

Protocol H8H-CD-LAHG (COL MIG-106)

A Phase I, Randomized, Double-Blind, Placebo-Controlled, 5-Period, Cross-Over Study Assessing the Effects of Lasmiditan on Simulated Driving Performance in Normal Healthy Volunteers

NCT03012334

Approval Date: 06-Dec-2016

CLINICAL TRIAL PROTOCOL: COL MIG-106

Title:	A Phase I, Randomized, Double-Blind, Placebo-Controlled, 5-Period, Cross-Over Study Assessing the Effects of Lasmiditan on Simulated Driving Performance in Normal Healthy Volunteers
Substance Identifier	Lasmiditan
IND number	103,420
Protocol Number	COL MIG-106 Algorithme Pharma Number (CUD-P8-917)
Sponsor	CoLucid Pharmaceuticals, Inc. 222 Third Street, Suite 1320 Cambridge, MA 02142 USA
Principal Investigator	PPD 1200 Beaumont Ave. Mount-Royal, Quebec, Canada H3P 3P1 Phone: PPD
Date of Protocol	6 December 2016
Sponsor Representative	PPD 222 Third Street, sute 1320 Cambridge, MA 02142 Phone: PPD
Amendment #	NA

Confidentiality Statement

The present protocol is property of CoLucid Pharmaceuticals, Inc. and it may not in full or in part be passed on, reproduced, published or otherwise employed without the express permission of CoLucid Pharmaceuticals, Inc..

1 SIGNATURES

1.1 Sponsor's Representative



SIGNATURE

PPD

PPD

Date: 2016.12.13 13:55:18 -05'00'

DATE

1.2 Investigator

I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with Good Clinical Practice guidelines. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in this protocol. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol.

It is obligatory that the Investigator become familiar with all the sections of the lasmiditan Investigator's Brochure prior to initiation of the study.

SIGNATURE

PPD

DATE

2016/12/13

PRINTED NAME

PPD

2 SYNOPSIS

Sponsor: CoLucid Pharmaceuticals, Inc.
Name of Finished Product: Lasmiditan
Name of Active Ingredient: Lasmiditan
Study Title: A Phase I, Randomized, Double-Blind, Placebo-Controlled, 5-Period, Cross-Over Study Assessing the Effects of Lasmiditan on Simulated Driving Performance in Normal Healthy Volunteers
Study Number: COL MIG-106
Study Phase: Phase 1
Primary Objective: <ul style="list-style-type: none">To determine the effects of acute doses of lasmiditan 50 mg, 100 mg and 200 mg compared to placebo and positive control (alprazolam 1.0 mg) on simulated driving performance in healthy subjects as measured by standard deviation of lateral position (SDLP) using the Cognitive Research Corporation Driving Simulator-MiniSim (CRCDS-MiniSim).
Secondary Objective: <ul style="list-style-type: none">To determine the effects of lasmiditan 50 mg, 100 mg, and 200 mg compared to placebo and positive control (alprazolam 1.0 mg) on other measures of simulated driving performance (e.g., speed deviation, lane exceedance and other measures of lane position and speed control, cornering, collisions, and divided attention [DA]), CogScreen Symbol Digit Coding (SDC) test, and self-report measures (i.e., Karolinska Sleepiness Scale (KSS), Visual Analog Scales (VAS) addressing motivation and performance, and if the subject feels safe to drive).

Sponsor: CoLucid Pharmaceuticals, Inc.
Name of Finished Product: Lasmiditan
Name of Active Ingredient: Lasmiditan
Endpoints: Primary Endpoint: <ul style="list-style-type: none">• SDLP Secondary Endpoints: <ul style="list-style-type: none">• Sleepiness Endpoint - KSS• Self-reported readiness to drive (“Right now do you feel safe to drive?”)• VAS to assess subject’s motivation and self-appraisal of their driving performance• Performance Endpoints<ul style="list-style-type: none">▪ CogScreen SDC test<ul style="list-style-type: none">○ CogScreen SDC test○ Number of correct responses○ Response Accuracy○ Standard deviation of reaction time• Driving Performance Endpoints<ul style="list-style-type: none">▪ Lane exceedance; including number, maximum, duration, and area of exceedance▪ Ratio above speed limit, excessive speed count, excessive speed ratio▪ Average speed, speed deviation, speed count, speedings ratio▪ Excessive Ay (cornering speed threshold exceeded)▪ Collision count, off-road crashes, total collisions▪ DA: Correct Responses, Omission Errors, Commission Errors, Reaction Time, Standard Deviation of Reaction Times• Single-dose plasma drug levels and driving performance
Study Design: <p>This will be a randomized, single dose, double-blind, placebo-controlled, Latin-square design with 5-period (full) crossover study with subjects randomized to treatment sequences. Subjects will complete all 5 Periods within the treatment sequence that they are randomized to.</p> <p>Treatments:</p> <ul style="list-style-type: none">• Treatment A: Lasmiditan 50 mg• Treatment B: Lasmiditan 100 mg• Treatment C: Lasmiditan 200 mg• Treatment D: Alprazolam 1 mg

Sponsor:
CoLucid Pharmaceuticals, Inc.

Name of Finished Product:
Lasmiditan

Name of Active Ingredient:
Lasmiditan

- Treatment E: Placebo

Subjects will be randomized equally into one of ten treatment sequences:

Treatment Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
1	A	B	E	C	D
2	B	C	A	D	E
3	C	D	B	E	A
4	D	E	C	A	B
5	E	A	D	B	C
6	D	C	E	B	A
7	E	D	A	C	B
8	A	E	B	D	C
9	B	A	C	E	D
10	C	B	D	A	E

Each Period will be approximately 5 days in duration (5-7 days).

Study drug will be administered by site staff on Day 1 of each Period. Subjects will wear a blindfold when taking each dose to maintain the blind. The tablet size and shape are deemed similar enough to maintain the blind with a blindfolded subject.

Testing is conducted 1.5 hours post-dose (on Days 1, 7, 14, 21, and 28 of each Period).

Schematic of Design:

Period 1 → Washout 1 → Period 2 → Washout 2 → Period 3 → Washout 3 → Period 4 → Washout 4 → Period 5 → EOS
Day 1 Days 2-6 Day 7 Days 8-13 Day 14 Days 15-20 Day 21 Days 22-27 Day 28 Day 35

A sufficient number of subjects will be enrolled to complete 80 healthy volunteers in the 5-period crossover study. The washout between Periods will be at least 5 days. Subjects will be evaluated following a single dose.

The positive control (alprazolam 1.0 mg) is included to establish the sensitivity of the study endpoints to detecting residual sedation.

Screening (Visit 1) will include procedures as described in the Schedule of Activities and further in the protocol. Prior to randomization, subjects will be screened for simulator sickness and will receive standardized training on the driving simulator and cognitive test battery. Screening procedures and screening assessments may be performed on different days but must be

Sponsor: CoLucid Pharmaceuticals, Inc.
Name of Finished Product: Lasmiditan
Name of Active Ingredient: Lasmiditan
completed within 28 days before Period 1 (Visit 2). The Familiarization and Practice drives on the driving simulator must be completed no more than 21 days prior to Period 1. <u>Treatments within each Period</u> Subjects will return to the site where, according to the randomization schedule, they will be assigned and dosed with study medication (lasmiditan, alprazolam or placebo). Prior to dosing (the evening of clinical research unit [CRU] admission) they will complete a 20-minute practice drive on the CRCDS-MiniSim and a practice trial on the CogScreen SDC test. Within approximately 85 minutes of dosing, subjects will perform the CogScreen SDC Test, KSS, and indicate their self-perceived safety to drive. Subjects will then perform the Country Vigilance-Divided Attention (CVDA) driving scenario on the CRCDS-MiniSim commencing approximately 90 minutes (1.5 hours) post-dosing. Upon completion of the driving scenario subjects will be administered a VAS to assess subject's motivation and self-appraisal of their driving performance. Subjects will leave the clinical site at approximately 24-hour post-dose. Blood draws for pharmacokinetics will be taken during the Periods predose and approximately 155 minutes (-15 to +30 minutes) post-dose. The total duration of subject participation will be approximately 5 weeks (range 5-7 weeks).
Subject Population: <u>Inclusion Criteria:</u> <ol style="list-style-type: none">1. Able and willing to voluntarily consent to participate in this study and provide written informed consent prior to start of any study-specific procedures.2. Males and females between the ages of 21 and 50 years of age (inclusive). No more than 60% of one gender will be enrolled on the study.3. Body Mass Index (BMI) between 18 and 32 kg/m² (inclusive).4. Subject is able to reliably perform study assessments (SDLP no higher than 1 standard deviation greater than the mean for normal healthy adults completing the practice scenario; SDC Correct no less than 1 standard deviation below the mean for healthy adults in their age range); demonstrates the ability to understand task instructions, and is physically capable (e.g., adequate manual dexterity, vision, and hearing) and cognitively capable of performing study tasks.5. Subject possesses a valid driver's license and is an active driver. Drives a minimum of 10,000 miles (about 16,000 km) per year for the previous 3 years.

