

Protocol H8H-CD-LAHH

A PHASE 1 STUDY TO INVESTIGATE THE ABSORPTION, METABOLISM, AND  
EXCRETION OF [14C]-LASMIDITAN FOLLOWING SINGLE ORAL DOSE  
ADMINISTRATION IN HEALTHY MALE AND FEMALE SUBJECTS

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**16.1.1 Protocol and Amendments**

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AND EXCRETION OF [<sup>14</sup>C]-LASMIDITAN FOLLOWING SINGLE ORAL  
DOSE ADMINISTRATION IN HEALTHY MALE AND FEMALE SUBJECTS**

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Covance Study 8331469

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## ABBREVIATIONS

AUC <sub>extrap</sub>	percentage of AUC that is due to extrapolation from the last measurable concentration
%FR	percentage of lasmiditan recovered in feces
%UR	percentage of lasmiditan recovered in urine
5-HT	serotonin
5-HT <sub>1B</sub>	5-HT 1B receptor
5-HT <sub>1F</sub>	5-HT 1F receptor
AE	adverse event
A <sub>ef</sub>	amount excreted in feces over sampling interval
A <sub>eu</sub>	amount excreted in urine over sampling interval
AME	absorption, metabolism, and excretion
AUC	area under the concentration-time curve
AUC <sub>0-∞</sub>	area under the concentration-time curve extrapolated to infinity
AUC <sub>0-∞</sub> Blood/Plasma Ratio	AUC <sub>0-∞</sub> of total radioactivity in blood/AUC <sub>0-∞</sub> of total radioactivity in plasma
AUC <sub>0-∞</sub> Plasma Lasmiditan/ Total Radioactivity Ratio	AUC <sub>0-∞</sub> of lasmiditan in plasma/AUC <sub>0-∞</sub> of total radioactivity in plasma
AUC <sub>0-t</sub>	area under the concentration-time curve from Hour 0 to the last measurable concentration
BMI	body mass index
CBC	complete blood count
CFR	Code of Federal Regulations
CL/F	apparent oral clearance (for lasmiditan only)
CL <sub>R</sub>	renal clearance
C <sub>max</sub>	maximum observed concentration
CNS	central nervous system
CRF	Case Report Form
C-SSRS	Columbia Suicide Severity Rating Scale
CV%	coefficient of variation
CYP	cytochrome
ECG	electrocardiogram
eCRF	electronic Case Report Form

FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
HIV	human immunodeficiency virus
IB	Investigator Brochure
ICF	Informed Consent Form
IRB	Institutional Review Board
IV	intravenous
$\lambda_z$	apparent terminal elimination rate constant
No.	number
PK	pharmacokinetic(s)
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
$t_{1/2}$	apparent terminal elimination half-life
TFLs	tables, figures, and listings
$t_{max}$	time to maximum concentration
Total %FR	cumulative % FR
Total %UR	cumulative % UR
Total $A_{eu}$	cumulative $A_{eu}$
Total $A_{ef}$	cumulative $A_{ef}$
UA	urinalysis
US	United States
$V_z/F$	apparent volume of distribution
WBC	white blood cell

## 1 SYNOPSIS

Title of Study:	A Phase 1 Study to Investigate the Absorption, Metabolism, and Excretion of [ <sup>14</sup> C]-Lasmiditan Following Single Oral Dose Administration in Healthy Male and Female Subjects
Objectives:	<p>Primary:</p> <ul style="list-style-type: none"> <li>to assess the pharmacokinetics (PK), metabolism, and routes and extent of elimination of a single oral dose of 200 mg (approximately 100 μCi) [<sup>14</sup>C]-lasmiditan in healthy male and female subjects.</li> </ul> <p>Secondary:</p> <ul style="list-style-type: none"> <li>to characterize and identify metabolites of lasmiditan in plasma, urine, and feces;</li> <li>to assess the safety and tolerability of lasmiditan.</li> </ul>
Methodology/Study Design:	<p>This study will be an open-label, nonrandomized, absorption, metabolism, and excretion study of [<sup>14</sup>C]-lasmiditan administered as a 200-mg (approximately 100 μCi) oral solution to 8 healthy male and female subjects, following at least a 10-hour fast from food (not including water).</p> <div style="text-align: center; border: 1px solid black; padding: 5px; margin: 10px 0;"> </div> <p>PK = pharmacokinetic.        Note: Single oral dose of [<sup>14</sup>C]-lasmiditan at 200 mg (approximately 100 μCi) administered orally to subjects in a fasted state.</p> <p>Subjects will be confined at the clinical site from the time of Check-in (Day -1) until Discharge (between Days 9 and 14, inclusive). After completing discharge procedures, subjects will be discharged from the clinical site on Day 14 or as early as Day 9, provided radioactivity has reached all of the following threshold values:</p> <ul style="list-style-type: none"> <li>plasma radioactivity levels below the limit of quantitation; AND</li> <li>≥90% of the dose is recovered; AND</li> <li>urine total radioactivity ≤1% of the administered dose for 2 consecutive 24-hour intervals; AND</li> <li>fecal total radioactivity ≤1% of the administered dose for 2 consecutive 24-hour intervals.</li> </ul> <p>Pharmacokinetic and radioanalytical samples will be obtained through at least 192 hours (8 days) postdose and metabolism samples will be obtained through 96 hours (4 days) postdose.</p>
Number of Subjects:	Eight subjects will be enrolled in order that a minimum of 6 subjects complete the study. Every effort will be made to enroll 4 females and 4 males in this study.

<p>Diagnosis and Main Criteria for Inclusion:</p>	<p>Healthy male and female subjects between 18 and 60 years of age, inclusive, with a body mass index of 18.5 to 32.0 kg/m<sup>2</sup>, inclusive.</p> <p>Females must be nonpregnant, nonlactating, and either postmenopausal (defined as no menstrual period for at least 12 months and confirmed by a serum follicle-stimulating hormone level of <math>\geq 40</math> mIU/mL), surgically sterile (e.g., bilateral oophorectomy, salpingectomy, and/or hysterectomy) for at least 90 days prior to Screening, or must have undergone bilateral tubal ligation and agree to use effective contraception. For all females, the pregnancy test results must be negative at Screening and Check-in.</p>
<p>Test Product(s), Dose, and Mode of Administration:</p>	<p>Subjects will receive a single dose of 200 mg (approximately 100 <math>\mu</math>Ci) lasmiditan as an oral solution after at least a 10-hour fast.</p>
<p>Duration of Treatment:</p>	<p>Planned Enrollment/Screening Duration: up to 28 days        Length of Confinement: Day -1 through Day 9 or up to Day 14        Follow-up Phone Call: 4 <math>\pm</math> 2 days after Discharge        Planned Study Conduct Duration (Screening to Follow-up Phone Call): 13 days (minimum) to 49 days (maximum)</p>
<p>Criteria for Evaluation: Safety</p>	<p>Safety endpoints for this study include: adverse events, clinical laboratory evaluations, vital sign measurements (including orthostatic vital sign measurements), 12-lead electrocardiograms, physical examination findings, and the Columbia Suicide Severity Rating Scale.</p>
<p>Criteria for Evaluation: Pharmacokinetics</p>	<p>The following PK parameters will be calculated, whenever possible, based on the plasma concentrations of lasmiditan and total radioactivity in plasma and blood: maximum observed concentration (<math>C_{max}</math>), time to maximum concentration (<math>t_{max}</math>), area under the concentration-time curve (AUC) from Hour 0 to the last measurable concentration (<math>AUC_{0-t}</math>), AUC extrapolated to infinity (<math>AUC_{0-\infty}</math>), percentage of AUC that is due to extrapolation from the last measurable concentration (<math>\%AUC_{extrap}</math>), apparent terminal elimination rate constant (<math>\lambda_z</math>), apparent terminal elimination half-life (<math>t_{1/2}</math>), apparent oral clearance (<math>CL/F</math>, for lasmiditan only), apparent volume of distribution (<math>V_z/F</math>, for lasmiditan only), <math>AUC_{0-\infty}</math> of total radioactivity in blood/<math>AUC_{0-\infty}</math> of total radioactivity in plasma (<math>AUC_{0-\infty}</math> Blood/Plasma Ratio), and <math>AUC_{0-\infty}</math> of lasmiditan in plasma/<math>AUC_{0-\infty}</math> of total radioactivity in plasma (<math>AUC_{0-\infty}</math> Plasma Lasmiditan/Total Radioactivity Ratio).</p> <p>The following PK parameters will be calculated, whenever possible, based on the urine concentrations of lasmiditan and total radioactivity: amount excreted in urine over sampling interval (<math>A_{eu}</math>), cumulative <math>A_{eu}</math> (Total <math>A_{eu}</math>), renal clearance (<math>CL_R</math>, for lasmiditan only), percentage of lasmiditan recovered in urine (<math>\%UR</math>), and cumulative <math>\%UR</math> (Total <math>\%UR</math>).</p> <p>The following PK parameters will be calculated, whenever possible, based on the fecal concentrations of total radioactivity: amount excreted in the feces over sampling interval (<math>A_{ef}</math>), cumulative <math>A_{ef}</math> (Total <math>A_{ef}</math>), percentage of lasmiditan recovered in feces (<math>\%FR</math>), and cumulative <math>\%FR</math> (Total <math>\%FR</math>).</p> <p>Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the Statistical Analysis Plan.</p> <p>PK parameters for the metabolites of lasmiditan will be calculated, as deemed appropriate, based on plasma, urine, and fecal concentration levels.</p>

