Protocol H8H-CD-LAHF

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

NCT03040479

Approval Date: 09-Jan-2016

16.1 STUDY INFORMATION

16.1.1 Protocol and Protocol Amendments

Original Protocol CUD-P9-453 (COL MIG-114)

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

Protocol Number:	CUD-P9-453 (COL MIG-114)
Investigational Product:	Lasmiditan
Sponsor:	CoLucid Pharmaceuticals, Inc. 222 Third Street Suite 1320 Cambridge, MA, USA, 02142
Sponsor's contact person:	PPD PPD Tel. PPD Cell. PPD Email. PPD

Protocol Version		Date
1.0	Original	2017/01/09

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.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

STUDY SYNOPSIS

Name of Sponsor/Company:	CoLucid Pharmaceuticals, Inc.
Name of product:	Lasmiditan
Title of Study:	A Phase I, Multicenter, Open-Label, Parallel-Group, Pharmacokinetic Single Dose Study of Oral Lasmiditan in Subjects with Normal and Impaired Hepatic Function
Study Development Phase:	Phase I
Objectives:	The primary objective of this study is to evaluate the pharmacokinetic profile of lasmiditan following a single oral 200 mg dose in subjects with mild and moderate hepatic function relative to matched, healthy control subjects with normal hepatic 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, mild and moderate hepatic 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, single dose study. This study will enroll up to 24 subjects and will include 2 hepatic-impaired subject groups and one group of control subjects with normal hepatic function. Approximately four subjects with mild hepatic impairment will be enrolled first (Group 1). To ensure subject safety, following dosing of these first four subjects, a safety meeting will take place to review the safety data prior to dosing additional subjects. After safety and PK results from the first four subjects have been reviewed, an additional four subjects with mild hepatic impairment (remainder of Group 1) will be enrolled concurrently with the moderated hepatic impairment group (Group 2). Thereafter, matched subjects with normal hepatic function (Group 3) will be enrolled. 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 at least 10 hours prior to dosing until 36 hours after drug administration.
Duration of Study:	Up to 35 days including Screening.
Study Population:	Male and female adult subjects with normal hepatic function and male and female adult patients with mild or moderate hepatic impairment. Hepatic impairment will be classified using Child-Pugh scores as follows:

	5 to 6 points = Class A, mild hepatic impairment (Group 1); 7 to 9 points = Class B, moderate hepatic impairment (Group 2); Normal hepatic function will be included in Group 3.
Planned Number of Subjects:	The study is planned to enroll up to 24 subjects: 8 subjects with mild hepatic impairment, 8 subjects with moderate hepatic impairment, and 8 healthy subjects with normal hepatic function. Subjects with moderate hepatic impairment will be enrolled as determined by review of safety data from the previously dosed group.
Main Criteria for Inclusion:	• Male or female aged ≥ 18 years • Body mass index ≥ 18.50 kg/m^2 • Non clinical significant findings on 12-lead electrocardiogram (ECG) • For females, negative result on a pregnancy test **Group 1 (Mild Hepatic Impairment)** • Presence of mild hepatic impairment (Child-Pugh Class A) **Group 2 (Moderate Hepatic Impairment)** • Presence of moderate hepatic impairment (Child-Pugh Class B) **Group 3 (Normal Hepatic Function)** • Subjects will be matched by age (±10 years), weight (±20%), and gender to the pooled mean values of subjects with hepatic impairment. Hepatic function will be classified once at the Screening Visit, using the Child-Pugh score for each subject.
Procedures and Assessments	Safety evaluations including vital signs (body temperature, pulse rate and blood pressure), physical exams, safety laboratory tests (clinical chemistry, hematology, endocrinology, 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. Pharmacokinetic (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.
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 adverse events/concomitant medication. **Pharmacokinetics:**

	The following plasma 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 and V_D/F.
Statistical Analyses:	Safety data will be listed by subject and summarized by hepatic function group using frequency of event/abnormality or descriptive statistical summaries, as appropriate. PK parameters will be listed and summarized by hepatic function group using descriptive statistics. Mean and individual plasma concentration-time profiles will be presented graphically. A regression analysis in which the Child-Pugh classification and the pharmacokinetic parameters are treated as continuous variables will be used to evaluate the relationship between hepatic function and the estimated pharmacokinetic parameters of lasmiditan.