Sponsor: CoLucid Pharmaceuticals, Inc.
Name of Finished Product: Lasmiditan
Name of Active Ingredient: Lasmiditan
<ol style="list-style-type: none">6. Subject must also demonstrate simulator sickness questionnaire scores which are not indicative of simulator sickness as defined in the driving simulation operations manual.7. Subject has a regular sleep pattern, are not engaged in shift-work, and in general, have at least 7 hours of sleep each night (bedtime occurs between 21:00 and 24:00 hours).8. Subject has a score < 10 on the Epworth Sleepiness Scale.9. Use of a medically highly effective form of birth control during the study and for thirty (30) days:<ol style="list-style-type: none">a. A female volunteer must meet one of the following criteria:<ol style="list-style-type: none">i. 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:<ol style="list-style-type: none">ii. Abstinence from heterosexual intercourseiii. Systemic contraceptives (birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch)iv. Intrauterine device (with or without hormones)v. Condom with spermicide or condom with intra-vaginally applied spermicidevi. 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)b. A male volunteer with sexual partners who are pregnant, possibly pregnant, or who could become pregnant must meet the following criteria:<ol style="list-style-type: none">i. Participant is unable to procreate, defined as surgically sterile (i.e. has undergone a vasectomy within at least the last 6 months)ii. 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

Sponsor: CoLucid Pharmaceuticals, Inc.
Name of Finished Product: Lasmiditan
Name of Active Ingredient: Lasmiditan
<p>includes one of the following:</p> <ul style="list-style-type: none">iii. Abstinence from heterosexual intercourse.iv. Condom with spermicide or condom with intra-vaginally applied spermicide <p>c. A male volunteer agrees to refrain from sperm donation from drug administration until 3 months after the drug administration.</p> <p>10. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.</p> <p><u>Exclusion Criteria:</u></p> <ul style="list-style-type: none">1. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, neurological, oncologic, or psychiatric disease or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.2. A history within 2 years of, or current treatment for a sleeping disorder (including excessive snoring, obstructive sleep apnea), or a chronic painful condition that interferes with the subject's sleep.3. A history of difficulty in falling asleep or staying asleep in the previous 3 months, that is considered clinically significant by the investigator.4. Subject has a history or diagnosis of any of the following conditions:<ul style="list-style-type: none">a. Primary or secondary insomniab. Narcolepsyc. Cataplexy (familial or idiopathic)d. Circadian Rhythm Sleep Disordere. Parasomnia including nightmare disorder, sleep terror disorder, sleepwalking disorder, and rapid eye movement behavior disorderf. Sleep-related Breathing Disorder (obstructive or central sleep apnea syndrome, central alveolar hypoventilation syndrome)g. Periodic Limb Movement Disorderh. Restless Legs Syndromei. Primary Hypersomnia

Sponsor: CoLucid Pharmaceuticals, Inc.
Name of Finished Product: Lasmiditan
Name of Active Ingredient: Lasmiditan
<ul style="list-style-type: none">j. Excessive Daytime Sleepiness (EDS)k. Subject has visual or auditory impairment which in the opinion of the investigator would interfere with study related procedures or study conduct. <ul style="list-style-type: none">5. Expected to use any other medication or dietary supplement to promote sleep including over-the-counter sleep medications, during their participation in the study.6. Subject consumes excessive amounts of coffee, tea, cola, or other caffeinated beverages per day. Excessive amount is defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine)7. Subject has traveled across 1 or more time zones (transmeridian travel) in the last 2 weeks prior to randomization or is expected to travel across 1 or more time zones during the study.8. Expected to work on a rotating shift during their participation in the study.9. Subject works a night shift.10. History or presence of seizure disorder.11. History of urinary retention, angle closure glaucoma, or increased ocular pressure.12. History of gastrointestinal tract surgery, except appendectomy.13. Has abnormal finding on the physical exam, medical history, electrocardiogram (ECG), or clinical laboratory results at Screening, that are considered clinically significant by the investigator.14. Presence of out-of-range cardiac interval (PR < 110 msec, PR > 200 msec, QRS < 60 msec, QRS > 110 msec and QTc > 440 msec) on the screening ECG or other clinically significant ECG abnormalities15. History of orthostatic hypotension, fainting spells, or blackouts, that are considered clinically significant by the investigator.16. The presence of chronic or acute infections, that are considered clinically significant by the investigator.17. History of allergy/hypersensitivity (including drug allergies) that are deemed relevant to the study as judged by the Investigator.18. Use of psychoactive prescription or non-prescription medications, psychoactive nutritional supplements or herbal preparations within 2 weeks or 5 half-lives (whichever is longer) of admission to the CRU on Day 1.19. Has received any previous study drug within 30 days prior to the first dose of this study drug.

Sponsor: CoLucid Pharmaceuticals, Inc.
Name of Finished Product: Lasmiditan
Name of Active Ingredient: Lasmiditan
<ol style="list-style-type: none">20. Is a smoker of more than 10 cigarettes or eCigarettes, or 3 cigars or 3 pipes per day, and is unable to refrain from smoking while confined to the CRU.21. Has any history of dependency or treatment for substance abuse within the past 2 years.22. Subject with a history of alcoholism or who consumes excessive amounts of alcohol, defined as greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [284 mL/9 ounces], wine [125 mL/4 ounces], or distilled spirits [25 mL/1 ounce]) per day.23. Subjects who consume alcohol on a regular basis (i.e., ≥ 5 times/week) before bedtime will be excluded from the study.24. Inability to comply with the dietary regimen of the clinical research center.25. Pregnancy / positive pregnancy test.26. Planning to become pregnant during the study or within 30 days of study completion.27. Inability to use adequate contraception (as defined in item 9 of the Inclusion Criteria) during the study. It is recommended that adequate contraception be used for 1 month following completion of the study.28. Has a positive screen for alcohol or other drugs of abuse (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, opiates).29. Has a history for Hepatitis B, Hepatitis C, or Human Immunodeficiency Virus (HIV) at Screening or has been previously treated for Hepatitis B, Hepatitis C, or HIV.
Planned Number of Subjects: A sufficient number of subjects will be enrolled to ensure completion of 80 subjects.
Test Product; Dose; and Mode of Administration: Lasmiditan 50, 100, and 200 mg tablets and alprazolam 1.0 mg tablets will be provided for the study by the Sponsor. The subjects will be instructed to swallow the tablets whole, with approximately 240 mL of water. Study drug will be administered by qualified unblinded CRU personnel and a mouth check performed.
Duration of Treatment: The total duration of study participation will be approximately 5 weeks (5-7 weeks).
Safety Assessments:

Sponsor: CoLucid Pharmaceuticals, Inc.
Name of Finished Product: Lasmiditan
Name of Active Ingredient: Lasmiditan
<u>Adverse Events:</u> Adverse events (AEs) will be captured from the time of obtaining informed consent until discharge from the study.
<u>Pregnancy Test:</u> A serum pregnancy test will be done at screening and end of study for females of child-bearing potential. A serum pregnancy test will also be collected at each CRU check-in for females of child-bearing potential. A positive pregnancy test at any time during the study will automatically disqualify the subject from further participation in the trial.
<u>Serum Chemistries, Hematology and Urinalysis:</u> Blood will be collected for serum chemistries and hematology and urine will be collected for urinalysis at the following visits: <ul style="list-style-type: none">• Screening,• Day 35 or end of study (EOS).
<u>Vital Signs:</u> Vital signs (blood pressure and heart rate) will be collected at the following visits/time points: <ul style="list-style-type: none">• Screening,• Day -1, 6, 13, 20, and 27 upon clinic check-in,• Day 1, 7, 14, 21, and 28 prior to dosing and at 70 minutes (prior to CogScreen testing) post morning dose. Temperature will be measured at Screening and Day 35 or End of Study.
<u>Electrocardiogram</u> Twelve-lead ECG recording will be collected at Screening and Day 35 or EOS prior to discharge.
Pharmacokinetic (PK) Blood Sampling: Lasmiditan: Blood samples for the determination of plasma lasmiditan concentrations will be drawn at the following time points following each lasmiditan or placebo dose: <ul style="list-style-type: none">• Days 1, 7, 14, 21, and 28 pre-dose• Days 1, 7, 14, 21, and 28 at 155 minutes (-15 to +30 minutes) post-dose
Statistical Plan and Methods:

Sponsor: CoLucid Pharmaceuticals, Inc.
Name of Finished Product: Lasmiditan
Name of Active Ingredient: Lasmiditan
Safety: <p>Safety analysis will be based on all subjects enrolled who receive at least 1 dose of the study medication. The safety analysis will evaluate adverse events and additional safety parameters. The number and percentage of subjects experiencing at least one AE will be summarized by body system, preferred term, and treatment. If appropriate, AEs will also be summarized by intensity and relationship to study drug. SAEs, if any, will be tabulated.</p> <p>Additional safety parameters will be assessed from summaries of physical examinations, 12-lead ECGs and vital signs. The 12-lead ECG results will be categorized as normal, clinically significant abnormal, and not clinically significant abnormal. Hematology, chemistry and urinalysis laboratory test results will be categorized relative to the normal ranges. The changes from baseline for each of these parameters at post-dose time points will be presented. Complete listings and summary tables for all safety information including AEs, laboratory safety data, ECG, vital signs and physical examination will be included in the study report.</p>
Pharmacokinetics: <p>The decision as to which plasma samples collected will be assayed for evaluation of pharmacokinetics/pharmacodynamics will be determined by CoLucid Pharmaceutical, Inc. The relationship between single-dose and steady-state plasma drug levels and driving performance will be evaluated, data permitting. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers.</p>
Pharmacodynamics: <p>The primary end point, SDLP, will be analyzed using a mixed model with fixed effects for sequence, period, and treatment, and a random effect for subject within sequence.</p> <p>Secondary endpoints will be evaluated similarly, however Lane Exceedance will be log transformed (more specifically $\ln(x+1)$) prior to analyses. Pair-wise comparisons for readiness to drive will be analyzed using McNemar test.</p>

