Protocol H8H-CD-LAHI

A Randomized, Double-Blind, Three Period, Cross-Over Study to Evaluate the Effect of Single Oral Doses of Lasmiditan when Coadministered with Single Oral Doses of Sumatriptan (Imitrex) in Healthy Male and Female Subjects

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Approval Date: 17-Feb-2017

CoLucid
pharmaceuticals, inc.

Clinical Protocol

A Randomized, Double-Blind, Three Period, Cross-Over Study to Evaluate the Effect of Single Oral Doses of Lasmiditan when Coadministered with Single Oral Doses of Sumatriptan (Imitrex) in Healthy Male and Female Subjects

Protocol No. COL MIG-118

February 17, 2017

Version 1.0

CoLucid Pharmaceuticals, Inc.
222 Third Street
Suite 1320
Cambridge, MA 02142

SPONSOR SIGNATORY

CoLucid Pharmaceuticals, Inc.
222 Third Street
Suite 1320
Cambridge, MA 02142

Protocol: COL MIG-118 "A Randomized, Double-Blind, Three Period, Cross-Over Study to Evaluate the Effect of Single Oral Doses of Lasmiditan when Coadministered with Single Oral Doses of Sumatriptan (Imitrex) in Healthy Male and Female Subjects"

Version 1.0 date 17 Feb 2017

This protocol has been approved by CoLucid Pharmaceuticals, Inc. The following signatures document this approval.

PPD
Head Clinical/Regulatory Operations
CoLucid Pharmaceuticals, Inc.

Date (dd/month/year)

PPD
PPD MD
Medical Monitor

17/02/2017
Date (dd/month/year)

SPONSOR SIGNATORY

CoLucid Pharmaceuticals, Inc.
222 Third Street
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PPD Digitally signed by Bernice Kuca
DN: cn=Bernice Kuca, o=CoLucid Pharmaceuticals, Inc, ou, PPD
Date: 2017.02.17 14:17:48 -05'00'

PPD
Head Clinical/Regulatory Operations
CoLucid Pharmaceuticals, Inc.

Date (dd/month/year)

PPD MD
Medical Monitor

Date (dd/month/year)

INVESTIGATOR STATEMENT

Protocol Number: COL MIG-118

Protocol Title: A Randomized, Double-Blind, Three Period, Cross-Over Study to Evaluate the Effect of Single Oral Doses of Lasmiditan when Co-administered with Single Oral Doses of Sumatriptan (Imitrex) in Healthy Male and Female Subjects

I understand that all information concerning lasmiditan in connection with this study and not previously published is confidential. This confidential information includes the Investigator's Brochure, Clinical Study Protocol, Case Report Form, clinical methodology, and basic scientific data.

I will not initiate this study without approval from the Institutional Review Board/Ethics Committee and I understand that any changes in the protocol must be approved in writing by CoLucid Pharmaceuticals, Inc., and the Institutional Review Board/Ethics Committee before they can be implemented, except when necessary to eliminate immediate hazards to the subjects.

By my signature below, I attest that I have read, understand, and agree to abide by all the conditions, instructions, and restrictions contained in Protocol Number COL MIG-118, and will conduct the trial in accordance with Good Clinical Practice (GCP) and applicable regulatory requirements.

PPD

Investigator's Printed Name

PPD

Investigator's Signature

22 Feb 2017

Date

SYNOPSIS

Name of Sponsor Company: CoLucid Pharmaceuticals, Inc.	**Drug Under Study:** Lasmiditan (COL-144)
Title of Protocol: A Randomized, Double-Blind, Three Period, Cross-Over Study to Evaluate the Effect of Single Oral Doses of Lasmiditan when Co-administered with Single Oral Doses of Sumatriptan (Imitrex) in Healthy Male and Female Subjects	
Protocol Number: COL MIG-118	**Phase:** 1

Study Objectives

Primary Objective: To compare and contrast the pharmacodynamics of lasmiditan 200 mg and sumatriptan (Imitrex) 100 mg administered together to the pharmacodynamics of single doses of either drug administered alone.

Secondary Objectives:

- To compare and contrast the pharmacokinetics of lasmiditan 200 mg and sumatriptan (Imitrex) 100 mg administered together to the pharmacokinetics of single doses of either drug administered alone.
- To evaluate the safety and tolerability of lasmiditan 200 mg and sumatriptan (Imitrex) 100 mg administered together to the safety and tolerability of single doses of either drug administered alone.
- To compare and contrast the subjective drug effects of lasmiditan 200 mg and sumatriptan (Imitrex) 100 mg administered together to the subjective drug effects of single doses of either drug administered alone.

Study Endpoints

Primary Endpoint: The pharmacodynamics of lasmiditan as measured by serial vital signs, ECGs, and AEs.