Statistical Methods:	Descriptive statistics (mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, etc.) will be calculated for the PK parameters. No formal statistical analyses are planned.
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## 2 INTRODUCTION

### 2.1 Background

Migraine is a common neurological disorder characterized by severe headaches, nausea, photophobia, phonophobia, and vomiting. In its 2010 Global Burden of Disease survey, the World Health Organizations ranked migraine as one of the 7 most debilitating conditions and as the third most common disease in the world in both males and females.

Migraine was previously attributed to cycles of vasoconstriction with reactive vasodilation that activated the nociceptive terminals on the cerebral and extracerebral vasculature. It is now believed that this dilation of cerebral and extracerebral blood vessels is secondary to noxious sensory signals transmitted through the trigeminal system.<sup>1</sup>

The current first-line treatment for migraine is triptans, selective serotonin (5-HT) 1B receptor (5-HT<sub>1B</sub>) agonists. Agonism at 5-HT<sub>1B</sub> results in vasoconstriction and subsequent migraine relief. Because of their vasoconstrictive mechanism, triptans are contraindicated in patients with coronary artery disease. In addition, triptans are associated with a relatively high incidence of neck, jaw, and chest symptoms of unknown etiology that limit tolerability. Concerns about cardiovascular safety are believed to limit the prescription of triptans to less than 50% of those suffering from migraine.<sup>2</sup> There is a large, unmet need to provide migraine treatment for individuals for whom triptans are not an option.

CoLucid Pharmaceuticals, Inc. (CoLucid) is developing lasmiditan (COL-144), a small molecule 5-HT<sub>1F</sub> receptor (5-HT<sub>1F</sub>) agonist. Lasmiditan is intended for the acute treatment of migraine patients with and without aura. In preclinical models relevant to migraine, selective 5-HT<sub>1F</sub> agonists have been shown to inhibit trigeminal nociceptive processing without affecting blood vessel tone. The non-vasoconstrictive mechanism of selective 5-HT<sub>1F</sub> agonists may offer migraine relief to those unable to use triptans.

#### 2.1.1 Nonclinical Background

The primary adverse events (AEs) identified in single- and repeat-dose toxicology studies with intravenous (IV) or oral administration of lasmiditan were central nervous system (CNS)-related and were accompanied by emesis in dogs and reductions in body weight or body weight gain across species. The incidence and severity of CNS-related clinical signs

was dose dependent and onset tended to coincide with the time to maximum observed concentration ( $t_{max}$ ). These signs were transient and spontaneously resolved within 1 and 6 hours, respectively, of IV and oral dosing. Aside from the CNS-related clinical signs, there was no consistent evidence of a common, specific target organ of toxicity across species.

The no-observed-adverse-effect levels calculated from a 26-week repeat-dose study in rats, a 39-week repeat-dose study in dogs, and a 13-week repeat-dose study in mice were 2 to 5 times higher than the projected exposures at the 200-mg dose.

#### **2.1.1.1 Nonclinical Metabolism and Excretion**

Lasmiditan showed negligible *in vitro* metabolism by microsomes and human recombinant cytochromes (CYPs), but there was higher turnover in hepatocytes and S9 fractions, suggesting that metabolism may depend on other enzymes than CYPs. A total of 13 metabolites were detected in incubations with hepatocytes of animal species and 12 with human hepatocytes. No metabolites were unique to humans.

The excretion of drug-related products from rats and dogs dosed with either oral or IV [ $^{14}$ C]-lasmiditan was relatively rapid with the majority excreted within 48 hours of dosing. During the first 48 hours, urinary excretion was approximately 60% in rats and 45% in dogs.

#### **2.1.2 Clinical Background**

Five Phase 1 studies of lasmiditan have been completed using IV, sublingual, and oral formulations of lasmiditan in 213 healthy subjects, two Phase 2 studies have been completed with lasmiditan in the acute treatment of migraine in 393 patients, and one Phase 3 study (COL MIG-301) has been completed with 1239 patients treated with lasmiditan. A second Phase 3 study (COL MIG-302) evaluating 50, 100, and 200 mg lasmiditan compared to placebo in the acute treatment of migraine is ongoing as is a Phase 3, open-label, one-year dosing study to assess long-term safety (COL MIG-305).

In healthy male and female subjects, oral doses of lasmiditan up to 400 mg were not associated with drug-related serious AEs (SAEs) or withdrawals due to AEs. The most frequently reported AEs in all lasmiditan groups were tiredness, drowsiness, dizziness, and paresthesia. At the highest dose of 400 mg lasmiditan, most AEs were mild in intensity and none were severe.



### 2.1.2.1 Clinical Pharmacokinetics

The pharmacokinetics (PK) of lasmiditan were linear with respect to maximum observed concentration ( $C_{\max}$ ) and area under the concentration-time curve (AUC) following administration of 25 to 400 mg lasmiditan as an oral solution. The  $t_{\max}$  was approximately 1.9 hours and the mean terminal elimination half-life ( $t_{1/2}$ ) ranged from 4.66 to 6.38 hours.

In subjects receiving oral lasmiditan, 3 major metabolites (M7, M8, and [S, R]-M18) were detected. These 3 metabolites were pharmacologically inactive against over 40 G protein-coupled receptors, ion channels, and transporters. The non-reduced metabolites exhibited a  $t_{1/2}$  of ~4.5 hours, while the reduced metabolites had a  $t_{1/2}$  greater than 12 hours.

### 2.2 Dose Rationale

A dose of 200 mg was chosen for this study. The 200-mg dose level, currently under investigation as a therapeutic dose in Phase 3 clinical trials, is safe and well tolerated. The radioactive dose will be approximately 100  $\mu\text{Ci}$  in 200 mg of [ $^{14}\text{C}$ ]-lasmiditan (i.e., 0.5  $\mu\text{Ci}/\text{mg}$ ).

Based on data in male and female Lister Hooded rats (with supporting data from male Sprague Dawley rats), the overall whole body radiation dose following administration of a single 100  $\mu\text{Ci}$  dose of [ $^{14}\text{C}$ ]-lasmiditan is calculated to be 65.9 and 77.0 mrem in human male and female subjects, respectively.<sup>3</sup> These values for whole body exposure are well below the FDA exposure limit of 3000 mrem after a single dose for human isotope studies. Based on these results, a single 100- $\mu\text{Ci}$  oral dose of [ $^{14}\text{C}$ ]-lasmiditan is not expected to represent a significant radiation exposure risk to human male or female subjects.

### 2.3 Study Rationale

The purpose of this study is to determine the absorption and excretion kinetics of lasmiditan, and to determine and characterize metabolites present in plasma, urine, and feces in healthy male and female subjects following a single dose of 200 mg (approximately 100  $\mu\text{Ci}$ ) of [ $^{14}\text{C}$ ]-lasmiditan administered as an oral solution.