3 TABLE OF CONTENTS

1	SIGNATURES.....	2
	1.1 Sponsor’s Representative.....	2
	1.2 Investigator.....	3
2	SYNOPSIS.....	4
3	TABLE OF CONTENTS.....	14
4	ABBREVIATIONS AND DEFINITIONS OF TERMS.....	17
5	STUDY ADMINISTRATION SCHEDULE.....	19
	5.1 Principal Investigator.....	19
	5.2 Study Director.....	19
	5.3 Medical Monitor.....	19
	5.4 SAE Reporting Contact Information - Sponsor.....	19
6	BACKGROUND AND RATIONALE FOR THE STUDY.....	20
	6.1 Introduction.....	20
	6.2 Drug Profile.....	20
	6.2.1 Lasmiditan.....	20
	6.2.2 Alprazolam.....	20
	6.3 Rationale.....	21
	6.3.1 Study design.....	21
	6.3.2 Lasmiditan Dose Level.....	21
	6.3.3 Positive Control Dose Level.....	21
7	STUDY OBJECTIVES AND ENDPOINTS.....	22
	7.1 Primary Objective.....	22
	7.2 Secondary Objectives.....	22
	7.3 Primary Endpoint.....	22
	7.4 Secondary Endpoints.....	22
8	SUBJECT DEFINITION.....	24
	8.1 Inclusion Criteria.....	24
	8.2 Exclusion Criteria.....	25
9	STUDY DESIGN.....	28
	9.1 Summary of Study Design.....	28
	9.2 Meals.....	29
	9.3 Subject Assignment.....	29
10	DAILY STUDY ACTIVITIES.....	30
	10.1 Screening.....	30
	10.2 Study Periods.....	30
	10.2.1 CRU Admission Days (Visits 2, 5, 8, 11, and 14: Days -1, 6, 13, 20, and 27).....	30
	10.2.2 Dosing Days (Visits 3, 6, 9, 12, and 15: Days 1, 7, 14, 21, and 28).....	31
	10.3 Estimated Daily Schedule.....	31
	10.4 Day 35±2 (Follow-up).....	32

11	STUDY PROCEDURES	33
11.1	CVDA Driving Scenario on the CRCDS-MiniSim	33
11.2	Karolinska Sleepiness Scale	33
11.3	Self-perceived Safety to Drive Question	33
11.4	Digit Symbol Substitution Test (CogScreen Symbol Digit Coding)	34
11.5	Visual Analog Scale (VAS) to Assess Subject’s Motivation and Self-Appraisal	34
11.6	Vital Signs	34
11.7	Clinical Laboratory Assessments	34
11.8	Blood Collection for Lasmiditan Plasma Concentrations	35
11.8.1	Sample Storage and Shipment	36
11.9	Blood Collection Volume for the Study	36
11.10	Medical and Social History	36
11.11	Physical Examination	36
11.12	Columbia-Suicide Severity Rating Scale	36
11.13	Pregnancy Test	36
11.14	Study Drug Preparation and Dispensing	37
11.15	Study Drug Administration	37
11.16	Concurrent Medication	38
11.17	Fluid, Food, and Lifestyle Restrictions	38
11.18	Discontinuation Criteria and Procedures	38
11.18.1	Premature Termination of Study/Closure of Study Sites	39
12	EVALUATION AND REPORTING OF ADVERSE EVENTS	40
12.1	Adverse Event Definitions	40
12.1.1	Severity Assessment	40
12.1.2	Causality Assessment	41
12.2	Routine Reporting	41
12.3	Serious Adverse Event Reporting	42
13	STATISTICAL METHODS	43
13.1	Determination of Sample Size	43
13.2	Analysis Populations	44
13.3	Statistical Analysis – General Considerations	44
13.4	Safety Analysis	44
13.4.1	Adverse Events	45
13.4.2	Clinical Laboratory	45
13.4.3	Vital Signs	45
13.4.4	Twelve-lead ECG	45
13.4.5	Physical Examination	45
13.5	Pharmacokinetic Analysis	46
13.6	Pharmacodynamic Analyses	46
14	CLINICAL SUPPLIES	47
14.1	Product Description	47

14.2	Storage Requirements.....	47
14.3	Accountability	47
15	BIOLOGICAL SPECIMENS	48
16	CLINICAL AND LABORATORY DATA COLLECTION.....	48
16.1	Case Report Forms	48
16.2	Laboratory Results	48
17	STUDY DOCUMENTATION	49
17.1	Source Documents.....	49
17.2	Access to Records	49
17.3	Retention of Records	49
18	INSTITUTIONAL REVIEW BOARD (IRB)	49
19	ETHICAL CONDUCT OF THE STUDY	50
20	INFORMED CONSENT	50
21	CONFIDENTIALITY	50
21.1	Confidentiality of Data.....	50
21.2	Confidentiality of Subject Records	50
22	COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT	51
23	QUALITY CONTROL AND QUALITY ASSURANCE.....	52
24	PUBLICATIONS.....	52
25	REFERENCES	53
26	SCHEDULE OF ACTIVITIES.....	54

4 ABBREVIATIONS AND DEFINITIONS OF TERMS

5-HT	5-Hydroxytryptamine
λ_z	Apparent terminal rate constant determined from the slope of the log transformed plasma concentration curve
AE(s)	Adverse event(s)
$AUC_{0-\infty}$	Area under the plasma concentration vs. time curve from time 0 to infinity, calculated as $AUC = AUC_{0-t} + AUC_{extra}$. AUC_{extra} represents an extrapolated value obtained by C/λ_z , where C is the observed concentration at time t at or above LOQ, and λ_z is the estimated apparent terminal rate constant
AUC_{0-t}	Area under the plasma concentration vs. time curve from time 0 to the time t of the last quantifiable concentration, calculated by means of the mixed log-linear trapezoidal rule
BMI	Body mass index
cm	Centimeter
C_{max}	Maximum plasma concentration as observed
CNS	Central Nervous System
CRA	Clinical research associate
CRCDS-MiniSim	Cognitive Research Corporation Driving Simulator-MiniSim
CRO	Contract research organization
CRU	Clinical research unit
CS	Clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
CVDA	Country Vigilance-Divided Attention
DA	Divided attention
ECG	Electrocardiogram
eCRF	Electronic case report form
EDS	Excessive daytime sleepiness
EOS	End of study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
kg/m^2	Kilogram per meter squared

km	Kilometer
KSS	Karolinska Sleepiness Scale
LC	Liquid chromatography
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
NI	Non-inferiority
PK	Pharmacokinetic
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDC	Symbol digit coding
SDLP	Standard deviation of lateral position
SOPs	Standard operating procedures
TEAE	Treatment Emergent Adverse Event
$t_{1/2}$	Apparent terminal elimination half-life, calculated as $\ln(2)/\lambda_z$
T_{max}	Time to maximum plasma concentration
VAS	Visual analog scale
WHO	World Health Organization

5 STUDY ADMINISTRATION SCHEDULE

5.1 Principal Investigator

PPD

1200 Beaumont Ave.
Mount-Royal, Quebec, Canada
H3P 3P1
Phone: **PPD**

5.2 Study Director

PPD

200 Central Avenue, Suite 1230
Saint Petersburg, FL 33701
Office: **PPD**
Mobile: **PPD**

5.3 Medical Monitor

Algorithme Pharma
1200 Beaumont Ave.
Mount-Royal, Quebec, Canada
H3P 3P1
Phone: **PPD**

5.4 SAE Reporting Contact Information - Sponsor

Serious adverse events (SAEs) should be reported to the Medical Monitor at Algorithme Pharma within 24 hours after Investigator or Investigator's representative becomes aware of their occurrence.

6 BACKGROUND AND RATIONALE FOR THE STUDY

6.1 Introduction

Migraine is a common neurological disorder and was ranked by the World Health Organization (WHO) in its 2010 Global Burden of Disease survey as one of 7 most debilitating conditions, and as the third most common disease in the world among both males and females [1]. CoLucid Pharmaceuticals, Inc. is developing lasmiditan (COL-144), which is intended for the acute treatment of migraine patients with and without aura and will be orally administered. Lasmiditan is a small molecule 5-HT_{1F} (5-Hydroxytryptamine)_{1F} receptor agonist with the chemical name of 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.

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 [2-4]. Unlike triptans, lasmiditan did not constrict rabbit saphenous vein [2], an assay predictive of human coronary artery constriction [5]. Lasmiditan is under development as a neurally acting treatment for migraine without the vasoconstrictor liability of triptans.

The most frequently reported adverse events identified in the lasmiditan clinical development program are CNS in nature based on the mechanism of action of the drug. The most common reported AEs are dizziness and fatigue, therefore a driving study evaluating the impact of lasmiditan on driving performance will be conducted.

6.2 Drug Profile

6.2.1 Lasmiditan

Full details of lasmiditan pre-clinical and clinical safety and tolerability data are contained in the Investigator's Brochure.

6.2.2 Alprazolam

Full details of alprazolam pre-clinical and clinical safety and tolerability data are contained in the Package Insert.

6.3 Rationale

6.3.1 Study design

This will be a randomized, single dose, double-blind, placebo-controlled, Latin-square design with 5-period (full) crossover study with subjects randomized to treatment sequences. Subjects will complete all 5 Periods.

During each Period, subjects will come to the clinical research unit (CRU) and remain overnight before being dosed with a single dose of either lasmiditan, alprazolam, or placebo in the morning. Cognitive testing and driving simulation will be conducted approximately 1.25 hours and 1.5 hours post dosing, respectively. Subjects will have a washout of at least 5 days between each Period.

6.3.2 Lasmiditan Dose Level

Lasmiditan 50 mg, 100 mg, and 200 mg will be given as single doses on Day 1, 7, 14, 21, or 28 (dependent upon the assigned treatment sequence) in the morning.

6.3.3 Positive Control Dose Level

Alprazolam 1.0 mg will be given as a single dose on Day 1, 7, 14, 21, or 28 (dependent upon the assigned treatment sequence) in the morning and will serve as the positive control.

7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Primary Objective

The primary objective of this study is to determine the effects of acute doses of lasmiditan 50 mg, 100 mg and 200 mg compared to placebo and positive control (alprazolam 1.0 mg) on simulated driving performance in healthy subjects as measured by standard deviation of lateral position (SDLP) using the Cognitive Research Corporation Driving Simulator-MiniSim (CRCDS-MiniSim).