Secondary Endpoints:

- The pharmacokinetic (PK) parameters of lasmiditan 200 mg when given with sumatriptan (Imitrex) 100 mg.
- The safety and tolerability of lasmiditan 200 mg as defined by adverse events, laboratory parameters, vital signs and electrocardiograms (ECGs) when given with sumatriptan (Imitrex) 100 mg.

Exploratory Endpoint: The subjective drug effects of lasmiditan 200 mg when given with sumatriptan (Imitrex) 100 mg as compared with either drug alone and as measured by results of the VAS scales and the DEQ-5.

Study Design:

This is a randomized, double-blind, three-period, cross-over study to investigate the effect of sumatriptan (Imitrex) 100 mg on the pharmacodynamics and pharmacokinetics of lasmiditan 200 mg.

Study Day	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Period 1	-1	1	2																			
Wash-out 1																						
Period 2								-1	1	2												
Wash-out 2																						
Period 3															-1	1	2					
EoS																						

The dosing periods are:

- A: Lasmiditan 200 mg + lasmiditan 200 mg placebo
- B: Sumatriptan (Imitrex) 100 mg + lasmiditan 200 mg placebo
- C: Lasmiditan 200 mg co-administered with sumatriptan (Imitrex) 100 mg

There will be a six day wash-out period between each dose.

Each subject will be randomly allocated to one of six treatment sequences: ABC, ACB, BAC, BCA, CAB or CBA.

Subject Population: Healthy male and female subjects aged 18–60 years, inclusive.

Number of Subjects: At least 42 subjects, (approximately 60% female subjects are planned) to ensure that approximately 36 subjects complete the study.	**Number of Centers:** One Phase 1 unit
Test Products and Doses Lasmiditan 200 mg tablet Sumatriptan (Imitrex) 100 mg tablet Lasmiditan 200 mg placebo tablet	**Route of Administration:** Oral

Duration: The duration of the study is approximately 6 weeks, including up to 3 weeks for screening and 22 days on study.

Criteria for Inclusion/Exclusion:

Inclusion: Subjects may be included in the study only if all the following criteria are met:

1. Male or female aged 18-60 years, inclusive.
2. Able and willing to give written informed consent.
3. BMI between 18 and 32 kg/m^2, inclusive.
4. Subjects must be able to refrain from consuming xanthine, quinine and caffeine containing beverages, and must refrain from prolonged intensive physical exercise during the study (from 72 hours prior to dosing until the last study visit).
5. Women must be:
   - not pregnant
   - not breast-feeding
   - not planning to become pregnant during the study
6. All females must have a negative serum pregnancy test at screening and a negative urine pregnancy test at check-in on Day -1 of each period. All women must agree to use an adequate method of contraception during the study and for 30 days following the end-of-study visit. Accepted methods of contraception include: mechanical products (e.g., intrauterine device) or double-barrier methods (e.g., diaphragm, condoms, cervical cap) with spermicide,

hormonal contraceptives (i.e., oral, implanted or injectable contraceptive hormones) or be surgically sterile (i.e hysterectomy, bilateral tubal ligation, bilateral oophorectomy). The subject's understanding of this requirement must be documented by the Investigator or designee.

7. Male subjects must agree to utilize a highly effective method of contraception (condom plus spermicide) during heterosexual intercourse from clinic admission until 30 days following the end of study visit.
8. Male subjects must agree to refrain from sperm donation from clinic admission until at least 30 days following the end of study visit.
9. Subjects must be able to swallow multiple pills simultaneously.
10. Subjects must be able to understand the requirements of the study and must be willing to comply with the requirements of the study.

Exclusion: Subjects are excluded from the study if any of the following criteria are met:

1. Any medical condition, clinical laboratory test or other reason which in the judgment of the Investigator or designee makes the subject unsuitable for the study.
2. Any clinically significant abnormalities (as determined by the Principal Investigator or designee) in hematology, blood chemistry and/or urinalysis lab tests at screening or at Period 1 D-1.
3. Known hypersensitivity to lasmiditan, sumatriptan (Imitrex), or to any excipient of lasmiditan or sumatriptan (Imitrex) oral tablets.
4. Use of any prescription medication, including MAO-A inhibitors and other drugs associated with serotonin syndrome, within 14 days prior to dosing (except hormonal contraceptives) except for 5-HT1 (serotonin) agonists and selective serotonin reuptake inhibitors which are restricted as noted in the table below. Any exceptions must be approved by the Investigator and Medical Monitor. Use of over-the-counter medications, including vitamins and herbal or dietary supplements within 7 days prior to dosing unless approved by the Investigator and Medical Monitor. Acetaminophen for symptomatic relief of pain is allowed until 24 hours prior to dosing in each period.