The optimization of absorption, metabolism, and excretion (AME) parameters is a key part of the drug development process. The characteristics of AME modulate the efficacy

and toxicity of a drug and inform the researcher of the potential impacts of hepatic or renal impairment on drug disposition. It is therefore crucial to understand the clearance mechanism and characteristics of metabolism of a new drug.

It has been established that migranes are more common in the female population, with onset typically occurring during peak child-bearing years. Because lasmiditan will be administered to more females than males, females will be included in this AME study. The inclusion of females in this study will elucidate any relevant differences in lasmiditan AME between male and females.

### **3 STUDY OBJECTIVES**

The primary objectives of this study are:

- to assess the PK, metabolism, and routes and extent of elimination of a single oral dose of 200 mg (approximately 100  $\mu$ Ci) [ $^{14}$ C]-lasmiditan in healthy male and female subjects.

The secondary objectives of this study are:

- to characterize and identify metabolites of lasmiditan in plasma, urine, and feces;
- to assess the safety and tolerability of lasmiditan.

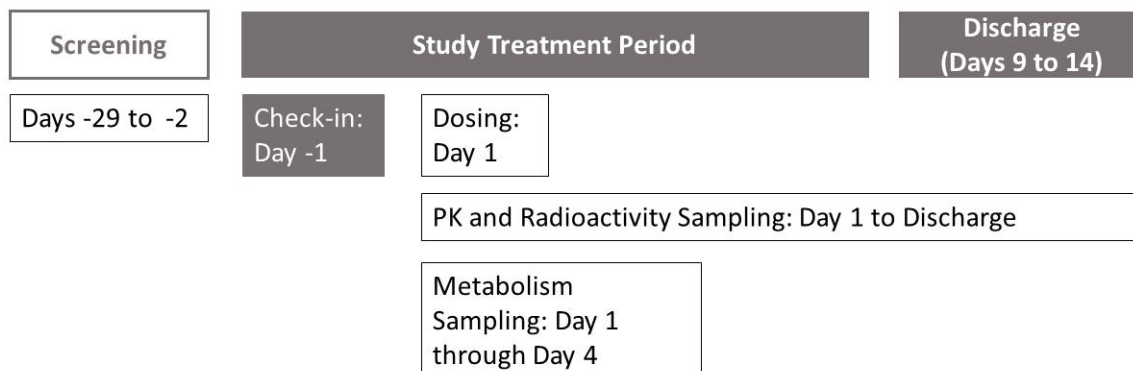
### **4 INVESTIGATIONAL PLAN**

#### **4.1 Study Design**

This study will be an open-label, nonrandomized, AME study of [ $^{14}$ C]-lasmiditan administered as a 200-mg (approximately 100  $\mu$ Ci) oral solution to 8 healthy male and female subjects following at least a 10-hour fast from food (not including water).

A schematic of the study design is presented in [Figure 4-1](#). The start of the study is defined as the date the first subject enrolled in the study signs an Informed Consent Form (ICF). A subject who completes all PK, radioactivity, and metabolism sampling prior to Discharge is considered to have completed the study. The end of the study is defined as the date the last subject completes the Follow-up Phone Call. The planned duration of study conduct is up to approximately 49 days from Screening through the Follow-up Phone Call.

**Figure 4-1 Study Design Schematic**



PK = pharmacokinetic.

Note: Single oral dose of [<sup>14</sup>C]-lasmiditan at 200 mg (approximately 100 µCi) administered orally to subjects in a fasted state.

Subjects will be confined at the clinical site from the time of Check-in (Day -1) until Discharge (between Days 9 and 14, inclusive). After completing discharge procedures, subjects will be discharged from the clinical site on Day 14 or as early as Day 9, provided radioactivity has reached all of the following threshold values:

- plasma radioactivity levels below the limit of quantitation; AND
- $\geq 90\%$  of the dose is recovered; AND
- urine total radioactivity  $\leq 1\%$  of the administered dose for 2 consecutive 24-hour intervals; AND
- fecal total radioactivity  $\leq 1\%$  of the administered dose for 2 consecutive 24-hour intervals.

Sample collection and confinement will continue until discharge criteria are met or the maximum stay (Day 14) is reached, unless otherwise agreed upon by the Sponsor and Investigator. A Follow-up Phone Call will be conducted  $4 \pm 2$  days after Discharge.

Subjects experiencing emesis during the first 4 hours postdose may be discharged on the same day from the clinical site, provided there are no safety concerns, and after follow-up study procedures are performed. Subjects who are discharged from the study early will not be replaced.

Safety will be monitored with AE inquiries, clinical laboratory evaluations ([Appendix A](#)), vital sign measurements (including orthostatic vital sign measurements), 12-lead electrocardiograms (ECGs), physical examination findings, and the Columbia Suicide Severity Rating Scale (C-SSRS) during the study.

Pharmacokinetic and radioanalytical samples will be obtained through at least 192 hours (8 days) postdose and metabolism samples will be obtained through 96 hours (4 days) postdose. A study flow chart is presented in [Table 6-1](#).

## 4.2 Discussion of Study Design

This study is designed to characterize the AME of lasmiditan using radiolabeled drug in healthy adult male and female subjects to support its further development and registration.

The study will be conducted as an open-label trial because the study measures are objective outcomes (e.g., total radioactivity in select biological matrices, metabolite profiling/characterization). Conducting the trial in healthy subjects will allow the evaluation of lasmiditan metabolism in the absence of concomitant medications. The dose, subject population, study duration, and sample collection timing are considered adequate to achieve the study objectives.

## 5 SUBJECT SELECTION

Subjects who meet all the inclusion criteria and for whom none of the exclusion criteria apply will be eligible to be enrolled into the study. Safety evaluations may be repeated at the Investigator's (or designee's) discretion.

Eight subjects will be enrolled to have at least 6 subjects complete the study. Every effort will be made to enroll 4 females and 4 males in this study.

### 5.1 Inclusion Criteria

Subjects who meet the following criteria may be included in the study:

1. males and females, between 18 and 60 years of age, inclusive, at Screening;
2. have a body mass index range of 18.5 to 32.0 kg/m<sup>2</sup>, inclusive, at Screening;
3. in good health, determined by no clinically significant findings from medical history, 12-lead ECG, and vital signs measurements at Screening or Check-in (Day -1) as determined by the Investigator (or designee);
4. clinical laboratory evaluations (including clinical chemistry panel [fasted at least 10 hours], hematology/complete blood count [CBC], and urinalysis [UA]; [Appendix A](#)) within the reference range for the test

- laboratory at Screening and Check-in, unless deemed not clinically significant by the Investigator (or designee);
5. negative test for selected drugs of abuse at Screening (does not include alcohol) and at Check-in (does include alcohol; [Appendix A](#));
  6. negative hepatitis panel (including hepatitis B surface antigen and hepatitis C virus antibody and negative human immunodeficiency virus (HIV) antibody screens ([Appendix A](#)) at Screening;
  7. females must be nonpregnant, nonlactating, and either postmenopausal (defined as no menstrual period for at least 12 months and confirmed by a serum follicle-stimulating hormone [FSH] level of  $\geq 40$  mIU/mL), surgically sterile (e.g., bilateral oophorectomy, salpingectomy, and/or hysterectomy) for at least 90 days prior to Screening, or must have undergone bilateral tubal ligation and agree to use effective contraception as detailed in [Section 6.3.3](#). For all females, the pregnancy test results must be negative at Screening and Check-in;
  8. males will be surgically sterile for at least 90 days prior to Screening or when sexually-active with female partners of child-bearing potential will agree to use contraception as detailed in [Section 6.3.3](#) from Check-in until 90 days following Discharge. Male subjects must also be willing to refrain from donating sperm from Check-in until 90 days following Discharge;
  9. able to comprehend and willing to sign an ICF;
  10. a minimum of 1 to 2 bowel movements per day.