7.2 Secondary Objectives

The secondary objectives of this study are to determine the effects of lasmiditan 50 mg, 100 mg, and 200 mg compared to placebo and positive control (alprazolam 1.0 mg) on other measures of simulated driving performance (e.g., speed deviation, lane exceedance and other measures of lane position and speed control, cornering, collisions, and divided attention [DA]), CogScreen Symbol Digit Coding (SDC) test, and self-report measures (i.e., Karolinska Sleepiness Scale (KSS), Visual Analog Scales addressing motivation and performance, and if the subject feels safe to drive).

7.3 Primary Endpoint

The primary endpoint for this study is simulated driving performance as measured by SDLP using the CRCDS-MiniSim.

7.4 Secondary Endpoints

The secondary endpoints for this study include other measures of simulated driving performance, KSS and CogScreen SDC test.

- Sleepiness Endpoint - KSS
- Self-reported readiness to drive (“Right now do you feel safe to drive?”)
- Visual Analog Scales (VAS) to assess subject’s motivation and self-appraisal of their driving performance
- Performance Endpoints
 - CogScreen SDC test
 - CogScreen SDC test
 - Number of correct responses
 - Response Accuracy
 - Standard deviation of reaction time
- Driving Performance Endpoints
 - Lane exceedance; including number, maximum, duration, and area of exceedance
 - Ratio above speed limit, excessive speed count, excessive speed ratio
 - Average speed, speed deviation, speed count, speedings ratio

- Excessive Ay (cornering speed threshold exceeded)
- Collision count, off-road crashes, total collisions
- DA: Correct Responses, Omission Errors, Commission Errors, Reaction Time, Standard Deviation of Reaction Times
- Single-dose plasma drug levels and driving performance

8 SUBJECT DEFINITION

Individuals are eligible for this study if they meet all inclusion and no exclusion criteria. The criteria below will be assessed at the Screening visit. Continued eligibility will be assessed by serum pregnancy and screens for alcohol and drugs of abuse on Days -1, 6, 13, 20, and 27.

8.1 Inclusion Criteria

1. Able and willing to voluntarily consent to participate in this study and provide written informed consent prior to start of any study-specific procedures.
2. Males and females between the ages of 21 and 50 years of age (inclusive). No more than 60% of one gender will be enrolled in the study.
3. Body Mass Index (BMI) between 18 and 32 kg/m² (inclusive).
4. Subject is able to reliably perform study assessments (SDLP no higher than 1 standard deviation greater than the mean for normal healthy adults completing the practice scenario; SDC Correct no less than 1 standard deviation below the mean for healthy adults in their age range); demonstrates the ability to understand task instructions, and is physically capable (e.g., adequate manual dexterity, vision, and hearing) and cognitively capable of performing study tasks.
5. Subject possesses a valid driver's license and is an active driver. Drives a minimum of 10,000 miles (about 16,000 km) per year for the previous 3 years.
6. Subject must also demonstrate simulator sickness questionnaire scores which are not indicative of simulator sickness as defined in the driving simulation operations manual.
7. Subject has a regular sleep pattern, are not engaged in shift-work, and in general, have at least 7 hours of sleep each night (bedtime occurs between 21:00 and 24:00 hours).
8. Subject has a score < 10 on the Epworth Sleepiness Scale.
9. Use of a medically highly effective form of birth control during the study and for thirty (30) days:
 - a. A female volunteer must meet one of the following criteria:
 - i. 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:
 - ii. Abstinence from heterosexual intercourse
 - iii. Systemic contraceptives (birth control pills, injectable/implant/insertable hormonal birth control products, transdermal patch)

- iv. Intrauterine device (with or without hormones)
 - v. Condom with spermicide or condom with intra-vaginally applied spermicide
 - vi. 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)
- b. A male volunteer with sexual partners who are pregnant, possibly pregnant, or who could become pregnant must meet the following criteria:
- i. Participant is unable to procreate, defined as surgically sterile (i.e. has undergone a vasectomy within at least the last 6 months)
 - ii. 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:
 - iii. Abstinence from heterosexual intercourse.
 - iv. Condom with spermicide or condom with intra-vaginally applied spermicide
- c. A male volunteer agrees to refrain from sperm donation from drug administration until 3 months after the drug administration.
10. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

8.2 Exclusion Criteria

1. History or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, neurological, oncologic, or psychiatric disease or any other condition that, in the opinion of the Investigator, would jeopardize the safety of the subject or the validity of the study results.
2. A history within 2 years of, or current treatment for, a sleeping disorder (including excessive snoring, obstructive sleep apnea), or a chronic painful condition that interferes with the subject's sleep.
3. A history of difficulty either falling asleep or staying asleep in the previous 3 months, that is considered clinically significant by the investigator.
4. Subject has a history or diagnosis of any of the following conditions:
 - a. Primary or secondary insomnia
 - b. Narcolepsy
 - c. Cataplexy (familial or idiopathic)

- d. Circadian Rhythm Sleep Disorder
 - e. Parasomnia including nightmare disorder, sleep terror disorder, sleepwalking disorder, and rapid eye movement behavior disorder
 - f. Sleep-related Breathing Disorder (obstructive or central sleep apnea syndrome, central alveolar hypoventilation syndrome)
 - g. Periodic Limb Movement Disorder
 - h. Restless Legs Syndrome
 - i. Primary Hypersomnia
 - j. Excessive Daytime Sleepiness (EDS)
 - k. Subject has visual or auditory impairment which in the opinion of the investigator would interfere with study related procedures or study conduct.
5. Expected to use any other medication or dietary supplement to promote sleep including over-the-counter sleep medications, during their participation in the study.
 6. Subject consumes excessive amounts of coffee, tea, cola, or other caffeinated beverages per day. Excessive amount is defined as greater than 6 servings (1 serving is approximately equivalent to 120 mg of caffeine)
 7. Subject has traveled across 1 or more time zones (transmeridian travel) in the last 2 weeks prior to randomization or is expected to travel across 1 or more time zones during the study.
 8. Expected to work on a rotating shift during their participation in the study.
 9. Subject works a night shift.
 10. History or presence of seizure disorder.
 11. History of urinary retention, angle closure glaucoma, or increased ocular pressure.
 12. History of gastrointestinal tract surgery, except for appendectomy.
 13. Has abnormal finding on the physical exam, medical history, electrocardiogram (ECG), or clinical laboratory results at Screening, that are considered clinically significant by the investigator.
 14. Presence of out-of-range cardiac interval (PR < 110 msec, PR > 200 msec, QRS < 60 msec, QRS > 110 msec and QTc > 440 msec) on the screening ECG or other clinically significant ECG abnormalities
 15. History of orthostatic hypotension, fainting spells, or blackouts, that are considered clinically significant by the investigator.
 16. The presence of chronic or acute infections, that are considered clinically significant by the investigator.

17. History of allergy/hypersensitivity (including drug allergies) that are deemed relevant to the study as judged by the Investigator.
18. Use of psychoactive prescription or non-prescription medications, psychoactive nutritional supplements or herbal preparations within 2 weeks or 5 half-lives (whichever is longer) of admission to the CRU on Day -1.
19. Has received any previous study drug within 30 days prior to the first dose of this study drug.
20. Is a smoker of more than 10 cigarettes or eCigarettes, or 3 cigars or 3 pipes per day, and is unable to refrain from smoking while confined to the CRU.
21. Has any history of dependency or treatment for substance abuse within the past 2 years.
22. Subject with a history of alcoholism or who consumes excessive amounts of alcohol, defined as greater than 3 glasses of alcoholic beverages (1 glass is approximately equivalent to: beer [284 mL/9 ounces], wine [125 mL/4 ounces], or distilled spirits [25 mL/1 ounce]) per day.
23. Subjects who consume alcohol on a regular basis (i.e., ≥ 5 times/week) before bedtime will be excluded from the study.
24. Inability to comply with the dietary regimen of the clinical research center.
25. Pregnancy / positive pregnancy test.
26. Planning to become pregnant during the study or within 1 month of study completion.
27. Inability to use adequate contraception (as defined in item 9 of the Inclusion Criteria) during the study. It is recommended that adequate contraception be used for 30 days following completion of the study.
28. Has a positive screen for alcohol or other drugs of abuse (amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, opiates).
29. Has a history for Hepatitis B, Hepatitis C, or Human Immunodeficiency Virus (HIV) at Screening or has been previously treated for Hepatitis B, Hepatitis C, or HIV.

9 STUDY DESIGN

9.1 Summary of Study Design

This will be a randomized, single dose, double-blind, placebo-controlled, Latin-square design with 5-period (full) crossover study with subjects randomized to treatment sequences. Subjects will complete all 5 Periods within the treatment sequence that they are randomized to.

Treatments:

- Treatment A: Lasmiditan 50 mg
- Treatment B: Lasmiditan 100 mg
- Treatment C: Lasmiditan 200 mg
- Treatment D: Alprazolam 1 mg
- Treatment E: Placebo

Subjects will be randomized equally into one of ten treatment sequences:

Treatment Sequence	Period 1	Period 2	Period 3	Period 4	Period 5
1	A	B	E	C	D
2	B	C	A	D	E
3	C	D	B	E	A
4	D	E	C	A	B
5	E	A	D	B	C
6	D	C	E	B	A
7	E	D	A	C	B
8	A	E	B	D	C
9	B	A	C	E	D
10	C	B	D	A	E

Each Period will be approximately 5 days in duration (5-7 days).

Study drug will be administered by site staff on Day 1 of each Period. Subjects will wear a blindfold when taking each dose to maintain the blind. The tablet size and shape are deemed similar enough to maintain the blind with a blindfolded subject.