Drug Class	Brands (examples provided)	Restricted prior to Day -1 in all periods for:
5-HT1 (serotonin) agonists	Frova	6 weeks
Selective serotonin reuptake inhibitors (SSRI)/Serotonin norepinephrine reuptake inhibitors (SNRI)/tricyclic antidepressants (TCA)	Prozac	2.5 months
	Vivactil	3 weeks
Any other prescription medication(s)		14 days
Over-the-counter medications, including vitamins and herbal or dietary supplements	--	7 days

5. History, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes including but not limited to angina pectoris, myocardial infarction, silent myocardial ischemia (Ischemic cardiac syndromes), stroke, transient ischemic attacks (cerebrovascular syndromes), and ischemic bowel disease (peripheral vascular disease).
6. History, symptoms, or signs of vasospastic coronary artery disease.
7. History, symptoms, or signs of arrhythmia or Wolff Parkinson White (WPW) syndrome that

could affect the subject's safety in the opinion of the Investigator or designee.

8. History, symptoms, or signs of severe hepatic impairment.
9. History, symptoms, or signs of diabetes.
10. History within the previous 3 years or current evidence of abuse (according to DSM-IV criteria) of any drug, prescription or illicit, or alcohol; a positive urine screen for drugs of abuse or breathalyzer alcohol test.
11. Positive urinary test for drugs of abuse and/or alcohol breath test at Screening and/or at check-in on Day -1 of each Period. Cotinine will be included at screening only.
12. History of orthostatic hypotension with or without syncope.
13. Supine systolic blood pressure (BP) > 135 mm Hg, diastolic BP > 85 mm Hg, respiratory rate >20 breaths per minute, pulse >90 beats per minute, or temperature >37.5° at Screening. Low values on any vital sign measurement will be assessed at the discretion of the Investigator or designee. For orthostatic vital signs, any decrease in systolic and/or diastolic blood pressure great than 20 mmHg. Any other changes will be assessed at the discretion of the Investigator or designee.
14. ECG changes including QT interval prolongation and congenital long QT syndrome.
15. Electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, or other medicinal products that lead to QT prolongation.
16. Any clinically significant alanine aminotransferase (ALT), alkaline phosphatase (AP), aspartate aminotransferase (AST), or bilirubin abnormalities judged by the Investigator or designee at Screening.
17. Treatment with centrally active drugs or those affecting peripheral cholinergic transmission within 3 months of study entry.
18. Consumption of grapefruit, grapefruit juice, Seville oranges, Seville orange juice, or beverages containing any of these juices or consumption of members of the mustard green family (including kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, and mustard (i.e. seeds, greens, spice or the condiment)) within 72 hours of dosing.
19. Tobacco or nicotine users except subjects who stopped using tobacco or nicotine 1 year or more before signing the informed consent.
20. Subject is at imminent risk of suicide or had a suicide attempt within 6 months prior to the screening visit.
21. Participation in any clinical trial of an experimental drug or device in the previous 30 days.
22. Positive Hepatitis C antibody, Hepatitis B surface antigen, or positive human immunodeficiency virus (HIV) antibody.
23. Subjects who donated plasma in the 7 days or blood in the 3 months preceding study drug administration.
24. Subjects with an inability to communicate well with the Investigator or designee and study staff (i.e., language problem, poor mental development or impaired cerebral function).
25. Inability to fast or consume the food provided in the study.
26. Relatives of or staff directly reporting to the Investigator.

Subjects must give written informed consent for participation in the study before any study-specific screening tests or evaluations.

Subjects with test results which do not meet the above inclusion/exclusion criteria may have the relevant test repeated once if it is thought to represent a laboratory error, a reversible, clinically insignificant intermittent condition, or is not consistent with the subject's historical values. If inclusion/exclusion criteria are not met after the repeat test, the subject should be considered a screen failure and should not be enrolled in the study. Subjects may be rescreened once.

Criteria for Evaluation:

Pharmacodynamics: AEs, serial vital signs, ECGs, and physical examination results will be used to assess pharmacodynamics.

Pharmacokinetics: Standard PK parameters (including C_{max}, t_{max}, $t_{½}$, and AUC [$AUC_{(0\text{-last})}$ and $AUC_{(0\text{-}\infty)}$]) will be determined using noncompartmental (model independent) methods for lasmiditan from blood samples collected pre-dose and serially following oral administration of study drug during each of the dosing periods (at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24 and 30 hours following the dose at time 0 in each dosing period).

Safety: The incidence of adverse events, physical examination findings, measurement of vital signs (BP, HR, respiration rate, and temperature), 12-lead ECG results, and routine clinical laboratory findings (hematology, serum chemistry, and urinalysis) will be used to assess safety. The Drug Effects Questionnaire (DEQ) and Visual Analogue Scales (VAS) will be used as an exploratory assessment of safety.