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
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
LLOQ	Lower limit of quantification
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

FACILITIES

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PROTOCOL APPROVAL

RESEARCH PROTOCOL NUMBER: CUD-P9-453

Sponsor Project No COL-MIG-114

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

PPD
Coordinating Principal Investigator
Altasciences Company Inc. (doing business as Algorithme Pharma)

2017/01/27
Date (yyyy/mm/dd)

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Principal Investigator
New Orleans Center for Clinical Research

Date (yyyy/mm/dd)

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Principal Investigator
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2017/01/30
Date (yyyy/mm/dd)

PROTOCOL APPROVAL

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Date (yyyy/mm/dd)

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

PPD

Digitally signed by Bernice Kuca
DN: cn=Bernice Kuca, o=CoLucid Pharmaceuticals, Inc, ou, email=bkuca@colucid.com, c=US
Date: 2017.01.31 17:51:15 -05'00'

PPD
PPD
CoLucid Pharmaceuticals, Inc.

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 and seems to have significant extrahepatic metabolism. This study was designed to evaluate the effects of impaired hepatic function on lasmiditan PK parameters, and on its safety.

Results of this study may provide information on lasmiditan dosing recommendations in patients with hepatic 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 mild and moderate hepatic function relative to matched, healthy controls with normal hepatic 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, mild and moderate hepatic function.

3. STUDY DESIGN

3.1. General Study Design

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

This study will enroll up to 24 subjects and will include 2 hepatic impaired subject groups and one group of control subjects with normal hepatic 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.

Approximately four subjects with mild hepatic impairment will be enrolled first (Group 1). To ensure subject safety, following dosing of these first four subjects, a safety meeting will take place to review the safety data prior to dosing additional subjects. After safety and PK results from the first four subjects have been reviewed, an additional four subjects with mild hepatic impairment (remainder of Group 1) will be enrolled concurrently with the moderated hepatic impairment group (Group 2). Thereafter, matched subjects with normal hepatic function (Group 3) will be enrolled. There will be up to 8 subjects in each of the following groups, based on hepatic function at screening:

- Group 1: Mild hepatic impairment subjects (Child-Pugh Class A: 5 to 6 points)
- Group 2: Moderate hepatic impairment subjects (Child-Pugh Class B: 7 to 9 points)
- Group 3: Healthy subjects with normal hepatic function

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 at least 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 24 subjects in 3 centers. Up to 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 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 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 90 days after the drug administration
7. Volunteer aged of at least 18 years
8. Volunteer with a body mass index (BMI) ≥18.5 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 Hepatic 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, endocrinology, electrocardiogram [ECG], and urinalysis)
13. Must match by gender, as well as to the pooled mean values for age (± 10 years) and weight (± 20%) of subjects with hepatic impairment

Hepatic Impaired Subjects:

14. Considered clinically stable in the opinion of the Investigator
15. Presence of mild hepatic impairment (Child-Pugh Class A: 5-6 points) or moderate hepatic impairment (Child-Pugh Class B: 7-9 points) at screening (Appendix A)

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 tests (and HIV I & II screen at OCRC site)
8. Females who are pregnant according to a positive pregnancy test
9. Volunteers who took lasmiditan in the previous 28 days before Day 1 of this study
10. Volunteers who took an Investigational Product (in another clinical trial) in the previous 28 days before day 1 of this study
11. Volunteers who have already participated in this clinical study
12. 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 Hepatic Function:

13. Seated pulse rate less than or equal 50 Beats per Minute (bpm) or more than 100 bpm at screening
14. Seated blood pressure below 90/60 mmHg or higher than 140/90 mmHg at screening
15. 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
16. History of significant gastrointestinal, liver or kidney disease that may affect drug bioavailability
17. Presence of significant cardiovascular, pulmonary, hematologic, neurological, psychiatric, endocrine, immunologic or dermatologic disease
18. 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
19. 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)
20. Positive screening of alcohol and/or drugs of abuse

