of study drug will be recorded as a medical history; clinically significant findings after the drug administration will be recorded as an AE.

The laboratory tests will be carried out according to the standard operating procedures of the licensed medical laboratory. Abnormal results will be verified to rule out laboratory error. Persistent relevant abnormal values should be followed up until the cause is determined or until the values return to the pre-medication value.

After the ICF is signed, information about all local and systemic clinical events, whether volunteered by the subject, discovered by Investigator questioning, or detected through other means, will be collected, recorded and followed as appropriate.

6.1.1. Physical Examination

A complete physical examination will be performed by a medically qualified and licensed individual as scheduled in Table 2. The physical examination will include a review of the following: head and neck, heart, lungs, abdomen and general appearance.

Demographic data (age, gender, race, body weight adjusted for indoor clothing, height, BMI), and alcohol and smoking habits will be recorded.

During study days, not requiring a complete physical examination, a symptom-targeted physical exam should be done if a new AE is reported, if medically indicated.

6.1.2. C-SSRS Questionnaire

A Columbia Suicide Severity Rating Scale will be performed as scheduled in Table 2.

6.1.3. Vital Signs

Vital sign measurements (body temperature, pulse rate, blood pressure and orthostatic blood pressure) are specified in Table 2. Vital signs can also be monitored during the study when judged necessary by the physician in charge or designee. Vital signs are to be performed prior to blood draws.

6.1.4. Laboratory Evaluations

Laboratory evaluations will be performed as scheduled in Table 2. The physician in charge or designee will assess each abnormal value to determine if it is clinically significant. Postdose clinically significant laboratory values will be reported as AEs.

- General biochemistry: Sodium, potassium, chloride, glucose, blood urea nitrogen (BUN), creatinine, eGFR, total bilirubin, alkaline phosphatase, AST, ALT and albumin
- Hematology: White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and basophil), red cell count, hemoglobin, hemoglobin A1c, hematocrit, mean corpuscular volume (MCV), and platelets count
- Urinalysis: Color, appearance, specific gravity, pH, leukocyte, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. Microscopic examination will only be performed if the dipstick test is outside of the reference range for leukocyte, blood, nitrite or protein
- Serology: HIV Ag/Ab Combo, HBsAg and HCV
- Drug Screen: Alcohol, amphetamines, barbiturates, cannabinoids (THC), cocaine, opiates and phencyclidine (PCP)

6.1.4.1. Pregnancy Tests

A pregnancy test will be performed on female subjects as specified in Table 2.

6.1.5. 12-Lead Electrocardiogram

Twelve-lead ECGs will be performed as specified in Table 2. On study days ECGs are conducted, they should be scheduled prior to blood draws that occur for that day, as the blood draws can impact the ECG reading. Subjects must be in a supine position for 10 minutes prior to ECG.

6.1.6. Follow-up Call

A symptom-directed follow-up telephone call will be made to all subjects following drug administration as specified in Table 2.

6.1.7. Pharmacokinetic Sampling

Blood samples will be collected by direct venipuncture. However, as an option to the volunteer or if judged necessary by the clinical staff, blood samples may be collected from an indwelling cannula (stylet catheter that requires no flushing), which will be placed in the forearm vein of the subject. Blood samples will be kept in an ice-water bath pending processing. Blood samples will be collected in one tube of 6 mL each.

The complete schedule for each part is presented in Table 3. The time of blood sample collection will be calculated according to the drug administration schedule. The clock time of all blood draws will be recorded and reported for all subjects in the CRF. For postdose samples, all deviations from the scheduled sampling time of 2 minutes or more will be reported in the final report.

The total volume of blood withdrawn, including ~21 mL required for screening, on-study and poststudy tests, should not exceed 129 mL per subject.

During the study, a baseline urine sample will be collected before drug administration. After dosing, urine samples will be collected over 36 hours over 6 collection intervals (Table 3). The

total volume of urine collected at each interval will be measured and two containers (~ 5 mL each) will be preserved.

6.1.7.1. Sample processing, storage and shipping

Blood samples will be processed, split, stored, and shipped according to the sample processing instructions supplied by the bioanalytical facility.

Urine samples will be processed, split, stored, and shipped according to the sample processing instructions supplied by the bioanalytical facility.

6.2. Bioanalytical Methods

Plasma and urine lasmiditan concentrations will be measured according to validated bioanalytical methods.

Samples from all subjects who received the investigational product will be assayed.