Statistical Methods:

PD parameters:

The number and percentage of subjects who experience adverse events and/or vital signs that are outside the normal range and clinically significant will be presented by treatment at the time of finding. AEs will be presented by severity, relationship to study drug, System Organ Class, preferred term, and treatment at the time of event. Clinically significant ECG findings will be tabulated and summarized along with the treatment. For continuous variables, data will be summarized using descriptive statistics (sample size, mean, median, and standard deviation, minimum, maximum). For discrete variables, data will be summarized using frequencies and percentages or median and range, as applicable. Data listings will be tabulated by subject.

PK parameters:

All evaluable subjects will be included in the PK analysis. The evaluable PK population will include all subjects who completed at least one treatment period without any protocol violations that would likely affect the PK results, who have evaluable plasma concentration data for lasmiditan and/or sumatriptan (Imitrex), and for whom at least a subset of the designated PK parameters can be determined.

Data will be summarized using descriptive statistics (sample size, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequency and percentage for discrete variables for each treatment unless additional analysis is deemed appropriate based upon a review of the PK results.

Standard PK parameters (C_{max}, t_{max}, $t_{½}$ and AUC [$AUC_{(0\text{-last})}$ and $AUC_{(0\text{-}\infty)}$] of lasmiditan 200 mg will be used to describe the characteristics of the drug when co-administered with sumatriptan (Imitrex) or when taken alone.

The primary statistical analysis will use the paired t-test applied to log-transformed PK parameter (lasmiditan C_{max} or AUC_{30} separately) in the lasmiditan/sumatriptan (Imitrex) treatment period paired with the same subject's parameter value in the lasmiditan treatment period. From this model the means for each treatment and mean differences to the reference lasmiditan treatment will be estimated with the corresponding 90% confidence intervals. These estimates will then be exponentiated to produce the estimates of geometric mean ratios with their 90% confidence intervals.

It will be concluded that sumatriptan (Imitrex) has no effect on lasmiditan PK, if 90% confidence intervals for ratios of PK parameters derived in lasmiditan/sumatriptan (Imitrex) treatment period to those derived in lasmiditan treatment period are within the 80-125% interval.

The sample size of 36 subjects will provide at least 80% power to show equivalence of the PK of lasmiditan in the absence and presence of sumatriptan (Imitrex), assuming a 25% within subject coefficient of variation.

Safety:

All randomized subjects who receive at least one dose of study drug will be included in the safety and baseline analyses.

The safety analysis will evaluate adverse events and additional safety parameters. The number and percentage of subjects experiencing at least one adverse event will be summarized by body system, preferred term, and treatment. If appropriate, adverse events will also be summarized by intensity and relationship to study drug. Serious adverse events, 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 as low, normal, or high relative to the normal ranges and values outside the normal range will be assessed for clinical significance. The changes from baseline for each of these parameters at post-dose time points will be presented.

Table 1. Schedule of Events (Overview)

	Screening Visit 1	Dosing Period 1 Visit 2			Dosing Period 2 Visit 3			Dosing Period 3 Visit 4			EoS Visit 5
Day	–21 to –1	-1	1	2	-1	1	2	-1	1	2	21 (+/- 2)
In-house		X	X	X	X	X	X	X	X	X	
Outpatient	X										X
Informed consent	X										
Eligibility/Confirm continued eligibility	X	X			X			X			
Demographics, Body Weight, Height, Calculate BMI	X										
Medical history review/update	X	X			X			X			
Complete physical examination[1]	X										X
Targeted physical exam (symptom related, if applicable)		X	X	X	X	X	X	X	X	X	
Urine screen for drugs of abuse[2] and Breathalyzer test	X	X			X			X			
Hepatitis B/C and HIV-Screen	X										
Serum pregnancy test[3]	X										X
Urine pregnancy test[3]		X			X			X			
12-lead ECG[4]	X		X	X		X	X		X	X	X
Vital signs (BP, HR, RR and oral temperature)[5]	X	X	X	X	X	X	X	X	X	X	X
Orthostatic Vital signs (BP and HR)[6]	X		X			X			X		
Clinical Laboratory Tests (CBC, Chemistry, Urinalysis)	X	X			X			X			X
Training on VAS instruments[7]		X			X			X			
Bipolar Drug liking VAS			X			X			X		
Bipolar High VAS			X			X			X		
Unipolar Sedation VAS			X			X			X		
DEQ-5			X	X		X	X		X	X	
Unipolar Overall drug liking VAS			X	X		X	X		X	X	

	Screening Visit 1	Dosing Period 1 Visit 2			Dosing Period 2 Visit 3			Dosing Period 3 Visit 4			EoS Visit 5
Day	**–21 to –1**	**-1**	**1**	**2**	**-1**	**1**	**2**	**-1**	**1**	**2**	**21 (+/- 2)**
Unipolar Take drug again VAS			X	X		X	X		X	X	
C-SSRS[8]	X	X		X	X		X	X		X	X
Randomization			X								
Study drug administration[9]			X			X			X		
Adverse events[10]		←	←	←	←	←	X	→	→	→	→
Prior / Concomitant medication[11]	←	←	←	←	←	←	X	→	→	→	→
PK blood sampling[12]			X	X		X	X		X	X	