## 5.2 Exclusion Criteria

The following will exclude potential subjects from the study:

1. significant history or clinical manifestation of any metabolic, allergic, infectious, dermatological, hepatic, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, or psychiatric disorder (as determined by the Investigator [or designee]) prior to Check-in;
2. history of significant hypersensitivity, intolerance, or allergy to any drug compound, food, or other substance, unless approved by the Investigator (or designee) prior to Check-in;
3. history of stomach or intestinal surgery or resection that could alter absorption or excretion of orally administered drugs prior to Check-in, except that cholecystectomy, appendectomy, and hernia repair will be allowed if it was not associated with complications;

4. history or presence of an abnormal ECG that, in the Investigator's (or designee's) opinion, is clinically significant at Screening or Check-in;
5. history of orthostatic hypotension with or without syncope;
6. a sustained seated systolic blood pressure >150 mmHg or <90 mmHg or a diastolic blood pressure >90 mmHg or <50 mmHg at Screening or Check-in. Blood pressure may be retested twice at intervals of 5 minutes. The out-of-range blood pressure values will be considered sustained if either the systolic or diastolic blood pressures are outside the stated limits after these 3 assessments;
7. history of alcoholism or drug addiction within 1 year prior to Check-in;
8. use of any tobacco- or nicotine-containing products (including but not limited to cigarettes, e-cigarettes, pipes, cigars, chewing tobacco, nicotine patches, nicotine lozenges, or nicotine gum) within 6 months prior to Check-in, or positive cotinine screen at Screening or Check-in;
9. participation in more than 1 other radiolabeled investigational study drug trial within 12 months prior to Check-in. The previous radiolabeled study drug must have been received more than 6 months prior to Check-in for this study and the total exposure from this study and the previous study will be within the recommended levels considered safe, per United States (US) Title 21 Code of Federal Regulations (CFR) 361.1 (e.g., less than 5,000 mrem whole body annual exposure);
10. exposure to significant radiation (e.g., serial x-ray or computed tomography scans, barium meal, current employment in a job requiring radiation exposure monitoring) within 12 months prior to Check-in;
11. participation in any other investigational study drug trial in which receipt of an investigational study drug occurred within 5 half-lives (if known) or 30 days prior to Check-in, whichever is longer;
12. use of any prescription medications/products within 14 days prior to Check-in, unless deemed acceptable by the Investigator (or designee);
13. use of any over-the-counter, nonprescription preparations (including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations) within 7 days prior to Check-in, unless deemed acceptable by the Investigator (or designee);
14. poor peripheral venous access prior to Check-in;

15. donation of whole blood from 56 days prior to Screening through Discharge, inclusive, or of plasma from 30 days prior to Screening through Discharge, inclusive;
16. receipt of blood products within 2 months prior to Check-in;
17. subject is at imminent risk of suicide (positive response to question 4 or 5 on the baseline C-SSRS) or had a suicide attempt within 6 months prior to the Screening visit;
18. any acute or chronic condition that, in the opinion of the Investigator (or designee), would limit the subject's ability to complete or participate in this clinical study;
19. any other unspecified reason that, in the opinion of the Investigator (or designee) or Sponsor, makes the subject unsuitable for enrollment.

### **5.3 Removal of Subjects from Study Participation**

Subjects will be informed that they are free to withdraw from the study at any time and for any reason. The Investigator (or designee) may remove a subject from the study if, in the Investigator's (or designee's) opinion, it is not in the best interest of the subject to continue the study. Subjects may be withdrawn due to the following: change in compliance with inclusion/exclusion criterion that is clinically relevant and affects subject safety, occurrence of AEs, intake of nonpermitted concomitant medication that might affect subject safety or study assessments/objectives, etc. Notification of withdrawal will immediately be made to the Sponsor's Study Monitor. In case of withdrawal of study participation, efforts will be made to perform all final study day assessments ([Table 6-1](#)). The date the subject is withdrawn from the study and the reason for withdrawal will be recorded on the subject's Case Report Form (CRF). All withdrawn subjects will be followed until resolution of all their AEs or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized.

The entire study may be discontinued at the discretion of the Investigator (or designee), Sponsor, or Sponsor's Medical Monitor based on the occurrence of the following:

- AEs unknown to date with respect to their nature, severity, and/or duration;
- increased frequency and/or severity and/or duration of known AEs;
- medical or ethical reasons affecting the continued performance of the study;
- difficulties in the recruitment of subjects;

- cancellation of drug development.

## **6 STUDY PROCEDURES**

### **6.1 Schedule of Study Procedures**

A study flow chart is presented in [Table 6-1](#). The total blood volume that will be taken during the study is outlined in [Appendix B](#).



**Table 6-1 Study Flow Chart**

	Screening	Check -in									Discharge	Follow-up Phone Call
Study Procedures	Days (-29 through -2)	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	(Day 9 or up to Day 14) <sup>a</sup>	4 ± 2 days after Discharge
Informed Consent	X											
Demographics	X											
Medical History	X	X <sup>b</sup>										
Height, Weight, and BMI	X	X <sup>c</sup>										
Hepatitis and HIV Screen	X											
Alcohol and Drug Screen <sup>d</sup>	X	X										
Pregnancy Test <sup>e</sup>	X	X										
FSH <sup>f</sup>	X											
Confined to the Clinical Site		X	X	X	X	X	X	X	X	X	X	
Physical Examination		X									X <sup>g</sup>	
C-SSRS <sup>h</sup>	X	X		X							X	
Vital Signs <sup>i</sup>	X	X	X	X	X	X	X	X	X	X	X	
Orthostatic Vital Signs <sup>j</sup>	X	X	X									
12-lead ECG <sup>k</sup>	X	X									X	

	Screening	Check -in									Discharge	Follow-up Phone Call
Study Procedures	Days (-29 through -2)	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	(Day 9 or up to Day 14) <sup>a</sup>	4 ± 2 days after Discharge
Clinical Chemistry Panel, Complete Blood Count, Urinalysis	X	X		X							X	
SAE Monitoring <sup>l</sup>	X	X	X	X	X	X	X	X	X	X	X	X
AE Monitoring <sup>m</sup>			X	X	X	X	X	X	X	X	X	X
Prior/Concomitant Medication Monitoring	X	X	X	X	X	X	X	X	X	X	X	X
[ <sup>14</sup> C]-Lasmiditan Administration <sup>n</sup>			X									
Pharmacokinetic/ Radioactivity Blood Samples <sup>o</sup>			X	X	X	X	X	X	X	X	X	
Metabolism Blood Samples <sup>p</sup>			X	X		X	X					
Urine Samples <sup>q</sup>			X	X	X	X	X	X	X	X	X	
Fecal Samples <sup>r</sup>			X	X	X	X	X	X	X	X	X	

AE = adverse event; BMI = body mass index; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; SAE = serious adverse event

<sup>a</sup> Early termination procedures to be performed in close proximity to discontinuation of subject from the study. Other procedures may be performed at Investigator (or designee) or Sponsor discretion.

<sup>b</sup> Interim medical history only.

<sup>c</sup> Weight only.

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<sup>d</sup> Drug screen does not include alcohol testing at Screening but does include an alcohol breath test at Check-in (Day -1).

<sup>e</sup> Females only. A serum pregnancy test will be collected at Screening and Check-in.

<sup>f</sup> To confirm postmenopausal status in females only.

<sup>g</sup> Abbreviated physical examination only.

<sup>h</sup> A baseline version of the C-SSRS survey will be given at Screening and the “since last visit” version of the C-SSRS will be given at Check-in, on Day 2, and at Discharge.

<sup>i</sup> Vital sign measurements (oral temperature, respiratory rate, and seated blood pressure and pulse) will be obtained at single timepoints at Screening, Check-in, and at 1, 2, 4, 24, 48, 72, 96, 120, 168, and 192 hours postdose. If the subject is not discharged on Day 9, additional vital sign measurements will be performed every 24 hours until Discharge. Vital sign measurements will be performed with the subject in a seated position after the subject has rested for at least 5 minutes. When the timepoints for blood draws and vital sign measurements coincide, the vital sign measurements will be collected prior to the blood draws and as close to the scheduled timepoint as possible.