21. Positive results to Hepatitis B surface Antigen (HBsAG (B) (hepatitis B)) or Hepatitis C Virus (HCV (C)) tests
22. Any clinically significant illness in the previous 28 days before day 1 of this study
23. 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
24. Volunteers who donated 50 mL or more of blood in the previous 28 days before day 1 of this study

Hepatic Impaired Subjects:

25. Seated pulse rate less than 40 bpm or more than 110 bpm at screening
26. Seated blood pressure below 90/50 mmHg or higher than 170/100 mmHg at screening
27. History of hepatic transplant
28. Acute exacerbation of hepatic disease within 14 days of study drug administration
29. History or presence, in the opinion of the Investigator, of significant clinically unstable respiratory, cardiovascular, pulmonary, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, or psychiatric disease
30. Have poorly controlled Type 1 or Type 2 diabetes as defined by Hemoglobin A1c > 10%
31. Evidence of hepatocellular carcinoma present or acute hepatic disease from infection or drug toxicity at the time of screening
32. Presence of severe encephalopathy
33. Presence of surgically-created or transjugular intrahepatic portal systemic shunts
34. History of any major surgery within 6 months before Day 1
35. History of bariatric surgery or any other gastrointestinal surgery that may induce malabsorption
36. Estimated creatinine clearance by Cockcroft-Gault equation < 40 mL/min/1.73 m^2 at screening
37. Presence of clinically significant physical, laboratory, or electrocardiogram (ECG) finding that, in the opinion of the Investigator and/or Sponsor, may interfere with any aspect of study conduct or interpretation of results
38. Subjects with acute, unstable, or untreated significant medical conditions. Subjects requiring treatment for hepatic impairment or other chronic disease (e.g., 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

39. Positive screening of alcohol and/or drugs of abuse unless results can be explained by a prescription medication
40. Volunteers who donated 100 mL or more of blood in the previous 28 days before day 1 of this study

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
- Adverse event (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 adverse event, 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 5-HT_{1F} receptor agonists, developed by CoLucid Pharmaceuticals, Inc. for the acute treatment of migraine. Oral doses of lasmiditan 50 mg, 100 mg and 200 mg are being investigated in Phase 3 clinical trials. The Test product used in this study will be provided by the Sponsor as a single 200 mg oral tablet. 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 the US Food and Drug Administration (FDA).

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-104°F).

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 hepatic function, or into one of the two groups of subjects with varying degrees of hepatic impairment (mild or moderate hepatic 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

The 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.

Subjects will be asked to fast overnight (no food or drink, except water) prior to 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 during the 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, and at adequate intervals, 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

Hepatic-impaired subjects will be permitted to continue taking any prescription or OTC medication necessary for the management of their hepatic disease or other concurrent illness. The dosing schedules for such medications must be stable for 2 weeks before day 1 of the study (except for insulin) 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 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 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 dosing and during the study.

If a medication (including OTC) other than those specified in the protocol is used after dosing 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 the 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.
- 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 adverse events 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 part is indicated with an "X" when the

assessments have to be performed. Any deviation from protocol should be noted in the Case Report Forms (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 & MedicalHistory	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[b]	X		X		X	
Height, Weight, and BMI	X					
12-lead ECG[c]	X		X		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[d]	X	X			X	
PK Blood Sample[e]			X	X		
Follow-up Call						X
Adverse Events Recording	X	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, including orthostatic blood pressure.
[c] 12-lead ECG will be performed prior to dosing and approximately 2 hours after study drug administration.
[d] Clinical laboratory tests (hematology, biochemistry, coagulation (screening only), endocrinology (screening only) and urinalysis) will be performed. On Day -1, these will be done in the evening prior to drug administration.
[e] PK blood samples will be collected according to schedule of PK assessments in Table 3.