1. Physical examination will include general appearance, skin, HEENT, heart, lymph nodes, lungs, abdomen, extremities/joints, neurological systems, and mental status.
2. Urine drug screen at screening will include amphetamine, opiate, cocaine, barbiturates, benzodiazepines, cotinine and marijuana (tetrahydrocannabinol [THC]). Urine drug screen at D-1 for all periods will include amphetamine, opiate, cocaine, barbiturates, benzodiazepines, and marijuana (tetrahydrocannabinol [THC]).
3. Serum and urine pregnancy tests will be done on all females.
4. 12-lead ECGs will be taken after the subject has been supine for at least 5 minutes. ECGs are recorded +/- 15 minutes of the nominal times and at all times after the subject has been supine for at least 5 minutes according to the schedule in the Detailed Schedule of Events, Table 2.
5. Vital signs will be taken after the subject has been supine for at least 5 minutes. Vitals signs are recorded +/- 15 minutes of the nominal times and at all times, after the subject has been supine for at least 5 minutes according to the schedule in the Detailed Schedule of Events, Table 2.
6. Orthostatic vital signs are recorded after the subject has been at least 5 minutes supine then at least 2 minutes standing and will include systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) according to the schedule in the Detailed Schedule of Events, Table 2.
7. Training on VAS scoring will be comprised of three bipolar VAS scales unrelated to drug use that will be administered to each subject at the beginning of each period. The same three scales will be used in all periods.
8. C-SSRS Screening version will be used at Screening. On Day -1 and Day 2 of each period and at EoS, C-SSRS Since the last visit version will be used.
9. Study drug administration on Day 1 at approximately the same time in each period at time 0. Subjects will fast 10 hours before and 4 hours after study drug administration.
10. Adverse event collection will start at the time of signing the ICF and continue throughout the study. Adverse events that occur prior to dosing in period 1 will be recorded as medical history.
11. Prior medications are medications that were being taken within 30 days of signing the informed consent and finished prior to administration of the study drug. Concomitant medications are medications started prior to the start of the study and continued after administration of study drug or started during the study after administration of study drug
12. Blood samples for PK will be taken serially for 30 hours relative to time 0 (dosing) following the schedule in the Detailed Schedule of events, Table 2. In cases where blood sampling for PK analysis and other assessments (vital signs or ECGs) are scheduled to occur at the same time, the order of procedures will be: 5 minutes supine rest, ECG, supine vitals followed by standing vitals, and PK blood draw. Every effort should be made to collect the PK samples at the exact times as specified (Table 2). Samples taken pre-dose and up to and including 8 hours post-dose will be taken +/-5 minutes of the nominal time. Samples taken after 8 hours post-dose will be taken +/-10 minutes of the nominal time.

Table 2. Detailed Schedule of Events

Day of each Dosing Period	1														2	
Hour	Pre-dose	0	0.25	0.5	1	1.5	2	2.5	3	4	6	8	12	16	24	30
Targeted physical exam (symptom-related, if applicable)[1]	X															X
12-lead ECG	X[2]				X	X	X	X		X		X			X	
Vital signs (BP, HR, RR and Temperature)	X[3]				X		X			X		X			X	
Orthostatic vital signs (BP, HR)	X[3]				X		X									
Bipolar Drug liking VAS	X[3]				X		X			X		X				
Bipolar High VAS	X[3]				X		X			X		X				
Unipolar Sedation VAS	X[3]				X		X			X		X				
DEQ-5	X[3]				X		X			X		X			X	
Unipolar Overall drug liking VAS	X[3]														X	
Unipolar Take drug again VAS	X[3]														X	
C-SSRS[4]																X
Randomization[5]	X															
Study Drug Administration[6]		X														
Adverse Events[7]	←	←	←	←	←	←	←	X	→	→	→	→	→	→	→	→
Concomitant Medications[8]	←	←	←	←	←	←	←	X	→	→	→	→	→	→	→	→
PK blood sampling[9]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Targeted physical exam to be performed in each period on Day 1 pre-dose, as needed during Days 1 and 2 depending upon emergent symptoms, and on Day 2 at 30 hours +/- 10 hours.
2. Pre-dose 12-lead ECG to be collected within 75 minutes of dosing.
3. Pre-dose vital signs, orthostatic vital signs, VAS scales, and DEQ-5 to be collected within 60 minutes of dosing.
4. C-SSRS Since the last visit version to be used on Day 2 at 30 hours +/- 10 hours.