<sup>j</sup> Orthostatic blood pressure and pulse will be obtained at Screening, Check-in, at 0 Hour (predose), and at 1.25, 1.75, and 2.25 hours postdose. Blood pressure and pulse will first be collected with the subject in a seated position after the subject has rested for at least 5 minutes. Blood pressure and pulse will be taken again after the subject has been standing for 2 to 4 minutes. The same arm will be used during each assessment of blood pressure and pulse. When the timepoints for blood draws and orthostatic vital sign measurements coincide, the orthostatic vital sign measurements will be collected prior to the blood draws and as close to the scheduled timepoint as possible.

<sup>k</sup> Single 12-lead ECGs obtained at Screening, Check-in, and Discharge. The 12-lead ECGs will be collected after the subject has been resting in a supine position for at least 10 minutes. When the timepoints for blood draws and ECGs coincide, the ECGs will be collected prior to the blood draws and as close to the scheduled timepoint as possible.

<sup>l</sup> Any SAEs occurring after the subject signs the Informed Consent Form will be recorded.

<sup>m</sup> Subjects will be monitored for AEs beginning at initiation of study drug. An AE inquiry will be performed at each postdose vital sign measurement.

<sup>n</sup> Single oral dose of [<sup>14</sup>C]-lasmiditan at 200 mg (approximately 100 µCi) administered orally to subjects in a fasted state.

<sup>o</sup> Blood samples for pharmacokinetics and radioanalysis will be collected at 0 Hour (predose) and at 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, and 192 hours postdose. If the subject is not discharged on Day 9, additional blood samples will be collected every 24 hours until Discharge. If the plasma radioactivity levels fall below the limit of quantitation, then samples for radioanalysis will no longer be collected.

<sup>p</sup> Blood samples for metabolite profiling and identification collected at 0 Hour (predose) and at 2, 4, 8, 24, 72, and 96 hours postdose.

<sup>q</sup> Urine samples collected at -12 to 0 hours (predose, the last void within 1 hour prior to dosing) and at the following collection intervals: 0 to 6, 6 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, 96 to 120, 120 to 144, 144 to 168, and 168 to 192 hours postdose. If the subject is not discharged on Day 9 (after the 192 hour postdose timepoint), then urine will be collected at 24-hour intervals until Discharge.

<sup>r</sup> If possible, a baseline fecal sample will be collected predose (within 24 hours of dosing). Fecal samples will also be collected daily (24-hour intervals) from Days 1 through 9. If a subject is not discharged on Day 9, then fecal samples will be collected at 24-hour intervals until Discharge.

## 6.2 Study Treatment

### 6.2.1 Drug Supplies and Accountability

The Sponsor (or designee) will provide the Investigator (or designee) with adequate quantities of the study drugs (Table 6-2).

**Table 6-2 Study Drugs**

Study Drug	[ <sup>14</sup> C]-Lasmiditan	Lasmiditan
Form <sup>a</sup>	Powder	Powder
Specific Activity	0.5µCi/mg	Not applicable
Supplier	ARCINOVA Ltd.	Aptuit (UK) Ltd. OR Produits Chimiques Auxillaires et de Synthèse (PCAS)
Manufacturer	ARCINOVA Ltd.	Aptuit (UK) Ltd. OR Produits Chimiques Auxillaires et de Synthèse (PCAS)

<sup>a</sup>Specific ingredients/purity will be identified in the Certificate of Analysis (or equivalent) that is supplied with the study drug(s).

The lot numbers for the study drug(s) will be provided to the clinical site by the supplier/manufacturer as soon as available.

Nonradiolabeled study drugs will be stored at room temperature (between 15°C and 30°C) under secure conditions and protected from light). Radiolabeled study drug will be stored in a freezer set to maintain -80°C (±10°C).

The Investigator (or designee) will maintain an accurate record of the receipt of the clinical trial materials as shipped by the Sponsor (or designee), including the date received. One copy of this receipt will be returned to the Sponsor when the contents of the shipment have been verified. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensation. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor on request.

At the completion of the study, all unused drug supplies will be returned to the Sponsor (or designee) or disposed of by the clinical site, per the Sponsor's (or designee's) written instructions.

### **6.2.2 Subject Number and Identification**

Subjects will be assigned a number by clinical site staff. Assignment of numbers will be in ascending order and no numbers will be omitted. Subject numbers will be used on all study documentation. For subjects who are withdrawn by the Investigator (or designee) or who voluntarily withdraw prematurely from the study, replacement subjects will not be enrolled.

### **6.2.3 Dose Preparation and Administration**

Each unit dose will be prepared by qualified clinical staff. Each unit dose container will be appropriately labeled.

Appropriate unit doses will be administered to consecutively-numbered subjects. Although the timing of events requires that each subject will be consistently administered the appropriate dose at specific times, the exact dose time of consecutive subjects may be staggered to obviate the need to have all subjects on precisely the same study schedule. For each dose, the subject's actual dose time will be recorded in the source documents and transcribed into the CRFs.

Each dose will be administered orally with room temperature water to attain a total volume of 240 mL (dose volume + bottle rinses + room temperature water). A hand and mouth check will be performed to verify that the dose administered was swallowed. Doses will be preceded by an overnight fast (i.e., at least 10 hours) from food (not including water) and will be followed by a fast from food (not including water) for at least 4 hours postdose. Except as part of dose administration, subjects will restrict their consumption of water for 1 hour predose and for 2 hours postdose; at all other times during the study, subjects may consume water ad libitum.

Except when they are using the toilet, study subjects will be observed for approximately 4 hours postdose to monitor potential AEs and/or nausea. Subjects will not lay supine for 1 hour following each dose administered, except as necessitated by the occurrence of an AE(s) and/or study procedures.

### **6.2.4 Blinding**

This is an open-label study.

## **6.3 Study Restrictions**

### **6.3.1 Diet, Fluid, and Activity Control**

Subjects are required to refrain from use of tobacco- or nicotine-containing products within 6 months prior to Check-in until Discharge.

Subjects are required to abstain from consuming alcohol-, grapefruit-, or caffeine-containing foods and beverages for 72 hours prior to Check-in until Discharge, unless deemed acceptable by the Investigator (or designee).

Subjects will refrain from strenuous exercise from 48 hours prior to Check-in until Discharge and will otherwise maintain their normal level of physical activity throughout the entire study (i.e., will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

While confined at the clinical site, subjects will receive a standardized high fiber diet at scheduled times that do not conflict with other study-related activities. Prune juice may be administered on an as-needed basis to aid in normal bowel function and will not be considered a concomitant medication.

### **6.3.2 Concomitant Medications**

Subjects will refrain from participation in any other investigational study drug trial in which receipt of any investigational drug occurred within 5 half-lives (if known) or 30 days, whichever is longer, prior to Check-in until Discharge.

Subjects will also refrain from the use of any prescription medications/products during the interval from 14 days prior to Check-in through Discharge, unless deemed acceptable by the Investigator (or designee). In addition, subjects will refrain from the use of any over-the-counter nonprescription medications (including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations) from 7 days prior to Check-in through Discharge, unless deemed acceptable by the Investigator (or designee).

A mild laxative (i.e., Milk of Magnesia<sup>®</sup>, Colace<sup>®</sup>) may be used to help with bowel movements if necessary. Up to 2 grams per day of acetaminophen may be administered if approved by the Investigator (or designee). Subjects on hormone replacement therapy will be allowed to continue their regimen throughout the study. The administration of any other concomitant medications during the study is prohibited without prior approval of

the Investigator (or designee), unless its use is deemed necessary in a medical emergency. Any medication taken by a subject during the study and the reason for its use will be documented in the source documents and the CRF.

### **6.3.3 Contraception**

Males will be surgically sterile for at least 90 days prior to Screening or must use a male condom with spermicide from Check-in (Day -1) until 90 days following Discharge when sexually-active with female partners of child-bearing potential.

Males will refrain from sperm donation from Check-in until 90 days following Discharge.

Females will be surgically sterile (e.g., bilateral oophorectomy, salpingectomy, and/or hysterectomy) for at least 90 days prior to Screening, postmenopausal, or will have undergone bilateral tubal ligation AND will agree to use 1 of the following methods of contraception from Check-in until 90 days following Discharge:

- diaphragm with spermicide;
- cervical cap with spermicide;
- use by the male partner of a condom with spermicide.