Table 3. Schedule of Pharmacokinetic Assessments

PK Blood Sampling
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

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 adverse event (AE) monitoring. Body weight and height will be measured at Screening and BMI will be calculated.

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 adverse events.

- General biochemistry: Sodium, potassium, chloride, glucose, blood urea nitrogen (BUN), creatinine, ClCr, eGFR, total bilirubin, alkaline phosphatase, uric acid (screening only), 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
- Coagulation: PT/INR and PTT levels (screening only)
- 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
- Endocrinology: Ferritin (screening only)
- 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 the study days where 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 recording.

6.1.6. Follow-up Call

A symptom-directed follow-up telephone call will be made to all subjects following drug application 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 ~47 mL required for screening and poststudy tests, should not exceed 155 mL per subject.

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.

6.2. Bioanalytical Methods

Plasma lasmiditan concentrations will be measured according to a validated bioanalytical method.

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. 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 are 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*$AUC_{0-\infty}$

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

An AE may be:

- A new illness,
- Worsening of a concomitant illness,
- An effect of the study medication; 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 adverse events 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 adverse event 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 adverse event 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 adverse events extends from the screening visit until the follow-up call. During this period, all adverse events 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 (e.g., 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 representative:

Bernice Kuca, Head Clinical/Regulatory Operations

CoLucid Pharmaceuticals, Inc.

Tel. PPD

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 adverse event 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 FDA and to the Health Canada Therapeutic Products Directorate (TPD). If so, Algorithme Pharma Inc, on the behalf of the Sponsor will report the event to the FDA, TPD, 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 has to 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 24; including 8 subjects/patients for each hepatic function group (8 subjects with normal hepatic function, 8 patients with mildly impaired hepatic function and 8 patients with moderately impaired hepatic function) was chosen because it is considered typical for studies evaluating the effect of hepatic 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.

Adverse events 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, 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).

Regression Analysis

The Child-Pugh classification at baseline will be used the primary measure of hepatic function for a regression analysis to evaluate the relationships between estimated hepatic function and PK parameters. Hepatic function in affected subjects will be entered in separate regression models as the following:

- Individual Child-Pugh scores;
- Hepatic Impairment Group:

- 1: Child-Pugh classification A;
- 2: Child-Pugh classification B;
- 3: Subject with normal hepatic function

For each PK parameter, a regression analysis will be performed to assess the impact of impaired Hepatic Function, using a regression model of the form $\alpha + \beta*(\text{Hepatic Function}) + \varepsilon$ where the errors (ε) will be assumed to be independent and normally distributed with mean zero and variance $\sigma 2$. The parameter β represents the correlation between the relevant PK parameter and the Hepatic Function 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.

8.3.2.1. Interim Analysis

Approximately four subjects with mild hepatic impairment will be enrolled first (Group 1). To ensure subject safety, following dosing of these first four subjects, a safety meeting will take place to review the safety data prior to dosing additional subjects. After safety and PK results from the first four subjects have been reviewed, an additional four subjects with mild hepatic impairment (remainder of Group 1) will be enrolled concurrently with the moderated hepatic impairment group (Group 2). Thereafter, matched subjects with normal hepatic function (Group 3) will be enrolled.

Interim PK analysis of subjects with mild hepatic function will be performed as described in Section 6.3.

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 clinical sites, 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 trial is conducted and clinical/PK/statistical data are generated, documented and reported in compliance with the protocol and ICH Guideline E6 for Good Clinical Practices.

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

13. APPENDIX A

Child-Pugh Scores

The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

	1 Point	**2 Points**	**3 Points**
Bilirubin, total, µmol (mg/dL)	<34 (<2)	34-50 (2-3)	>50 (>3)
Albumin, mg/L	>35	28-35	<28
INR	<1.7	1.71-2.20	>2.20
Ascites	None	Suppressed with medication	Refractory
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Class A=5-6 points; class B=7-9 points

INR=International Normalized Ratio

Source: http://www.doctorslounge.com/gastroenterology/scores/child.htm