Testing is conducted 1.5 hours post-dose (on Days 1, 7, 14, 21, and 28).

Schematic of Design:

Period 1 → Washout 1 → Period 2 → Washout 2 → Period 3 → Washout 3 → Period 4 → Washout 4 → Period 5 → EOS
Day 1 Days 2-6 Day 7 Days 8-13 Day 14 Days 15-20 Day 21 Days 22-27 Day 28 Day 35

A sufficient number of subjects will be enrolled to complete 80 healthy volunteers in the 5-period crossover study. The washout between Periods will be at least 5 days and not more than 14 days. Subjects will be evaluated following a single dose.

The positive control (alprazolam 1.0 mg) is included to establish the sensitivity of the study endpoints to detecting residual sedation.

The total duration of subject participation will be approximately 5 weeks (range 5-7 weeks).

9.2 Meals

During each confinement period, subjects will consume only food and beverages that are provided to them by the CRU staff. Standard meals (e.g. breakfast, dinner, and evening snack) will be provided to the subjects while confined to the CRU. On the morning of testing, subjects will be provided a low fat breakfast. The breakfast menu will include non-caffeinated breakfast foods and beverages: e.g., cereal, fruit, pastry, microwavable breakfast sandwiches, and juices. The breakfast menu will be standardized such that menu items will be the same at each study visit and at each study site. Breakfast will be provided after the morning dose.

9.3 Subject Assignment

Prior to dosing, subjects will be randomly assigned to one of ten treatment sequences and dosed with study medication (lasmiditan, alprazolam or placebo) based upon a randomization scheme provided by Algorithme Pharma. Only the qualified person(nel) assigned to prepare and administer the study treatment will have access to the randomization schedule and dispensing records during the study period.

10 DAILY STUDY ACTIVITIES

A complete Schedule of Events can be found in [Section 26](#).

10.1 Screening

Screening (Visit 1) will include procedures as described in the Schedule of Activities and further in the protocol. Prior to randomization, subjects will be screened for simulator sickness and will receive standardized training on the driving simulator and cognitive test battery. Screening procedures and screening assessments may be performed on different days but must be completed within 28 days before Period 1 (Visit 2). The Familiarization and Practice drives on the driving simulator must be completed no more than 21 days prior to Period 1.

In addition, each potential study participant will have the following assessments done by the Investigator or designee within 28 days prior to study start: medical and social history and demographic data, including sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m²), and smoking habits. Each potential participant will receive a physical examination, vital signs (including blood pressure, heart rate, and temperature), ECG, Epworth Sleepiness Scale, and the laboratory tests for hematologic, hepatic, and renal function. Urine drug and alcohol screen tests will be conducted on all potential subjects. Serum pregnancy tests will be conducted on all female subjects. The Columbia-Suicide Severity Rating Scale (C-SSRS) will also be administered.

Only medically healthy subjects with clinically acceptable laboratory profiles and ECGs will be enrolled in the study. The informed consent documents will be discussed with each potential participant, and each individual will sign an informed consent document for the study prior to any study-specific procedures being performed.

A positive test result for pregnancy, urine drug or alcohol screen will end the screening process.

10.2 Study Periods

10.2.1 CRU Admission Days (Visits 2, 5, 8, 11, and 14: Days -1, 6, 13, 20, and 27)

Within 28 days after the Screening visit, eligible subjects will return for Period 1 (Visit 2). Subjects who meet the inclusion and no exclusion criteria will be instructed to return to the clinic on Day -1.

- A serum pregnancy test will be performed for all females of child-bearing potential upon admission to the unit.
- Continued subject eligibility will be verified, including serum pregnancy and screens for alcohol and drugs of abuse.
- The alcohol and drug screens will be repeated.
- A practice drive (approximately 20 minutes) will be performed on the driving simulator.
- A practice trial on the CogScreen SDC test.

- Vital signs will be measured.
- C-SSRS
- Any concurrent medication use will be recorded.
- Adverse Events (AEs) will be assessed.

Subjects will spend the night at the CRU.

10.2.2 Dosing Days (Visits 3, 6, 9, 12, and 15: Days 1, 7, 14, 21, and 28)

After a period of 8.5 hours in bed, subjects will be awakened. According to the randomization schedule, subjects will be assigned and dosed with study medication (lasmiditan, alprazolam, or placebo).

The following procedures will be performed:

- Pre-dose vital signs will be taken.
- A pre-dose pharmacokinetic (PK) blood sample will be taken (within 30 minutes before dosing).
- Subject will receive the study drug dose.
- Vital signs will be measured pre-dose and at 1.17 hours after dosing.

Approximately 1.25 hours after dosing, subjects will perform the CogScreen SDC Test and KSS, and indicate their self-perceived safety to drive.

Subjects will then perform the Country Vigilance-Divided Attention (CVDA) driving scenario on the CRCDS-MiniSim commencing approximately 1.5 hours post-dosing. Upon completion of the driving scenario subjects will be administered a VAS to assess subject's motivation and self-appraisal of their driving performance. The following procedures will also be performed:

- A post-dose PK blood sample will be taken approximately 155 minutes (-15 to +30 minutes) post-dose.
- AEs will be recorded.
- Any concurrent medication use will be recorded.

Subjects will leave the clinical site at approximately 24-hour post-dose. However, they will be advised to stay at the clinical site, if judged necessary by the physician in charge, for safety reasons.

10.3 Estimated Daily Schedule

Following is a schedule of events from dosing through the study testing that will be followed for all Periods:

Procedure	Clock Time*	Hours Post-Dose
BEDTIME/AWAKENING	23:00/07:30	0
Vitals	8:00	0
PK Draw	8:15	0
Dosing	8:30	0
Breakfast	9:00	0.5
Vitals	9:40	1.17
CogScreen	9:45	1.25
KSS	9:55	1.42
Self-perceived safety to drive	9:55	1.42
CRCDS	10:00	1.5
VAS of Motivation and Driving Performance	11:05	2.58
PK Draw	11:05	2.58

The VAS should be completed upon termination of the drive.

*Actual times may vary based on dosing time (e.g., if dosing begins between at 8:00 and 8:30 and is slightly staggered for each subject, all times would then change relative to the actual dosing time of the individual subject).

10.4 Day 35±2 (Follow-up)

The following procedures will be performed 5 to 9 days after Study Day 28 dosing during the Follow-up visit:

- Body weight will be obtained.
- Vital signs including temperature will be measured.
- Physical Exam
- C-SSRS will be obtained
- Twelve-lead ECG recording will be collected
- Blood samples for chemistry and hematology will be drawn.
- Urine samples will be collected for urinalysis.
- Blood samples for pregnancy testing will be collected.
- AEs will be recorded.
- Any concurrent medication use will be recorded.

If an AE has not resolved, an additional Follow-up visit or visits may be scheduled until the event resolves or is deemed to be an indefinitely continuing event. At the Investigator's discretion, minor AEs may be followed until resolution via telephone contact. All SAEs must be followed for at least 30 days after the last dose of study drug. During the added follow-up visit(s), any tests indicated based on clinical signs or symptoms may be performed to aid in the evaluation of AEs.

11 STUDY PROCEDURES

11.1 CVDA Driving Scenario on the CRCDS-MiniSim

The present study employs the CVDA driving scenario, a 62.1 mile (100 km), monotonous, two-lane highway driving task that includes a secondary visual vigilance task (DA). The monotonous Country Vigilance scenario has been demonstrated to be sensitive to detect the effects of fatigue or sleepiness on driving performance [6]. This scenario has been useful in measuring the effects of sleep deprivation, Obstructive Sleep Apnea, chronic primary insomnia, and is sensitive to central nervous system (CNS) depressants (e.g., alcohol and sedating antihistamines). Results obtained using this methodology are comparable to those obtained using over-the-road driving tests [7].

Subjects will perform the driving simulator test at the times specified in [Section 10](#). Data will be captured in electronic format. Details are provided in the Cognitive Research Corporation CRCDS Testing Operations Manual.

11.2 Karolinska Sleepiness Scale

The KSS [8] will be used to assess subjective level of sleepiness. This is a subject self-report measure of situational sleepiness and provides an assessment of alertness/sleepiness at a particular point in time. The KSS has been found to correlate with electroencephalogram and behavioral variables [9]. It is a 9-point categorical Likert scale:

- (1) “extremely alert”
- (2)
- (3) “alert
- (4)
- (5) “neither sleepy nor alert”
- (6)
- (7) “sleepy”
- (8)
- (9) “extremely sleepy-fighting sleep”

Subjects will self-report their KSS assessments at the times specified in [Section 10](#). The subject’s self-reported scores will be recorded in the electronic case report form (eCRF).

11.3 Self-perceived Safety to Drive Question

Prior to driving the subject will be asked a simple question as to whether they feel safe to drive (“Right now do you feel safe to drive?”). Subject will answer “yes” or “no”. The answer will be recorded in the eCRF.

11.4 Digit Symbol Substitution Test (CogScreen Symbol Digit Coding)

Symbol Digit Coding (SDC) will be used in this study to measure attention, visual scanning, working memory, and speed of information processing. Symbol Digit Coding is a computer analogue of the conventional symbol-substitution task found in the WAIS-R Digit Symbol subtest and the Symbol Digit Modalities Test [10].

The Symbol Digit Coding test will be administered by trained study site personnel. Subjects will perform the test prior to the driving simulation test at the times specified in [Section 10](#). The subject will perform the test by interacting with an electronic monitor screen. Data will be captured in electronic format. Details are provided in the CogScreen[®] Examiner Manual, CogScreen LLC, 2016.

11.5 Visual Analog Scale (VAS) to Assess Subject's Motivation and Self-Appraisal

After completing the driving simulation, subjects will assess their own performance and their level of motivation to perform at their best during the driving simulation.