## **6.4 Pharmacokinetic, [<sup>14</sup>C] Radioactivity, and Metabolism Procedures**

### **6.4.1 Pharmacokinetic, [<sup>14</sup>C] Radioactivity, and Metabolism Blood Sample Collection**

Blood samples for PK analysis, total radioactivity, and metabolite profiling and identification will be collected via direct venipuncture. Blood samples will be collected at the timepoints specified in [Table 6-1](#). The number of blood samples and total blood volume required for analysis of PK, radioactivity, and/or for metabolite characterization are presented in [Appendix B](#).

### **6.4.2 Pharmacokinetic, [<sup>14</sup>C] Radioactivity, and Metabolism Urine Sample Collection**

Urine samples for PK analysis, total radioactivity, and metabolite profiling and identification will be collected during the time intervals specified in [Table 6-1](#).

### **6.4.3 [14C] Radioactivity and Metabolism Fecal Sample Collection**

Fecal samples for total radioactivity and metabolite profiling and identification will be collected during the time intervals specified in [Table 6-1](#).

### **6.4.4 Emesis Sample Collection**

For subjects experiencing emesis within 4 hours following dosing, vomitus will be collected. Attempts will be made to collect vomitus from subjects experiencing emesis after 4 hours postdose. All vomitus collected will be stored for possible analysis. The time and date of collection will be recorded on the subject's source documents and CRF. Vomitus will be analyzed as deemed appropriate.

### **6.4.5 Collection of Feminine Hygiene Products**

For female subjects experiencing menses, all feminine hygiene products (e.g., tampons, pads, etc.) will be collected from dosing until Discharge and will be stored for possible future analysis, as determined by the Sponsor. The time and date of collection will be recorded on the subject's source documents and CRF. Feminine hygiene products will be analyzed for radioactivity only as deemed appropriate by the Sponsor (based on the overall recovery data).

### **6.4.6 Analytical Methodology**

Plasma and urine concentrations of lasmiditan will be determined by Covance Laboratories, Inc. using a validated analytical procedure. Total radioactivity concentrations will be determined by Covance Laboratories, Inc. in whole blood, plasma, urine, and feces using liquid scintillation counting. Profiling and characterization of metabolites in plasma, urine, and feces will be conducted by Covance Laboratories, Inc. using standard laboratory procedures. Specifics of the analytical methods will be provided in a separate document.

## **6.5 Safety Procedures**

Safety evaluations may be repeated at the Investigator's (or designee's) discretion.

Every effort will be made to schedule and perform the procedures in accordance with the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint. The order of priority for scheduling procedures around a timepoint is (in descending order of priority):



- dosing
- blood sampling for PK, radioanalysis, and metabolite identification
- start and end of urine and feces collections (for drug assay)
- vital sign measurements
- ECGs
- blood and urine samples for clinical laboratories
- physical examinations
- C-SSRS

### **6.5.1 Adverse Events**

Adverse event definitions (assignment of severity, causality, action taken, and outcome) and procedures for reporting serious AEs are detailed in [Appendix C](#).

Subjects will be asked a nonleading question such as “Have there been any changes in your health status since Screening/since you were last asked?” at the timepoints specified in [Table 6-1](#) to assess for the occurrence of AEs. Subjects will also be encouraged to voluntarily report AEs occurring at any other time during the study.

All nonserious AEs, whether volunteered, reported during AE inquiries, or noted on physical examination, will be recorded from initiation of study drug until study completion. Nonserious AE information should also be collected from the start of a washout period or other observational period intended to establish a baseline status for the subjects. Serious AEs will be recorded from the time the subject signs the ICF until study completion.

All AEs (nonserious and serious) should be followed until the event has resolved, returned to baseline, or is assessed as stable by the Investigator (or designee).

### **6.5.2 Clinical Laboratory Evaluations**

Clinical laboratory evaluations (including clinical chemistry panel [fasted at least 10 hours], CBC, and UA; [Appendix A](#)) will be collected at the timepoints specified in [Table 6-1](#).

Screens for a hepatitis panel and HIV antibody will be performed at Screening. A drug screen for selected drugs of abuse (not including alcohol) will be performed at Screening and repeated (including alcohol) at Check-in.

### **6.5.3 Vital Signs**

Vital sign measurements (including oral temperature, respiratory rate, and seated blood pressure and pulse) will be obtained at the timepoints specified in [Table 6-1](#). Seated blood pressure and pulse will be measured after the subject has been seated for at least 5 minutes.

### **6.5.4 Orthostatic Vital Signs**

Orthostatic vital sign measurements (seated and standing blood pressure and pulse) will be obtained at the timepoints specified in [Table 6-1](#). The seated blood pressure and pulse will be measured after the subject has been seated for at least 5 minutes. The subject will then stand for at least 2 minutes, but no more than 4 minutes, and the standing blood pressure and pulse will be measured.

Postural hypotension will be defined as a drop in blood pressure of >10 mmHg for diastolic blood pressure, >20 mmHg for systolic blood pressure, or an increase of >30 beats per minute in heart rate.

### **6.5.5 Twelve-lead Electrocardiograms**

A 12-lead ECG will be obtained at the timepoints specified in [Table 6-1](#). Subjects will be supine for at least 10 minutes prior to obtaining an ECG measurement.

Electrocardiogram parameters (including heart rate; PR, QRS, and QT intervals; and QT interval corrected for heart rate using Fridericia's formula [QTcF]) and the Investigator's overall interpretation of the ECG will be recorded in the CRF.

### **6.5.6 Physical Examinations**

A routine physical examination will be performed at the timepoints specified in [Table 6-1](#). An abbreviated exam (including exam of general appearance, skin, thorax/lungs, cardiovascular system, and abdomen) will be performed at the timepoints specified in [Table 6-1](#).

The time and date of the physical examination will be recorded in the CRF and any clinically significant findings will be recorded as AEs.

### 6.5.7 Columbia Suicide Severity Rating Scale

The C-SSRS rates an individual's degree of suicidal ideation on a scale ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent". The scale intends to prospectively identify and classify suicidal ideation and behavior based on a semi-structured interview by the Investigator or designee trained in administering the questionnaire. Two versions of the C-SSRS will be used:

- the baseline version will be administered at Screening;
- the "since last visit" version will be administered on Days -1, 2, and at Discharge.

If present, suicidal ideation will be classified in 5 classes (1-5), the intensity of suicidal ideation will be classified in 5 dimensions, and any suicidal behavior will be classified in 6 classes (actual attempt, interrupted attempt, aborted attempt, preparatory acts towards an attempt, suicidal behavior, suicide).

## 7 DATA ANALYSES AND SAMPLE SIZE

### 7.1 Sample Size

The sample size chosen for this study was based on precedent set by other PK studies of similar nature and was not based on power calculations.

### 7.2 Study Populations

The PK population will consist of all subjects who received at least 1 dose of study drug and have evaluable PK data.

The safety population will consist of all subjects who received at least 1 dose of study drug and have at least 1 postdose safety assessment.

### 7.3 Pharmacokinetic Analysis

For each subject, the following PK parameters will be calculated, whenever possible, based on the plasma concentrations of lasmiditan and total radioactivity in plasma and blood, according to the model independent approach<sup>4</sup>:

$C_{\max}$	maximum observed concentration
$t_{\max}$	time to maximum concentration
$AUC_{0-t}$	area under the concentration-time curve (AUC) from Hour 0 to the last measurable concentration, calculated

using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations

$AUC_{0-\infty}$  AUC extrapolated to infinity, calculated using the formula:

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{\lambda_z}$$

where  $C_t$  is the last measurable concentration and  $\lambda_z$  is the apparent terminal elimination rate constant

$\%AUC_{\text{extrap}}$  percentage of AUC that is due to extrapolation from the last measurable concentration to infinity.