5. Randomization to take place in period 1 only
6. Study drug administration on Day 1 at time 0, approximately the same time in each period. Subjects will fast 10 hours before and 4 hours after study drug administration.
7. Adverse event collection will start at the time of signing the ICF and continue throughout the study. Adverse events that occur prior to dosing in period 1 will be recorded as medical history.
8. Documentation of concomitant medication use will be made throughout Days 1 and 2 of each period.
9. The pre-dose PK sample will be collected within 60 minutes of dosing. Blood samples for PK will be taken serially for 30 hours, at pre-dose and 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24 and 30 h following the dose at time 0 in each dosing period. In cases where blood sampling for PK analysis and other assessments (vital signs or ECGs) are scheduled to occur at the same time, the order of procedures will be: 5 minutes supine rest, ECG, supine vitals followed by standing vitals, and PK blood draw. Every effort should be made to collect the PK samples at the exact times as specified (Table 2). Samples taken pre-dose and up to and including 8 hours post-dose will be taken +/- 5 minutes of the nominal time. Samples taken after 8 hours post-dose will be taken +/- 10 minutes of the nominal time.

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LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

~	Approximately
>	Greater than
≥	Greater than or equal to

5-HT	5-Hydroxytryptamine
AE	Adverse event
ALT	Alanine aminotransferase
AMPP	American Migraine Prevalence and Prevention
AP	Alkaline phosphatase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to last measurable concentration
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
βHCG	Beta human chorionic gonadotropin
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats per minute
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
Cmax	Maximum observed concentration
CNS	Central nervous system
CPC	Clinical Pharmacology Center
CRF	Case report form
CS	Clinically significant
C-SSRS	Columbia-suicide severity rating scale
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic blood pressure
DCF	Data Correction Forms
DEQ-5	Drug Effects Questionnaire
DMP	Data Management Plan
DSM	Diagnostic and statistical manual
ECG	Electrocardiogram

EDTA	Ethylenediaminetetraacetic acid
EoS	End of Study
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPCR	G-Protein coupled receptor
h	Hour(s)
HDL	High density lipoprotein
HDPE	High-density polyethylene
HEENT	Head, eyes, ears, nose, and throat
HIV	Human Immunodeficiency Virus
HR	Heart rate
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
LDL	Low density lipoprotein
LOC	Limit of quantitation
MAO-A	Monoamine oxidase A
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
Min	Minutes
mL	Milliliters
mmHg	Millimeters of mercury
MOS	Margins of safety
nM	Nanomolar
NCS	Not clinically significant
PCAS	Produits Chimiques Auxillaires et de Synthèse
PD	Pharmacodynamic(s)

PI	Principal investigator
PK	Pharmacokinetic(s)
PQ	PQ interval
PR	PR interval
QRS	QRS complex
QT	Interval measured from the start of the Q wave to the end of the T wave
QTc	Corrected QT interval
QTcB	QTc obtained using Bazett's formula
QTcF	QTc obtained using Fridericia's formula
RBC	Red blood cells
RN	Registered nurse
RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SNRI	Serotonin norepinephrine reuptake inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
$t_{1/2}$	Terminal half-life
tmax	Time of occurrence of Cmax
TCA	Tricyclic antidepressant
THC	Tetrahydrocannabinol
TEAE	Treatment emergent adverse event
US	United States of America
VAS	Visual Analogue Scale
WBC	White blood cells
WHO	World Health Organization
WPW	Wolff Parkinson White syndrome

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]

Although the introduction of triptans greatly improved the acute treatment of migraine, a large percentage of patients still lack adequate treatment. A recent American Migraine Prevalence and Prevention (AMPP) study concluded that 40% of episodic migraineurs have significant unmet needs; the most frequent complaints were headache-related disability (19%) and dissatisfaction with current medications (15%).[2] In addition, concerns about cardiovascular safety are believed to limit the prescription of triptans to less than 50% of migraineurs in the US.[3] Hence, there is a significant unmet need for novel migraine therapies with a distinct mechanism of action from triptans. One such agent is lasmiditan (COL-144). Unlike any approved acute treatment for migraine, lasmiditan selectively targets 5-HT_{1F} receptors on neurons in the central and peripheral trigeminal system to alleviate migraine, and lacks the vasoconstrictor activity inherent with triptans.

Lasmiditan is being developed as a novel acute therapy for migraine and to fulfill significant unmet needs in migraine patients with risk factors for undiagnosed cardiovascular disease.