6.2.1. Aberrant values and retested samples

Unacceptable values attributable to bioanalytical reasons will be determined according to the bioanalytical Facility's SOPs. Such re-assayed samples will be termed "repeats". The method of re-assay and the acceptance criteria for selecting which value to report for the re-assayed samples will follow the bioanalytical Facility's SOPs. All cases of re-assay will be reported in the final report.

No samples will be repeated for pharmacokinetic reasons.

6.2.2. Incurred sample reproducibility

In order to establish the reproducibility of the assay with incurred samples, at least 10% of the total analyzable study samples will be selected and re-assayed. The replicate measurement is not to be averaged with the original one, but both values will be presented in the bioanalytical report with the initial value being used for PK calculations. The concentrations of the original and replicate samples will be tabulated, along with the percent difference between the two values.

6.3. Pharmacokinetic Measurements

The PK parameters are presented in Table 4. Below limit of quantitation concentrations (coded BLQ) will be treated as zero for all PK analyses. All reported sampling time deviations (see Section 6.1.7) will be taken into consideration for evaluation of plasma PK parameters.

The pharmacokinetic parameters will be estimated using a non-compartmental approach with a log-linear terminal phase assumption. The trapezoidal rule will be used to estimate the area under the curve, and the terminal phase will be estimated by maximizing the coefficient of determination estimated from the log-linear regression model. Disposition parameters ($AUC_{0-\infty}$, $AUC_{0-T/\infty}$, λ_Z, T_{half}, Cl_{TOT}/F and V_D/F) will not be estimated for individual concentration-time profiles where the terminal log-linear phase cannot be reliably characterized.

In the case where less than 3 consecutive measurable plasma concentrations of lasmiditan is observed, the AUC parameters will not be estimated.

Table 4. Pharmacokinetic Parameters

PK Parameter	Definition
C_{max}	Maximum observed plasma concentration
T_{max}	Time of maximum observed plasma concentration; if it occurs at more than one time point, T_{max} is defined as the first time point with this value
AUC_{0-T}	Cumulative area under the plasma concentration time curve calculated from 0 to T_{LQC} using the linear trapezoidal method, where T_{LQC} represents time of last observed quantifiable plasma concentration
$AUC_{0-\infty}$	Area under the plasma concentration time curve extrapolated to infinity, calculated as $AUC_T + C_{LQC}/\lambda_Z$, where C_{LQC} is the measured concentration at time T_{LQC}
$AUC_{0-T/\infty}$	Relative percentage of AUC_{0-T} with respect to $AUC_{0-\infty}$
λ_Z	Apparent elimination rate constant, estimated by linear regression of the terminal linear portion of the log concentration *versus* time curve
T_{half}	Terminal elimination half-life, calculated as $\ln(2)/\lambda_Z$
Cl_{TOT}/F	Apparent Total Plasma Clearance, calculated as dose /$AUC_{0-\infty}$
V_D/F	Apparent Volume of Distribution, calculated as dose / λ_Z*$AUC_{0-\infty}$
Ae(0-t)	Amount excreted in urine (Total lasmiditan concentration * Volume of Urine)
fe	Fraction of dose excreted in urine (Ae / dose)
Cl_r	Renal Clearance (Ae(0-t)/AUC_{0-T})

Additional pharmacokinetic parameters may be calculated if deemed appropriate.

Pharmacokinetic analyses will be generated using Phoenix® WinNonlin® Version 6.3 (or higher).

7. ADVERSE EVENTS

7.1. Definitions

An AE is defined as any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. AEs occurring after the initiation of the treatment are referred to as treatment emergent adverse events (TEAEs). An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

An AE may be:

- A new illness,
- Worsening of a concomitant illness,
- An effect of the study medication including comparator; it could be an abnormal laboratory value as well as a significant shift from baseline within normal range which the Principal Investigator or medical qualified designate considers to be clinically important.

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the conditions(s) leading to these measures are not AEs, if the condition(s) was (were) known before the start of study treatment. In the latter case, the condition should be reported as medical history.

A serious adverse event (SAE) or reaction is 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 or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions),
- Is a congenital anomaly or birth defect,

Is an important medical event (including development of drug dependence or drug abuse) that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of the Principal Investigator).

7.1.1. Severity Assessment

All AEs will be graded as mild, moderate, or severe according to the following definitions:

Mild: Causing no limitation of usual activities; the subject may experience slight discomfort.

Moderate: Causing some limitation of usual activities; the subject may experience annoying discomfort.