$\lambda_z$  apparent terminal elimination rate constant, where  $\lambda_z$  is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase

$t_{1/2}$  apparent terminal elimination half-life (whenever possible), where  $t_{1/2} = \text{natural log } (2)/\lambda_z$

CL/F apparent oral clearance (for lasmiditan only)

V<sub>Z</sub>/F apparent volume of distribution (for lasmiditan only)

$AUC_{0-\infty}$  Blood/Plasma Ratio

$AUC_{0-\infty}$  of total radioactivity in blood/ $AUC_{0-\infty}$  of total radioactivity in plasma

$AUC_{0-\infty}$  Plasma lasmiditan/Total Radioactivity Ratio

$AUC_{0-\infty}$  of lasmiditan in plasma/ $AUC_{0-\infty}$  of total radioactivity in plasma

In addition, the following PK parameters will be calculated, whenever possible, for each subject based on the urine concentrations of lasmiditan and total radioactivity:

$A_{eu}$  amount excreted in urine over sampling interval

Total  $A_{eu}$  Cumulative  $A_{eu}$

$CL_R$  renal clearance, where  $CL_R = A_{eu}/AUC_{0-x}$  (where x is the last interval collected; for lasmiditan only)

$\%UR$  percentage of lasmiditan recovered in urine, where  $\%UR = 100 (A_{eu}/\text{dose})$

Total  $\%UR$  Cumulative  $\%UR$

The following PK parameters will be calculated, whenever possible, for each subject based on the fecal concentration of total radioactivity:

$A_{ef}$	amount excreted in the feces over sampling interval
Total $A_{ef}$	Cumulative $A_{ef}$
% FR	percentage of lasmiditan recovered in feces, where $\%FR = 100 (A_{ef}/dose)$
Total %FR	Cumulative %FR

Pharmacokinetic calculations will be performed, if appropriate, using commercial software such as Phoenix<sup>™</sup> WinNonlin<sup>®</sup> Version 6.4 or higher (Certara USA Inc.).

Pharmacokinetic parameters for the metabolites of lasmiditan may be calculated, as deemed appropriate, based on plasma, urine, and fecal concentration levels.

Other parameters may be added as appropriate. Final PK parameters reported will be detailed in the Statistical Analysis Plan (SAP).

Pharmacokinetic analysis will use actual times as recorded on the CRF. Other data handling procedures will be detailed in the SAP.

#### **7.4 Statistical Analysis of Pharmacokinetic Data**

Descriptive statistics (mean, standard deviation, coefficient of variation [CV%], geometric mean, geometric CV%, etc.) will be calculated for the PK parameters. No formal statistical analyses are planned.

Specification of PK parameters for analysis; statistical level of significance to be used; procedures for accounting for missing, unused, or spurious data; procedures for reporting deviations from the original statistical plan; and selection of subjects to be included in the analyses population(s), as applicable, will be presented in the Clinical Study Report and/or SAP as appropriate.

#### **7.5 Statistical Analyses of Safety Data**

Descriptive statistics will be calculated for the safety parameters. No formal statistical analyses are planned.

For change from baseline calculations, baseline will be defined as the last non-missing safety assessment (including any unscheduled assessments) prior to dose.

## **7.6 Data Handling and Record Keeping**

Any changes to information in the trial progress notes and other source documents will be initialed and dated on the day the change is made by a clinical site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data and clearly entering the correct data (e.g., ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

The Data Management Plan will be approved by the Sponsor.

Data will be validated during data entry by the clinical site and verified by the study monitor. Data will then be reviewed by the data management group to resolve any outstanding issues. Listings will be generated after the database is cleaned by Data Management and will be reviewed by the Covance scientific team. The CRF/electronic Case Report Form (eCRF) and ancillary data will be converted into final SAS datasets following Study Data Tabulation Model or client-provided specifications. The final datasets structure will be verified using Pinnacle 21 OpenCDISC<sup>®</sup>, while the dataset content will be peer-reviewed by an independent programmer.

The tables, figures, and listings (TFLs) will be programmed per the final SAP. All TFLs will be peer-reviewed by an independent programmer. In addition, draft TFLs will be reviewed by the Covance scientific team during the dry run and data review meetings.

The peer-review will be performed by independent programmers following the quality control process and programming checklists.

## **7.7 Quality Control and Quality Assurance**

Quality control and quality assurance will be performed according to Covance standard operating procedures or per client request and as applicable according to the contract between Covance and the Sponsor.

# **8 ADMINISTRATIVE ASPECTS**

## **8.1 Change in Protocol**

There will be no alterations in the protocol without agreement between the Sponsor and the Investigator.

There will be no alterations in the protocol affecting subject safety without the express written approval of the Sponsor, Investigator, and the Institutional Review Board (IRB; see Form FDA 1572).

## **8.2 Site Initiation Visit/Investigator Meeting**

Prior to the start of the clinical study, the representative(s) of the Sponsor will meet with the Investigator(s) and appropriate clinical staff to familiarize the Investigator(s) and clinical staff with the materials necessary for conducting the clinical study.

## **8.3 Disclosure**

All information provided regarding the study, as well as all information collected/documented during the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, in part or in total (e.g., articles in journals or newspapers, oral presentations, abstracts) by the Investigator(s) or their representative(s), shall require prior notification and review, within a reasonable time frame, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

## **8.4 Monitoring**

The Sponsor will designate a Sponsor's Study Monitor who will be responsible for monitoring this clinical trial. The Sponsor's Study Monitor will monitor the study conduct, proper CRF and source documentation completion and retention, and accurate study drug accountability. To this end, the Sponsor's Study Monitor will visit the clinical site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the Sponsor's Study Monitor has access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Sponsor's Study Monitor will adhere to all requirements for subject confidentiality as outlined in the ICF. The Investigator and Investigator's staff will be expected to cooperate with the Sponsor's Study Monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information.

## **8.5 Institutional Review Board**

In accordance with US Title 21 CFR 56, the protocol, advertisement, ICF, and other information provided to subjects will be reviewed and approved by the IRB. The Sponsor will supply relevant material for the Investigator (or designee) to submit to the IRB for the protocol's review and approval. Verification of the IRB unconditional approval of the protocol and the written ICF statement will be transmitted to the Investigator (or designee).

The IRB will be informed by the Investigator (or designee) of subsequent protocol amendments and of serious and unexpected AEs. Approval for protocol amendments will be transmitted in writing to the Investigator (or designee). If requested, the Investigator (or designee) will permit audits by the IRB and regulatory inspections by providing direct access to source data/documents.

The Investigator (or designee) will provide the IRB with progress reports at appropriate intervals (not to exceed 1 year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator's participation in the study.

## **8.6 Informed Consent**

Written informed consent for the study will be obtained from all subjects before protocol-specific procedures are carried out. The ICF will be approved (along with the protocol) by the IRB and will be acceptable to the Sponsor.

The Investigator (or designee) will explain the nature of the study and the action of the test product. The subjects will be informed that participation is voluntary and that they can withdraw from the study at any time. In accordance with 21 CFR 50, the informed consent process shall be documented by the use of a written ICF approved by the IRB and signed by the subject prior to protocol-specific procedures being performed.

The subject will sign 2 copies of the ICF. One copy will be given to the subject, and the other will be maintained with the subject's records.

## **8.7 Records**

The results from data collected at Screening and during the study will be recorded in the subject's CRF (paper or eCRF). To maintain confidentiality, the subjects will be identified only by numbers.



The completed CRFs will be transferred to the Sponsor (or designee). Copies of each CRF will be retained by the Investigator (or designee). All source documents, records, and reports will be retained by the clinical site in accordance with 21 CFR 312.62(c).

All primary data, or copies thereof (e.g., laboratory records, CRFs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the clinical site archives.

### **8.8 Reference to Declaration of Helsinki/Basic Principles**

The study procedures outlined in this protocol will be conducted in accordance with the US CFR governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), IRBs (21 CFR 56), Investigational New Drug Application (21 CFR 312), Applications for FDA Approval to Market a New Drug (21 CFR 314), and Radioactive Drugs For Certain Research Uses (21 CFR 361.1), as appropriate. As such, these sections of US Title 21 CFR, along with the applicable International Conference on Harmonisation Guidelines, are commonly known as Good Clinical Practices, which are consistent with the Declaration of Helsinki.

### **8.9 Financing and Insurance**

Financing and insurance will be addressed in a separate agreement.