1.1 Background

Lasmiditan is a highly selective and potent 5-HT_{1F} receptor agonist with $\geq$ 470-fold higher affinity (K_i 2.21 nM) for the 5-HT_{1F} receptor than for 5-$HT_{1B/1D}$ receptors in radioligand binding assays. Based on activation of G proteins, the agonist efficacy of lasmiditan at the 5-HT_{1F} receptor was ~80% that of 5-HT. Lasmiditan is a pyridinoylpiperidine derivative, structurally unrelated to existing migraine therapies. Lasmiditan (1 µM) was examined for its binding affinity at more than 50 other GPCRs, ion channels, and transporter sites, and had no significant affinities except at the benzodiazepine binding site of the $GABA_A$ channel (K_i 0.29 µM). Unlike diazepam, lasmiditan did not potentiate GABA currents in a human cloned $GABA_A$ channel functional assay, and hence this binding affinity was not considered to be biologically relevant.

In rodent models of migraine, selective 5-HT_{1F} receptor agonists inhibited trigeminal nociceptive processing without affecting blood vessel tone.[4,5,6] Unlike triptans, lasmiditan did not constrict rabbit saphenous vein,[4] an assay predictive of human coronary artery constriction.[7] Lasmiditan is under development as a neurally acting treatment for migraine without the vasoconstrictor liability of triptans.

The *in vivo* systemic response to lasmiditan has been defined in oral toxicology studies with durations ranging from one day (single dose) to 39 weeks (repeat dose) in rats,

dogs, mice and rabbits. Toxicokinetic data from pivotal toxicology studies provided robust margins of safety (MOS) for lasmiditan across species (mouse, rat, dog, rabbit), and demonstrated comprehensive toxicological characterization of the 4 major human metabolites in genotoxicity, general toxicity and reproductive toxicity studies. Common adverse effects across species were C_{max}-driven CNS-related clinical signs (tremors, ataxia, and convulsions). Aside from the CNS-related clinical signs, there was no evidence of test article-related target organ toxicity.

1.2 Clinical Studies to Date

Five Phase 1 studies have been completed in Europe using intravenous (IV), sublingual, and oral formulations of lasmiditan. These trials enrolled 213 healthy subjects. Two European Phase 2 studies have been completed with lasmiditan in the acute treatment of migraine. One Phase 3, randomized, double-blind, placebo-controlled trial in migraine patients has been completed in the United States. A second Phase 3, randomized, double-blind, placebo-controlled trial and an open-label, year-long safety study in migraine patients are ongoing in the United States. The open-label safety study is open to subjects who have completed one of the two Phase 3 trials.

Two trials, one in healthy volunteers and one in migraine patients, evaluated IV formulations of lasmiditan.

Lasmiditan was studied in healthy volunteers at IV dose levels ranging from 0.1 to 180 mg. Few AEs were reported following 20 minute IV infusions at dose levels of 0.1 to 20 mg (clinical study H8H-BD-LACA). The number of reported AEs increased after 20 minute IV infusions of higher doses (30 and 60 mg). Most of these were rated as mild. When the infusion time for the 60 mg dose was increased to 60 minutes, the number of subjects reporting AEs was similar to that following the shorter infusion time but the total number of AEs dropped. Similar numbers of AEs were reported after 60 minute infusions of 120 and 180 mg. The majority of AEs were mild in severity at all dose levels although there was a dose-related increase in the number of moderate AEs reported, with the highest incidence recorded at the two highest dose levels (120 and 180 mg of lasmiditan). The most frequently reported AEs considered to be related to the study drug were somnolence, paresthesia, dizziness and hot flushes. These occurred with rapid onset, generally within 10 minutes of the start of the infusion at all dose levels. Adverse events typical for the triptans such as chest pain, chest tightness, chest pressure, neck pain or stiffness were not reported, even after the highest dose of 180 mg was administered.

A Phase 2, placebo-controlled clinical study to assess the efficacy and safety of Lasmiditan IV in the acute treatment of migraine has been completed (clinical study COL MIG-201). This study was blinded with regard to dose and treatment allocation and employed doses of lasmiditan from 2.5 to 45 mg IV infused over 20 minutes. One hundred and thirty (130) patients were treated in the study and no serious adverse events (SAEs) were reported. The only AE that was clearly dose related was

paresthesia; however, most of these events were reported as mild. Lasmiditan given by the IV route was effective in the acute treatment of migraine in this study, showing a statistically significant dose-response relationship.

Oral formulations of lasmiditan have been studied in four Phase 1 and one Phase 2 trials as well as the one completed (clinical study COL MIG-301) and two ongoing (clinical studies COL MIG-302 and COL MIG-305) Phase 3 trials.