Severe: Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

Every effort will be made to obtain an adequate evaluation of the severity.

7.1.2. Causality Assessment

The Principal Investigator or a medical qualified designate will determine the relationship of any AE to study drug using the following guidelines in Table 5.

Table 5. Adverse Event Relationship to Study Drug

Relationship to Drug	Comment
Reasonable Possibility	A temporal relationship exists between the AE onset and administration of the investigational product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the investigational product. In case of cessation or reduction of the dose, the AE may abate or resolve and it may reappear upon rechallenge.
No Reasonable Possibility	Evidence exists that the AE has an etiology other than the investigational product. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

7.2. Routine Reporting

For the purposes of this study, the period of observation of AEs extends from the screening visit until the follow-up call. During this period, all AEs spontaneously reported by the subject, observed by the clinical staff, or elicited by general questioning will be recorded and reported in the CRF.

Any AE which remains unresolved as of the last visit will require an evaluation and follow-up until the AE has been resolved or a reasonable explanation for its persistence found, or is deemed mild and safely resolving.

In the case of AEs deemed related to the Investigational Product, every effort will be made to determine the final outcome.

It is the Investigator's responsibility to ensure subjects experiencing AE receive appropriate follow-up, treatment where required, and that every action is well documented.

Subjects will be questioned on their health status at the beginning of study period and before departure from the clinical site. Open-ended questions will be asked.

Subjects will be questioned on their health status at the beginning of the study period and before the departure from the clinical site. Open-ended questions will be asked.

Classification will be performed by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0 or higher.

In general, AEs occurring secondary to other events (eg, clinical sequelae or a cascade of events) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as SAE or AE in the CRF. However,

medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF.

Pregnancy in a female subject on the study shall be reported to the sponsor within 24 hours of the knowledge of its occurrence by the Principal Investigator or designee (for pregnancies occurring during the course of the study or immediately following the end of the study). Because of the possibility that the fetus/embryo could have been exposed to the study drug through the parent and for the subject's safety, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

The pregnancy will be recorded and reported by the Principal Investigator or designee to the sponsor. Pregnancy follow-up will also be properly recorded to ensure quality and completeness of the data belonging to the study drug and will include an assessment of the possible causal relation between the study drug and any pregnancy outcome. Any SAE experienced during pregnancy will be reported on a SAE Report Form.

7.3. Serious Adverse Event Reporting

Algorithme Pharma will notify any SAE to the sponsor, without regard to causality, within 24 hours after becoming aware of its occurrence.

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The initial SAE report must be as complete as possible, including details of the current illness and SAE, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (eg, an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented. All follow-up information must be reported as soon as the relevant info is available.

The notification should be directed to the following sponsor representatives:

PPD

Tel.
Fax. PPD

Email: PPD

An SAE will be considered "unexpected" if the AE is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Algorithme Pharma will determine whether any serious unexpected related AE must be reported to the IRB. If so, the event will be reported via fax or email within 15 calendar days of the investigator or staff becoming aware of the event.

The sponsor will determine whether the SAE must be reported in an expedited manner to the appropriate regulatory agencies. If so, Algorithme Pharma Inc, on the behalf of the sponsor will report the event to the appropriate regulatory agencies, and all participating investigators.

During a clinical trial conducted in Canada, it is required to inform Health Canada of any serious, unexpected adverse drug reaction that has occurred inside or outside Canada:

- Where it is neither fatal nor life-threatening, within 15 days after becoming aware of the information;
- Where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information; and
- Within 8 days after having informed Health Canada of the ADR, submit as complete a report as possible which includes an assessment of the importance and implication of any findings.

If reports of any new and unexpected AEs become available to the sponsor during the clinical portion of this study (related or not to the present study), the sponsor must advise Algorithme Pharma, through its Clinical Investigator, of those events. If required by the sponsor, Algorithme Pharma may advise the Canadian authorities.

8. STATISTICAL ANALYSIS

8.1. Analysis Sets

8.1.1. Safety Analysis Set

The safety population will include all subjects who received the investigational product under study.

8.1.2. Pharmacokinetic Analysis Set

All subjects who received lasmiditan, had no major protocol deviations, and completed the period with evaluable (sufficient and interpretable) data will be included in the PK analysis. Concentration data of the remaining subjects will be presented separately.