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## INVESTIGATOR AGREEMENT

I have read the foregoing protocol and agree to conduct the study as described herein.

PPD

PPD

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Date

PPD

Covance Clinical Research Unit, Inc.

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**SPONSOR AGREEMENT**

I have read the foregoing protocol and agree to conduct the study as described herein:

**PPD**

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PPD

PPD

CoLucid Pharmaceuticals, Inc.

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Date

## REFERENCES

1. Goadsby PJ, Lipton RB, Ferrari MD. Migraine-current understanding and treatment. *N Engl J Med.* 2002;346(4):257-270.
2. Dodick DW, Lipton RB, Martin V, et al. Triptan Cardiovascular Safety Expert Panel. Consensus statement: cardiovascular safety profile of triptans (5-HT agonists) in the acute treatment of migraine. *Headache.* 2004;44:414-425.
3. Potchoiba MJ and Oswald J. Covance 8332113. *Dosimetry Calculations for [<sup>14</sup>C]-Lasmiditan Base on Quantitative Whole-Body Autoradiographic Data in Rats.* Covance Laboratories, Inc.; Madison, Wisconsin; 2016.
4. Gibaldi M, Perrier D. *Pharmacokinetics.* 2nd edition. New York, NY: Marcel Dekker Inc.; 1982.
5. Department of Health and Human Services, Food and Drug Administration. International Conference on Harmonisation; Guidelines on Structure and Content of Clinical Study Reports; Availability. *Federal Register.* 1996;61(138):37320-37343.

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## APPENDIX A - CLINICAL LABORATORY EVALUATIONS

<b>Clinical Chemistry Panel (Fasted):</b>	<b>Complete Blood Count:</b>	<b>Urinalysis:</b>
Alanine aminotransferase	Hematocrit	Bilirubin
Albumin	Hemoglobin	Color and appearance
Alkaline phosphatase	Mean corpuscular hemoglobin	Glucose
Aspartate aminotransferase	Mean corpuscular hemoglobin concentration	Ketones
Blood urea nitrogen	Mean corpuscular volume	Leukocyte esterase
Calcium	Platelet count	Nitrite
Chloride	Red blood cell (RBC) count	Occult blood
Cholesterol	RBC distribution width	pH and specific gravity
Creatinine	White blood cell (WBC) count	Protein
Glucose	WBC differential (absolute):	Urobilinogen
Iron	Basophils	Microscopic exam including
Phosphorus	Eosinophils	bacteria, casts, crystals,
Potassium	Lymphocytes	epithelial cells, RBCs, and
Sodium	Monocytes	WBCs (if protein, leukocyte
	Neutrophils	esterase, nitrite, or blood is
		positive)
Total bilirubin		
Total protein		
Triglycerides		
Uric acid		
<b>Drug Screen:</b>	<b>Other Tests:</b>	<b>Hormone panel – females only:</b>
Including but not limited to the following:	Hepatitis B surface antigen	Follicle-stimulating hormone (postmenopausal females only)
Alcohol (ethanol; via breathalyzer; at Check-in only)	Hepatitis C virus antibody	Serum pregnancy test (human chorionic gonadotropin)
Amphetamines	Human Immunodeficiency Virus antibody	
Barbiturates		
Benzodiazepines		
Cannabinoids		
Cocaine (metabolite)		
Methadone		
Opiates		
Phencyclidine		
Cotinine		

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**APPENDIX B - BLOOD SAMPLING SUMMARY**

Purpose	Maximum Blood Volume per Sample (mL)	Maximum Number of Blood Samples	Maximum Total Volume (mL)
Serology	4	1	4
Pharmacokinetic and total radioactivity sampling	10	23	230
Metabolism sampling	10	7	70
Clinical laboratory tests	8	4	32
Pregnancy tests	4	2	8
FSH tests	4	1	4
Total			348

## APPENDIX C - ADVERSE EVENTS

### 1 ADVERSE EVENTS

#### 1.1 Definition of Adverse Events

An adverse event (AE; or adverse experience) is defined as any untoward medical occurrence experienced by a patient or healthy subject, whether or not considered drug related by the Investigator (or designee). A treatment-emergent AE is an AE that is reported after a dose of study drug.

The following are all AEs:

- unfavorable changes in general condition;
- subjective or objective signs/symptoms;
- concomitant diseases or accidents;
- clinically relevant adverse changes in laboratory parameters observed in a subject during a clinical study.

Adverse events comprise all disturbances of general health status, subjective and objective disease symptoms (including laboratory abnormalities), and accidents observed in the context of a clinical trial, irrespective of a possible causal relationship with the administration of the trial substance. Events occurring in the framework of a clinical trial during drug-free and post-treatment periods, under placebo, or in a reference group receiving drug or nondrug therapy are also to be designated as AEs.

#### 1.2 Categorization of Adverse Events

The severity of AEs will be categorized as follows:

- **MILD** = of little concern to the subject and/or of no clinical significance, is not expected to affect the subject's health or well-being;
- **MODERATE** = discomforting enough to cause interference with or change in usual activities, is likely to require medical intervention or close follow-up;
- **SEVERE** = incapacitating or causing inability to work or participate in many or all usual activities, is of concern to the subject or poses substantial risk to the subject's health or

well-being, is likely to require medical intervention or close follow-up.

The Investigator (or designee) will make a determination of the relationship of the AE to the study drug using a 2-category system according to the following guidelines:

- **Reasonable Possibility** = a plausible temporal relationship exists between the AE onset and administration of the investigational product, and the AE cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be possibly 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 and/or no plausible temporal relationship exists between the AE onset and administration of the investigational product. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

An AE is associated with the use of the drug if there is a reasonable possibility that the experience may have been caused by the drug.

The following categories will be used for the action taken with the study drug for the AE: drug withdrawn, dose not changed, drug interrupted, unknown, and not applicable.

The following categories will be used for the outcome of the AE: resolved, resolved with sequelae, ongoing, fatal, and unknown.

### 1.3 Pregnancy

As information is available, a pregnancy diagnosed during the study will be reported immediately to the Investigator (or designee) or Sponsor, including pregnancy in female partners of male subjects. The pregnancy may be followed to term or outcome and this outcome may be reported to the Sponsor. Pregnancy, in and of itself, is not regarded as an



AE or serious AE (SAE) unless the birth results in a congenital anomaly/birth defect or there is suspicion that the study medication may have interfered with the effectiveness of a contraceptive medication or method.

#### **1.4 Definition of Serious Adverse Events**

An SAE (by Food and Drug Administration [FDA] definition) is any adverse drug experience occurring at any dose that results in any of the following outcomes:

- death;
- a life-threatening adverse drug experience (i.e., places the subject, in the view of the Investigator (or designee), at immediate risk of death);
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant disability/incapacity;
- a congenital anomaly/birth defect;
- important medical event that may require medical or surgical intervention to prevent one of the above outcomes.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. All SAEs must be collected that occur after the subject signs the Informed Consent Form.

#### **1.5 Unexpected Adverse Drug Experience**

An unexpected adverse drug experience is any adverse drug experience, the specificity or severity of which is not consistent with the current Investigator Brochure (IB) or, if an IB is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

#### **1.6 Reporting**

Food and Drug Administration-reportable AEs are AEs that are associated with the use of the drug and are serious and unexpected. Food and Drug Administration-reportable AEs will be reported by the clinical site to the Sponsor, Medical Monitor assigned by the Sponsor, and the responsible Institutional Review Board (IRB).

The Sponsor and Medical Monitor will be notified in writing (e.g., facsimile) within 24 hours of when an AE that is potentially FDA-reportable is first recognized or reported.

Subsequently, a written confirmation or summary of the AE (using FDA Form 3500A, or equivalent) will be sent to the Sponsor within 3 working days of the original notification. (Instructions for completion of FDA Form 3500A may be obtained from the FDA website at [www.fda.gov/medwatch/how.htm](http://www.fda.gov/medwatch/how.htm)).

The IRB will be notified of any FDA-reportable AE within the timeframe required by the IRB. The IRB Serious and Unexpected Adverse Experience Submission Form will be completed and submitted with the copy of the written confirmation or summary of the AE.