Subjects will respond to 2 questions:

1. How well you think you drove for the last 60 minutes?
2. How motivated did you feel to drive at your best during the last 60 minutes of driving?

Subjects will record their response to each question by writing a vertical line on a 100 mm horizontal, linear visual analog scale indicating their level of performance (Not Satisfactory to Satisfactory) and motivation (Not Motivated to Motivated). Scores on the 100 mm linear scale will be measured to the nearest millimeter from the left. The subject's scores will be recorded in the eCRF.

11.6 Vital Signs

Vital signs will include the measurement of blood pressure (systolic and diastolic) using an appropriately sized cuff after subjects have rested in a seated position for a minimum of 5 minutes. Heart rate will also be measured. Temperature in degrees centigrade will be measured only at Screening and end of study (EOS).

11.7 Clinical Laboratory Assessments

A certified laboratory will be used to perform all routine hematology, clinical chemistry, and urinalysis. Planned laboratory analyses include:

Category	Test Name
Hematology	Hemoglobin Hematocrit Platelets Prothrombin Time (PT) ^c Red blood cells White blood cells with differential (absolute)
Chemistry	Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase Blood urea nitrogen (BUN) Creatinine Gamma glutamyltransferase (GGT) Glucose Potassium Sodium Total and direct bilirubin
Urinalysis	Bilirubin Erythrocytes Glucose Ketones Leukocytes Nitrite pH Protein Specific gravity Urobilinogen
Other	Urine drug and alcohol screen ^{a,b} Serum Pregnancy ^d
<p>^a Screening and check-in each Period (Days -1, 6, 13, 20, and 27). ^b Includes testing for amphetamines, methamphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol and opiates – ethanol may be determined by Breathalyzer. ^c Screening only. ^d Serum pregnancy at Screening, Days -1, 6, 13, 20, and 27, and Day 35/EOS. Note: The complete panel of safety labs (other than where footnoted) will be completed at Screening and Follow-up/Day 35 (or EOS). Other tests may be performed as deemed necessary by the investigator.</p>	

11.8 Blood Collection for Lasmiditan Plasma Concentrations

Within Periods (Days 1, 7, 14, 21, and 28), blood sampling will be performed prior to dosing (within 30 minutes prior to dose) and approximately 155 minutes (-15 to +30 minutes) after dosing for plasma determination of lasmiditan. Documentation stating the exact time of blood sampling in relation to the actual time of dosing for each subject by subject number, will be included with each shipment of plasma samples.

Blood samples will be collected into heparinized polypropylene tubes (~5.0 mL). The tubes should be mixed immediately after filling by gently inverting the tubes at least 8 to 10 times. Thereafter, the tubes will be centrifuged as soon as possible (within 30 minutes of collection) at a minimum of 1500 g for 15 minutes until cells and plasma are well separated. The resulting plasma samples will be transferred into two (duplicate) 2 ml cryovial tubes and labeled appropriately.

Plasma samples will be analyzed for lasmiditan at Covance Laboratories, Inc. Madison Wisconsin, using a validated liquid chromatography with tandem mass spectrometric detection (LC/MS/MS) method (limit of quantification (LOQ): 1 ng/mL). A detailed method description, including validation, calibration and quality assurance procedures will be included in the bioanalytical report which will be part of the Final Study Report.

11.8.1 Sample Storage and Shipment

The samples will be frozen as soon as possible (within 24 hours) of collection and stored frozen at -20°C until time of shipment to Covance Laboratories, Inc., 3301 Kinsman Blvd. Madison, WI 53704, USA for analysis. All samples will be shipped frozen with sufficient dry ice to maintain frozen conditions for at least 72 hours at times arranged between the study site and the analytical laboratory. The times of blood sample collection, pipetting and freezing will be recorded in the source documents.

11.9 Blood Collection Volume for the Study

For Periods 1-5, a total of approximately 50 mL (10 x 5 mL samples) will be collected from each subject for PK analysis. In addition, up to 48 mL of blood will be collected for screening and end-of-study clinical laboratory evaluations.

11.10 Medical and Social History

A medical and social history will be performed at Screening. Each subject's history of alcohol and drug use will be evaluated. Subject's caffeine consumption and tobacco use will be evaluated to ensure that the protocol will be followed during the course of the study. Continued eligibility will be evaluated on Day -1 and adherence to protocol restrictions will be confirmed throughout the study.

11.11 Physical Examination

A physical examination will be performed at Screening and Day 35 or EOS.

11.12 Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a suicidal ideation rating scale. The scale identifies behaviors and thoughts that are associated with an increased risk of suicidal actions in the future. The C-SSRS will be performed at Screening, on Days -1, 6, 13, 20, and 27, and Day 35 or EOS.

11.13 Pregnancy Test

A serum pregnancy test will be performed at Screening and Day 35 or EOS for all females of child-bearing potential. A serum pregnancy test will also be collected at each CRU check-in visit for females of child-bearing potential. A positive pregnancy test at any time during the study will immediately terminate the subject from further participation in the study.

11.14 Study Drug Preparation and Dispensing

The Sponsor will supply study treatment in an unblinded fashion. To maintain the double-blind status of the study, the following dispensing and dosing procedures will be followed. The site will identify a qualified party and alternate(s) who will be responsible for dispensing and administering the study treatment. Aside from dispensing and administering the study treatment, the qualified party dispenser will not be otherwise involved in the study. Algorithm Pharma will provide randomization codes directly to the individual identified by the study site. The randomization codes will be kept in a secured area with access limited to only the assigned qualified party dispenser.

The qualified party dispenser will prepare study treatment for each subject in a designated dispensing room. The qualified party dispenser will assign the next available randomization number and dispense the appropriate tablet into dispensing cups. The qualified party dispenser will complete the study treatment dispensing record. The study treatment dispensing record will remain in a secure locked area with access limited to the qualified party dispenser and the alternate(s). A second individual with no other study involvement will witness the preparation and dispensing process to confirm proper dispensation of study medication in accordance with the randomization schedule. No other study personnel will be present in the designated dispensing room at the time of study treatment dispensing.

The qualified party dispenser will inform the study coordinator once the study treatment is dispensed and is ready to be administered to the subject. The qualified party dispenser will deliver the study treatment from the designated dispensing room to the subject's room and will administer dosing

Study treatment administration will be completed in the subject's room. Study treatment will be dispensed in the morning, after a period of 8.5 hours in bed.

All study medications will be administered orally with 240 mL of room temperature water. A mouth check will be performed by CRU personnel for each dose of study drug administered.

11.15 Study Drug Administration

To maintain the study blind for lasmiditan 50 mg, 100 mg and 200 mg, alprazolam 1 mg, and placebo, subjects will be blindfolded during dosing in each Period. Subjects will be given one tablet in the morning on the day of testing in the CRU. Dosing will be observed by a study staff member (qualified party dispenser); no other study personnel will be present at the time of dosing.

The qualified party dispenser will place the tablet into a dispensing cup. The blindfolded subject will transfer the study treatment directly from the cup into their mouth. All study medications will be administered orally with 240 mL of room temperature water. The subjects will be instructed to swallow the study tablet whole, without chewing the tablet. Mouth and hand checks will be performed by CRU personnel for each dose of study drug administered.

11.16 Concurrent Medication

- Subjects are to abstain from using psychoactive prescription or non-prescription medications, psychoactive nutritional supplements or herbal preparations within 2 weeks or 5 half-lives (whichever is longer) of Day 1.
- Subjects are to abstain from using any other medication or dietary supplement to promote sleep, including over the counter sleep medications, during their participation in the study.
- Subject will abstain from using antihistamine or any other drugs that can cause drowsiness, and will discuss any new prescription with the investigator.
- No other medications (with the exception of birth control) are to be taken by the subjects without prior approval from the Principal Investigator and the Sponsor unless it is a medical emergency. All concomitant medication taken during the trial should be recorded with indication, daily dose, and start and stop dates of administration.

11.17 Fluid, Food, and Lifestyle Restrictions

- Subjects are not allowed to consume alcoholic beverages from 48 hours prior to admission to the CRU on Days -1, 6, 13, 20, and 27 until discharged from the CRU following completion of all procedures of each Period on Days 2, 8, 15, 22, and 29. At all other times alcohol consumption is limited to no more than 3 alcoholic beverages or equivalent (beer [284 mL], wine [125 mL], or distilled spirits [25 mL]) per day.
- The subject will be cautioned regarding the operation of automobiles or other dangerous machinery, and activities made hazardous by decreased alertness. Patients should also be cautioned that the CNS effects of alprazolam may be additive to those of alcohol and other CNS depressants.
- Subjects are not allowed to consume caffeine containing products from approximately 1 pm on the days of admission to the CRU (Days -1, 6, 13, 20, and 27) until discharged from the CRU following completion of all procedures on Days 2, 8, 15, 22, and 29. At all other times, caffeinated beverages will be permitted to no more than 4 units per day amounts (1 unit = 120 mg caffeine).
- Subjects are to refrain from vigorous physical activity from 24 hours prior to admission to the CRU on Days -1, 6, 13, 20, and 27 until discharged from the CRU following completions of all procedures on Days 2, 8, 15, 22, and 29.

11.18 Discontinuation Criteria and Procedures

According to the Declaration of Helsinki, all subjects have the right to withdraw from a study at any time, regardless of their reasons. In addition, it is the right of the Investigator to remove subjects from the study as a result of AEs, protocol violation, or any other reason.

11.18.1 Premature Termination of Study/Closure of Study Sites

The study may be terminated prematurely if new toxicological findings or results affecting the safety of the subjects become available. A site may be closed prematurely if recruitment is too slow, poor quality data is produced, or there is evidence of attempted or proven fraud.

In the event the Sponsor prematurely terminates the study, the Investigator will promptly notify the Institutional Review Board (IRB).