If some subjects do not complete the sampling schedule resulting in an inadequately characterized AUC and elimination parameters, samples of these subjects could be included in the statistical pharmacokinetic analysis for only the C_{max} and T_{max} parameters. This decision is to be documented by the SRA department and approved by the sponsor before the start of the sample analysis by the bioanalytical facility.

8.2. Sample Size Determination

There is no formal statistical sample size calculation for this study. A sample size of 32; including 8 subjects/patients for each renal function group (8 subjects with normal renal function 8 patients with mildly impaired renal function, 8 patients with moderately impaired renal function, and 8 with severely impaired renal function) was chosen because it is considered typical for studies evaluating the effect of renal function on the pharmacokinetics of a drug.

8.3. Statistical Analysis

A detailed statistical analysis plan (SAP) describing the methodology to be used will be prepared prior to the completion of the clinical phase of the study. The sections below summarize the data analysis to be undertaken.

8.3.1. Descriptive Analysis

8.3.1.1. Safety Analyses

Data to be listed by subject and summarized by group will include demographic data, AEs, vital signs, ECG parameters, and clinical laboratory evaluations. All values outside the clinical reference ranges will be flagged on the data listings. Other data to be listed by subject will include urinary drug screen, serology results, physical examination findings and concomitant medications.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA Version 19.0 or higher). Concomitant medications will be coded using the World Health Organisation drug dictionary (WHO-DDE March 1st, 2016).

8.3.1.2. Pharmacokinetic Endpoint Analyses

Descriptive statistics will be calculated for plasma concentrations at each individual time point and for all PK parameters. The individual plasma concentration/time profiles will be presented using the actual sampling times whereas the mean plasma concentration/time profiles will be presented using the theoretical sampling times.

8.3.2. Statistical Methodology

The natural logarithmic transformation of $C_{max,}$ $AUC_{0\text{-}T,}$ $AUC_{0\text{-}\infty}$, λ_Z, Ae(0-t), fe, Cl_r, Cl_{TOT}/F and V_D/F as well as the rank-transformation of T_{max} will be used for all statistical inference.

Statistical analyses will be generated using validated SAS® (version 9.4 or higher) using the Reg (and Mixed, if applicable) procedure(s).

The statistical analysis described in this section will be done using both eGFR and Cockcroft-Gault estimate of the creatinine clearance. However, analysis using the eGFR will be considered as the primary analysis and the analysis using the Cockcroft-Gault estimate of the creatinine clearance will be considered as supportive.

Regression Analysis

The eGFR and Cockcroft-Gault estimate of the creatinine clearance at baseline will be used as separate measures of renal function for a regression analysis to evaluate the relationships between estimated renal function and the PK parameters. For each PK parameter, a regression analysis will be performed to assess the impact of impaired eGFR and creatinine clearance (CLCR), using a regression model of the form $\alpha + \beta$*eGFR (or CLCR) + ε where the errors (ε) will be assumed to be independent and normally distributed with mean zero and variance σ^2. The parameter β represents the correlation between the relevant PK parameter and eGFR (or CL_{CR}) which will be treated as a continuous variable.

The hypothesis of the slope of trend being different from zero will be assumed if the two-sided test of the nullity of the parameter β is statistically significant at the 5% level.

Analysis of Variance

Based on the regression analysis described in the previous section, if the slope of trend of the regression analysis between a PK parameter and the estimated renal function (eGFR or CLCR) is found to be significant ($p < 0.05$), and if more than one group of subjects with impaired renal function are enrolled, an analysis of variance (ANOVA) will be performed to assess the difference in the PK parameter among the renal function groups.

The renal function (normal, mild, moderate and severe) will be entered as a fixed effect in the ANOVA model. Pairwise comparisons of renal function groups will be generated using the Tukey-Kramer's procedure of adjustment for multiple comparisons (if more than 2 renal function groups) and statistical significance will be assessed at the two-sided 5% level. The ratio of geometric LS means (of each renal function group being compared), with a corresponding 90% confidence interval (adjusted using Tukey-Kramer's procedure if applicable), will be computed. Heterogeneity of variance among groups will be assumed.

8.3.2.1. Interim Analysis

First, subjects with severe renal impairment and healthy subjects with normal renal function will be enrolled. Samples will be assayed and PK will be performed. If substantial changes in the exposure of lasmiditan are observed in subjects with severe renal impairment compared to subjects with normal renal function, subjects with mild and moderate renal impairment will be enrolled.

Interim analysis of subjects with severe renal impairment and healthy subjects with normal renal function will be performed as described in Section 8.3.2.