12 EVALUATION AND REPORTING OF ADVERSE EVENTS

12.1 Adverse Event Definitions

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

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

An AE may be:

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

Surgical procedures themselves are not AEs. They are therapeutic measures for conditions that required surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned surgical measures permitted by the clinical study protocol and the condition(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).

12.1.1 Severity Assessment

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

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

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

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

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

12.1.2 Causality Assessment

The Principal Investigator or a medical qualified designate will determine the relationship of any AE to study drug using the following guidelines in [Table 12-1](#).

Table 12-1 Adverse Event Relationship to Study Drug

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

12.2 Routine Reporting

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

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

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

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

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

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

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

In general, AEs occurring secondary to other events (eg, clinical sequelae or a cascade of events) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as SAE or AE in the CRF. However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF.

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

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

12.3 Serious Adverse Event Reporting

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

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

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

The notification should be directed to the following sponsor representatives:

PPD

Tel. **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 AE must be reported to the IRB. If so, the event will be reported via fax or email within 15 calendar days of the investigator or staff becoming aware of the event.

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

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

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

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

13 STATISTICAL METHODS

13.1 Determination of Sample Size

This study is designed to test non-inferiority of lasmiditan doses relative to placebo, with an alprazolam test versus placebo to confirm the sensitivity of the simulator to detect treatment effects. The following assumptions were made in the sample size computation: (a) within-subject standard deviation for SDLP is approximately 6 cm; (b) the true difference between lasmiditan doses and placebo is 0; and, (c) the non-inferiority (NI) margin is proposed to be

4.4 cm, which is the effect seen with 0.05% of BAC. Under these assumptions, a sample of 80 subjects would provide in excess of 90% power to establish non-inferiority of any given dose of lasmiditan compared to placebo in terms of the primary end point, SDLP. This sample size is considered more than adequate to detect alprazolam differences from placebo, which are anticipated to exceed the NI margin.

13.2 Analysis Populations

- PK Population – All subjects with evaluable PK data will be included in the pharmacokinetic population. Subjects with incomplete PK data, e.g. data missing from one entire study Period, will be listed and the derived PK parameters will not be considered for summary statistics and analytical evaluations.
- Intent-to-Treat (ITT) Population – The ITT Population includes all randomized and treated subjects. This is the analysis population for efficacy analysis. Subjects will (in general) be included in all analyses for which data are non-missing.
- Safety Population – The Safety Population includes all subjects who are treated with study medication.

13.3 Statistical Analysis – General Considerations

This section describes the general approaches planned to analyze the data from this study. Additional details of the planned analyses outlined here, will be further described in the Statistical Analysis Plan (SAP).

To address multiplicity of testing, for the primary endpoint of SDLP, ascending doses of lasmiditan will be interpreted in a sequential manner, starting with the 50 mg dose and proceeding to 100 mg and then 200 mg. Doses of lasmiditan will be considered non-inferior to placebo if the upper 95% confidence limit on the difference in SDLP between that dose and placebo is less than 4.4 cm and lower doses also do not exceed the NI margin. No adjustment to alpha levels will be made for either the comparison of alprazolam to placebo or lasmitidan, or for secondary endpoints or analyses. Formal statistical tests (where performed) will be two-sided and testing at the $\alpha=0.05$ level of significance.

In general, categorical variables will be summarized by the count (N) and percentage of subjects (%). Continuous variables will be summarized by the number of non-missing observations (N), mean, standard deviation (SD), median, minimum, and maximum values.

All study data are to be displayed in the data listings.

13.4 Safety Analysis

Safety analysis will be based on all subjects enrolled who receive at least 1 dose of the study medication. The safety analysis will evaluate adverse events and additional safety parameters. The number and percentage of subjects experiencing at least one AE will be summarized by

body system, preferred term, and treatment. If appropriate, AEs will also be summarized by intensity and relationship to study drug. SAEs, if any, will be tabulated.

Additional safety parameters will be assessed from summaries of physical examinations, 12-lead ECGs and vital signs. The 12-lead ECG results will be categorized as normal, clinically significant abnormal, and not clinically significant abnormal. Hematology, chemistry and urinalysis laboratory test results will be categorized relative to the normal ranges. The changes from baseline for each of these parameters at post-dose time points will be presented. Complete listings and summary tables for all safety information including AEs, laboratory safety data, ECG, vital signs and physical examination will be included in the study report.

13.4.1 Adverse Events

Adverse events will be summarized by dose, Medical dictionary for medical activities (MedDRA) terminology (latest version), severity and relation to study drug. The descriptive statistics presented for each system-organ class and preferred term will be the number of subjects with event (N), the percent of subjects exposed with event (%), and the number of events (E). All AEs will be listed by subject, including demographic information, dose, MedDRA latest version, system organ class, and preferred term.

13.4.2 Clinical Laboratory

Clinical laboratory values will be summarized by descriptive statistics by dose. Changes from baseline in clinical laboratory values will be summarized by descriptive statistics. All clinical laboratory values outside normal range (including Screening/Visit 1 and EoS/Visit 5 examination) will be listed by dose and subject number, including demographic information and flagging of values.

13.4.3 Vital Signs

Vital signs (BP, HR and body temperature) will be summarized by dose using descriptive statistics. Changes from baseline in vital signs will be summarized by descriptive statistics for each dose.

13.4.4 Twelve-lead ECG

All ECG endpoints will be listed by dose, subject and time of assessment and summarized by descriptive statistics. Changes from baseline in ECG parameters will be summarized by descriptive statistics by dose.

13.4.5 Physical Examination

Subjects with any changes in the physical examination evaluation from Screening/Visit 1 to EOS/Day 35 will be listed. A description of the study population in terms of baseline measures and demographics will be presented.

13.5 Pharmacokinetic Analysis

The decision as to which plasma samples collected will be assayed for evaluation of pharmacokinetics/pharmacodynamics will be determined by CoLucid Pharmaceuticals, Inc. The correlations between single-dose plasma drug concentrations the morning of the driving simulation and the primary and key secondary end points will be evaluated, data permitting. If indicated, these samples may also be assayed and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers. Details of the PK and associated statistical analyses will be included in the Pharmacokinetic Analysis Plan and Statistical Analysis Plan.

13.6 Pharmacodynamic Analyses

The primary endpoint, SDLP, will be analyzed using a mixed model with fixed effects for sequence, period, and treatment, and a random effect for subject within sequence.

Secondary endpoints will be evaluated similarly, however Lane Exceedance will be log transformed (more specifically $\ln(x+1)$) prior to analyses. Pair-wise comparisons for readiness to drive will be analyzed using McNemar test.

Secondary Endpoints:

- Sleepiness Endpoint - KSS
- Self-reported readiness to drive (“Right now do you feel safe to drive?”)
- VAS to assess subject’s motivation and self-appraisal of their driving performance
- Performance Endpoints
 - CogScreen SDC test
 - CogScreen SDC test
 - Number of correct responses
 - Response Accuracy
 - Standard deviation of reaction time
- Driving Performance Endpoints
 - Lane exceedance; including number, maximum, duration, and area of exceedance
 - Ratio above speed limit, excessive speed count, excessive speed ratio
 - Average speed, speed deviation, speed count, speedings ratio
 - Excessive Ay (cornering speed threshold exceeded)
 - Collision count, off-road crashes, total collisions
 - DA: Correct Responses, Omission Errors, Commission Errors, Reaction Time, Standard Deviation of Reaction Times
- Single-dose plasma drug levels and driving performance

For the primary and secondary endpoints, pair-wise comparisons (hypothesis tests) of differences in means, and 95 % confidence intervals on differences will be provided for:

1. Lasmiditan 50 mg versus placebo

2. Lasmiditan 100 mg versus placebo
3. Lasmiditan 200 mg versus placebo
4. Alprazolam 1.0 mg versus placebo
5. Lasmiditan 50 mg versus alprazolam 1.0 mg
6. Lasmiditan 100 mg versus alprazolam 1.0 mg
7. Lasmiditan 200 mg versus alprazolam 1.0 mg

In addition, pair-wise within-subject differences in SDLP greater than 4.4 cm in absolute value (equal to the previously found difference between placebo and 0.05% BAC for the CRCDS) will be compared using McNemar (MM) test[6]. Furthermore, these pair-wise, within subject differences in SDLP will be tested for symmetry about zero using the maximally selected McNemar test.

14 CLINICAL SUPPLIES

14.1 Product Description

Lasmiditan 50, 100, and 200 mg tablets and alprazolam 1.0 mg tablets will be provided for the study by the Sponsor.

14.2 Storage Requirements

Study drug supplies should be stored at room temperature and locked in a secure cabinet or room. Only the Investigator or designated third party study personnel will have access to study drug. Only the unblinded third party dispenser(s) will have access to randomization codes and study drug assignments.

14.3 Accountability

The Investigator or designated study personnel is responsible for keeping accurate records of the clinical supplies received from the Sponsor and the study drug administered to each subject. The study monitor(s) will review study drug records periodically during the conduct of the study. At the end of the study, all partial and empty containers must be returned to the Sponsor or they must be destroyed at the clinical study site according to site standard operating procedures (SOPs). Records of destruction of study drug at the study site must include bottle identifying information and number of tablets in each bottle.

In accordance with Good Pharmacy Practices, gloves should always be worn by study personnel when directly handling investigational products.

15 BIOLOGICAL SPECIMENS

Whole blood samples and urine samples will be collected as outlined in the study flow chart for clinical chemistry, hematology, pharmacokinetics, and urinalysis.

It is the responsibility of the Investigator to ensure that all personnel who will be handling, packaging, and/or shipping clinical specimens act in conformance with International Air Transport Association (IATA) regulations relating to the handling and shipping of hazardous goods.

16 CLINICAL AND LABORATORY DATA COLLECTION

16.1 Case Report Forms

An eCRF will be completed for each subject. All appropriate subject data gathered during the study will be recorded in English on these forms.

Whenever possible, all information requested on an eCRF should be completed. If information is not available, it should be documented as such. For all electronic based data fields, a tracking system for changes (i.e., an audit system) must be available.

The completed eCRFs for this study are the property of CoLucid Pharmaceuticals, Inc. and should not be made available to third parties, except for authorized representatives of appropriate health/regulatory authorities, without written permission from CoLucid Pharmaceuticals, Inc.

16.2 Laboratory Results

Laboratory tests (clinical chemistry, hematology and urinalysis) will be analyzed by a certified laboratory and reported to the clinical site as results are generated. The Investigator will review and comment on any laboratory value reported outside the normal range provided by the laboratory. The laboratory data must be signed and kept in the study subject file at the site for the Sponsor and will represent the source data.

17 STUDY DOCUMENTATION

17.1 Source Documents

Source documents may include, but are not limited to, laboratory reports, ECG tracings, x-rays, radiologist reports, biopsy reports, ultrasound photographs, clinic notes or pharmacy records and any other similar reports or records of any procedure performed in accordance with the protocol. Source documents may also include eCRFs or electronic devices when information is recorded directly onto such forms or devices.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

17.2 Access to Records

As required by the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines and regulatory authorities the Investigator will allow Sponsor's representative(s) direct access to all pertinent medical records in order to allow for the verification of data gathered in the eCRFs and for the review of the data collection process. The records, including source documentation, must also be available for inspection by relevant regulatory health authorities.

17.3 Retention of Records

All essential documents and records will be maintained at Algorithme Pharma for a period of 5 years. These documents may be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

18 INSTITUTIONAL REVIEW BOARD (IRB)

The Investigator is responsible for obtaining an approval for conduct of the study from the IRB, as well as approval of all subsequent major changes to the study, in compliance with local law. These approvals must be forwarded to the Sponsor. The IRB will comply with all federal, state, and local laws. Particular attention is drawn to the Food and Drug Administration (FDA) Regulation for IRB (21 CFR, Part 56 and ICH GCP guidelines).

The Investigator shall also obtain from the IRB and submit to the Sponsor, a signed statement indicating that it complies with Good Clinical Practices.

19 ETHICAL CONDUCT OF THE STUDY

The study will be performed according to the Declaration of Helsinki, latest edition (Edinburgh, Scotland, October 2000) with approval from the IRB.

20 INFORMED CONSENT

It is the responsibility of the Investigator to give each potential study subject, prior to inclusion into the study, full and adequate verbal and written information regarding the objectives and procedures of the study. The study subjects must be informed about their right to withdraw from the study at any time. It is the responsibility of the Investigator (who may delegate this task to other members of the study team) to obtain signed informed consent from all study subjects before any study related assessments are performed. Consent must be documented by the subject's dated signature on an informed consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form and any subsequent revised written informed consent form, and any written information provided to the subject must receive the IRB approval/favorable opinion in advance of use.

21 CONFIDENTIALITY

21.1 Confidentiality of Data

By signing this protocol, the Investigator affirms to the Sponsor that information furnished to the Investigator by the Sponsor will be maintained in confidence and such information will be divulged to the IRB and FDA, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the Investigator, except to the extent that it is included in a publication with prior approval of the Sponsor.

21.2 Confidentiality of Subject Records

By signing this protocol, the Investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC or regulatory agency representatives may consult and/or copy study documents in order to verify case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying case report form information, the subject will be identified by subject number only, full names/initials will be masked prior to transmission to the Sponsor, IRB/IEC or regulatory agency.

22 COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing this protocol, the Investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP; and all applicable local laws, rules and regulations relating to the conduct of the clinical study.

The Investigator also agrees to allow monitoring, audits, IRB review and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents including access to the electronic data base for the study.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable local laws, rules and regulations; and, for each subject participating in the study, provide all data, and upon completion or termination of the clinical study submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the Investigator upon request and also shall be made available at the Investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The Investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and eCRFs.

ICH-GCP guidelines recommend that the Investigator inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The Investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study and provide the final results (i.e. final observations and responses).

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this study. The Investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the Investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify the IRB/IEC.

23 QUALITY CONTROL AND QUALITY ASSURANCE

Designated personnel from Algorithm Pharma will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol, ICH Guideline E6 for Good Clinical Practices.

24 PUBLICATIONS

No publication or disclosure of study results will be permitted, except under the terms and conditions of a separate, written agreement between Sponsor and the Investigator and/or the Investigator's institution. The Sponsor must have the opportunity to review and approve all proposed abstracts, manuscripts, or presentations regarding this study prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission.

25 REFERENCES

1. Steiner, TJ, Stovner, LJ, Birbeck GL, Migraine: The seventh disabler. *Cephalalgia* 2013;0:1-2.
2. Nelson DL, Phebus LA, Johnson KW, Wainscott DB, Cohen ML, Calligaro DO, et al., Preclinical pharmacological profile of the selective 5-HT_{1F} receptor agonist lasmiditan. *Cephalalgia* 2010;30(10):1159-1169.
3. Shephard S, Edvinsson L, Cumberbatch M, Williamson D, Mason G, Webb J, et al., Possible antimigraine mechanisms of action of the 5HT_{1F} receptor agonist LY334370. *Cephalalgia* 1999;19(10):851-858.
4. Goadsby PJ, Classey JD, Evidence for serotonin (5-HT)_{1B}, 5-HT_{1D} and 5-HT_{1F} receptor inhibitory effects on trigeminal neurons with craniovascular input. *Neuroscience* 2003;122(2):491-498.
5. Cohen ML, Johnson KW, Schenck KW, Phebus LA, Migraine therapy: relationship between serotonergic contractile receptors in canine and rabbit saphenous veins to human cerebral and coronary arteries. *Cephalalgia* 1997;17(6):631-638.
6. CRCDS Operations Manual. Cognitive Research Corporation. Data on file.
7. Siemen A, Gargano C, Cha J, Drexel M, Bautmans A, heirman I, Laethem T, Hochadel T, Gheyle L, Bleys K, Beals C, Stoch A, Kay G, & Struyk A. (2015). A randomized, crossover, placebo-controlled clinical trial to assess the sensitivity of the CRCDS Mini-Sim to the next-day residual effects of zopiclone. *Therapeutic Advances in Drug Safety*, 6 (3), 86-97.
8. Åkerstedt T, Gillberg M. (1990). Subjective and objective sleepiness in the active individual. *International Journal of Neuroscience*, 52, 29–37.
9. Kaida M, Takahashi T, Åkerstedt A, Nakata Y, Otsuka T, Haratani K, et al. (2006). Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clinical Neurophysiology*, 117, 1574–81.
10. Wechsler, D. (1981). Wechsler Adult Intelligence Scale-Revised. San Antonio: Psychological Corporation.

26 SCHEDULE OF ACTIVITIES

Study Procedures	Screening (Within 28 Days Prior to 1st Dose) (Visit 1)	Period 1			Period 2			Period 3			Period 4			Period 5			Follow - Up/E OS
		Day- 1 (V2)	Day 1 (V3)	Day 2 (V4)	Day 6 (V5)	Day 7 (V6)	Day 8 (V7)	Day 13 (V8)	Day 14 (V9)	Day 15 (V10)	Day 20 (V11)	Day 21 (V12)	Day 22 (V13)	Day 27 (V14)	Day 28 (V15)	Day 29 (V16)	Day 35 (Visit 17)
Informed consent	X																
Medical/Social history	X																
Subject Eligibility	X	X			X			X				X		X			
Weight/Height ¹ (BMI)	X																X
Drug and alcohol screen	X	X			X			X				X		X			
Serum Pregnancy Test	X	X ⁹			X ⁹			X ⁹				X ⁹		X ⁹			X
Clinical safety labs	X																X ²
Physical examination	X																X
Epworth Sleepiness Scale	X																
Twelve-lead ECG ³	X																X
Vital signs ⁴	X	X	X		X	X		X	X		X	X		X	X		X
Temperature	X																X
Admission to clinic ⁵		X			X			X			X			X			
Discharge from clinic ⁶				X			X			X			X			X	
Study Drug Administration			X			X			X			X			X		
PK sampling ⁷			X			X			X			X			X		
CogScreen SDC Training/Practice	X	X			X			X			X			X			
Driving Sim Training/Practice	X	X			X			X			X			X			
Simulator Sickness Questionnaire	X																
KSS ⁸			X			X			X			X			X		
Self Perceived Questionnaire (safe to drive)			X			X			X			X			X		
CVDA Drive			X			X			X			X			X		

VAS			X			X			X			X			X		
CogScreen SDC Test			X			X			X			X			X		
C-SSRS	X	X			X			X			X			X			X
Adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant meds assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

¹ Height and BMI will be measured at Screening only.

² Safety labs (hematology, chemistry and urinalysis) at Screening and Day 35 or EOS only.

³ Twelve-lead ECG will be obtained at Screening and Day 35 or EOS only.

⁴ Vital signs will be collected at Screening, CRU check-in on Days -1, 6, 13, 20, and 27, predose and 1.17 hours post dose on Days 1, 7, 14, 21, and 28, and at Follow-up/Day 35 or EOS.

⁵ Subjects will be inpatient on Days -1, 6, 13, 20, and 27.

⁶ Subjects will be discharged approximately 24 hours post-dose.

⁷ Plasma PK samples for lasmiditan levels will be collected at the following time-points: Days 1, 7, 14, 21, and 28 pre-dose (within 30 minutes before dosing) and 2.58 hours (155 minutes -15 to +30 minutes) post dosing.

⁸ KSS is performed before each drive.

⁹ A serum pregnancy test will be performed upon admission to the unit for females of child-bearing potential.

*Days may vary depending on the exact wash-out period.