9. ETHICS

9.1. Institutional Review Board (IRB)

This protocol and the ICF will be submitted to IRBs (or IECs) (one for each study center) prior to initiation of the study and the study will not start until the Board has approved the documents. Notification of the Board's approval will be appended to the final report.

9.2. Ethical Conduct of the Study

This study will be conducted in compliance with the study protocol, the ethical principles in the latest version of the Declaration of Helsinki, the ICH Guideline E6 for GCP, the FDA GCP Code of Federal Regulations (CFR) Title 21, part 56, European regulation EU 536/2014 and the Tri-Council Policy Statement (Canada).

9.3. Participant Information and Consent

Before inclusion in the study, each prospective subject will be given a full explanation of the purpose of the study, the procedures to be carried out and the potential hazards. Once this essential information is provided to the volunteer and once the physician in charge or designee has the conviction that the volunteer understands the implications of participating in the study, the volunteers will be required to read, sign and date a properly executed written informed consent form prior to enrollment. Subjects will be assured that they may withdraw from the study at any time without jeopardizing their medical care. They will be given a copy of their informed consent form.

If an amended or revised ICF is introduced during the study, each subject's further consent should be obtained.

9.4. Subject Confidentiality

The Investigators and the sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. Subjects should be identified by a unique subject identifier on all study documents provided to the sponsor. In compliance with Federal regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and IRB access to review the subject's original medical records for verification of study-related procedures and data. The investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

10. DATA COLLECTION, RETENTION, AND MONITORING

10.1. Case Report Forms

A CRF is a gathering of all pertinent data collected for each subject included (i.e., who received an Investigational Product treatment) in a clinical trial. Once all CRF forms (including multi-subject CRF forms) are completed and reviewed. At Algorithme Pharma, the complete CRF will be approved and signed by the Study Manager, who received a signature delegation from the Principal Investigator. At the CIUSSS de l'est-de-l'île-de-Montréal - installation Hôpital Maisonneuve-Rosemont, the complete CRF will be approved and signed by the Principal Investigator.

The original source documents and a copy of the corresponding CRFs will be retained by the Investigator. Copies of the CRFs will be provided to the sponsor.

10.2. Data Management and Processing

Data entry will be performed according to clinical site facility procedures. Information will be entered into a Medrio database, which will be used for developing tables and listings for the final study report. Appropriately trained and designated individuals will be given access to the database and will perform entry of the data from the CRFs. The data management process will comply with all regulatory standards and will use from the clinical sites for generating the final locked database.

10.3. Quality Assurance

Designated personnel from Algorithme Pharma will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the portion of the trial conducted in the Algorithme Pharma clinic and the clinical/PK/statistical data are generated, documented and reported in compliance with the protocol and ICH Guideline E6 for Good Clinical Practices. Furthermore, Algorithme Pharma will qualify the vendor(s) or external clinical site(s) used in the conduct of the study.

All parts of the bioanalytical phase of the study and all its documentation will be subject to inspection by the quality assurance unit of the bioanalytical facility to ensure that the data are generated, documented and reported in compliance with the protocol and applicable requirements as outlined in the FDA and OECD Principles of GLP.

10.4. Record Retention

All essential documents and records will be maintained by the study centers for a period of 25 years. These documents may be retained for a longer period if required by the applicable regulatory requirement(s) (FDA CFR 312.57 (C)) or if needed by the sponsor.

10.5. Monitoring of the Study

The sponsor or its representative may visit the study facilities at any time in order to maintain current and personal knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and progress of the study. Algorithme Pharma will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents.

11. ADMINISTRATIVE PROCEDURES

11.1. Adherence to Protocol

Excluding an emergency situation in which proper treatment is required for the protection, safety and well-being of the study subjects, the study will be conducted as described in the approved protocol and performed according to ICH/GCP and FDA guidelines. Any deviation from the protocol will be recorded and explained.

If amendments to the protocol and/or amendments or revisions to the ICF are required, the modifications will be documented and submitted to an IRB for approval.

11.2. Investigator Responsibilities

The form "Qualified Investigator Undertaking" will be signed by the Investigator responsible for the medical decisions and care provided to the subjects (being also referred to as the "Qualified Investigator") at each site prior to the commencement of his responsibilities with respect to the clinical trial, as required by the Food and Drug Regulations. The undertaking form will be maintained with the trial records and will be made available upon request.

In addition, the FDA 1572 form, Statement of Investigator [Title 21, CFR Part 312], duly signed by the Principal Investigator and/or the Principal Investigator (if in charge of clinical assessment) as a condition for conducting the clinical investigation will be kept on file and will be available upon request.

11.3. Delegation of Investigator Duties

The Principal Investigator will ensure that all personnel involved in the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The Principal Investigator will maintain a list of sub-investigator and other appropriately-qualified persons to whom he delegates significant trial-related duties.

Should the Principal Investigator delegate the supervision of the investigational product administration to a designated person, this individual must have the appropriate medical qualifications to effectively conduct or supervise any potential resuscitation procedures.

11.4. Premature Termination or Suspension of a Study

The sponsor or its representative may terminate the study at any time for scientific or corporate reasons.

If the trial is prematurely terminated or suspended for any reason, Algorithme Pharma or the Principal Investigator should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects and should inform the regulatory authority (ies) when required. All procedures should be done according to clinical site procedures.

11.5. Clinical Trial Application (CTA)

A CTA must be submitted to Health Canada prior to the study, and a "No Objection Letter" (NOL) must be obtained before any drug administration.

11.6. Exemption Application for Controlled Substances

This trial does not involve a controlled substance.

11.7. Publications

The preparation and submission for publication of a manuscript containing the study results shall be in accordance with a process determined by mutual written agreement among the study

sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws.

12. REFERENCES

Investigational Brochure, Lasmiditan (COL-144), version 8.0, February 23, 2016

APPENDIX 01
AMENDMENT 01

RATIONALE:

Reason for amendment: To update the blood volume required per PK sample and in the study.

Requested by: CoLucid Pharmaceuticals, Inc.

TEXT OF AMENDMENT:

Amendment 01:

1) **Protocol, p. 32, Section 6.1.7 Pharmacokinetic Sampling, Changed:**

'Blood samples will be collected in one tube of 5 mL each.'

To

'Blood samples will be collected in one tube of 6 mL each.'

2) **Protocol, p. 32, Section 6.1.7 Pharmacokinetic Sampling, Changed:**

'The total volume of blood withdrawn, including ~21 mL required for screening, on-study and poststudy tests, should not exceed 111 mL per subject.'

To

'The total volume of blood withdrawn, including ~21 mL required for screening, on-study and poststudy tests, should not exceed 129 mL per subject.'

3) ICF, p. 5, Section Blood Sampling, Changed:

'The first sample (1 x 5 mL, approximately 1 teaspoon) will be collected prior to the administration of the drug. All other samples (1 x 5 mL each, approximately 1 teaspoon each) will be collected following drug administration.'

To

'The first sample (1 x 6 mL, approximately 1 teaspoon) will be collected prior to the administration of the drug. All other samples (1 x 6 mL each, approximately 1 teaspoon each) will be collected following drug administration.'

4) ICF, p. 5, Section Blood Sampling, Changed:

'The total volume of blood drawn over an approximate 35-day period (including the screening period), including the volume necessary for the laboratory tests, should not exceed 111 mL (about ½ cup) per participant.'

To

'The total volume of blood drawn over an approximate 35-day period (including the screening period), including the volume necessary for the laboratory tests, should not exceed 129 mL (about ½ cup) per participant.'

5) FCE, p. 5, Section Prélèvements sanguins, Changed:

'Le premier échantillon (1 x 5 mL, environ 1 cuillère à thé) sera prélevé avant l'administration du médicament. Tous les autres échantillons (1 x 5 mL chacun, environ 1 cuillère à thé chacun) seront prélevés suivant la prise du médicament.'

To

'Le premier échantillon (1 x 6 mL, environ 1 cuillère à thé) sera prélevé avant l'administration du médicament. Tous les autres échantillons (1 x 6 mL chacun, environ 1 cuillère à thé chacun) seront prélevés suivant la prise du médicament.'

6) FCE, p. 6, Section Prélèvements sanguins, Changed:

'Le volume total de sang prélevé sur une période d'environ 35 jours (incluant la période de sélection), y compris celui nécessaire pour les tests de laboratoire, ne devrait pas excéder 111 mL (environ ½ tasse) par participant.'

To

'Le volume total de sang prélevé sur une période d'environ 35 jours (incluant la période de sélection), y compris celui nécessaire pour les tests de laboratoire, ne devrait pas excéder 129 mL (environ ½ tasse) par participant.'

AUTHORED BY:

PPD

2017/01/11
Date (yyyy/mm/dd)

PPD