A Phase 1 placebo-controlled study assessed the safety and tolerability and pharmacokinetic (PK) profile of sublingual and oral lasmiditan (clinical study COL MIG-102). The sublingual route of administration was investigated using ascending single doses from 1 to 32 mg lasmiditan versus placebo in healthy subjects in one study arm. In a second study arm, single ascending oral doses of a solution formulation from 25 to 400 mg lasmiditan or placebo were administered to healthy subjects. In a third arm of the study, the safety and tolerability of 100 mg and 400 mg of the oral solution formulation were evaluated in an additional cohort of subjects. The tolerability of both the oral and sublingual route of administration was good. However, the sublingual route did not show any advantage in comparison to the oral route of administration since there was no evidence of enhanced bioavailability in terms of exposure (C_{max}, AUC_{0-t}) or time to peak concentration (t_{max}). The oral route of administration was therefore selected for further study. Oral doses of the solution formulation were generally well tolerated up to the maximum dose tested of lasmiditan 400 mg. There were no clinically significant changes in safety parameters or clinical laboratory results.

The assessment of bioequivalence of the oral solution and tablet formulations of 200 mg lasmiditan and of dose linearity of ascending doses of 50, 200 and 400 mg lasmiditan of a tablet formulation were investigated in a further clinical Phase 1 study (clinical study COL MIG-103). This study also assessed safety and tolerability of lasmiditan. In general, lasmiditan was well tolerated across all doses. The most common AEs across all doses with a dose-related increase in frequency were fatigue and dizziness followed by somnolence and paresthesia.

In the Thorough QT study (clinical study COL MIG-105) which was designed, performed and analyzed in accordance with the International Conference on Harmonization (ICH) E14 guidance,[8] the primary objective was to assess the effect of lasmiditan 100 mg and 400 mg on cardiac de- and re-polarization. Lasmiditan caused no significant QT prolongation either at 100 mg or at 400 mg. The results met the criteria for a negative Thorough QT/QTc study according to ICH E14. [8]

A food effect study (clinical study COL MIG-104) investigated the bioavailability, pharmacokinetics, safety, and tolerability of oral lasmiditan (200 mg) in 30 healthy subjects in the fed and fasted states. All subjects who enrolled completed the study which found that food had a small effect on the pharmacokinetics of lasmiditan. Somnolence and dizziness were the most commonly reported AEs.

The efficacy of oral lasmiditan in the acute treatment of migraine was evaluated in a Phase 2 double-blind, placebo-controlled, parallel-group dose-ranging study conducted in five European countries (clinical study COL MIG-202). A total of 391 subjects treated

a single migraine attack at home using one of four doses of lasmiditan (50, 100, 200 or 400 mg) or placebo. The proportion of patients with headache relief (moderate or severe headache becoming mild or none) or who were pain free showed statistically significant dose responses at 2 hours after treatment. Associated symptoms such as nausea, phonophobia and photophobia also responded to lasmiditan. There were no clinically significant changes in clinical laboratory parameters, ECGs or vital signs.

Treatment-emergent adverse events (TEAEs) were reported by 22% of the subjects receiving placebo and by 65, 73, 86 and 84% of subjects receiving 50, 100, 200 and 400 mg lasmiditan, respectively. The most common adverse events seen in the lasmiditan groups were related to the nervous system. These included dizziness, fatigue, vertigo, somnolence and paresthesia. Chest symptoms characteristic of triptan use were rare and occurred with a similar frequency in the placebo and active groups.

The first Phase 3 double-blind, placebo-controlled, parallel-group study of lasmiditan evaluated the proportion of subjects who were headache pain-free at 2 hours post-dose, safety, and other measures of migraine pain relief (clinical study COL MIG-301, SAMURAI). The study compared 100 mg and 200 mg doses of lasmiditan with placebo in 2232 adult subjects who treated one acute migraine attack. In this study both doses of lasmiditan were statistically significant over placebo ($p<.001$) on the primary endpoint of headache pain free at 2 hours post dose and on the key secondary endpoint of most bothersome symptom free at 2 hours post dose. [9]

During the clinical development of lasmiditan, there have been no deaths and no subjects have been withdrawn due to adverse events. One serious adverse event (SAE) of moderate dizziness leading to overnight hospitalization was reported in the oral dose-ranging study. This occurred in a female patient given lasmiditan 200 mg, and resolved without sequelae. Across the clinical trials in the lasmiditan development program, somnolence, dizziness, and fatigue have been the mostly frequently reported adverse events. The sponsor has thus advised subjects in ongoing trials to not drive or operate machinery for 12 hours after dosing and plans to complete a skilled performance study.

More information on the preclinical and clinical experience with lasmiditan are given in the Clinical Investigators' Brochure (IB). [10]

1.3 Rationale for the Clinical Study

This study will assess the effect of single doses of sumatriptan (Imitrex) 100 mg on the pharmacodynamics of single doses of lasmiditan 200 mg as measured by serial vital signs, ECGs, and adverse events. Safety and tolerability will also be reported.

1.4 Risk-Benefit Assessment

In previous Phase 1 studies including healthy male and female subjects, oral doses of lasmiditan up to 400 mg were well tolerated with no drug related SAEs or withdrawals due to adverse events (AEs). The AE profile was qualitatively similar to that observed in previous clinical studies with dizziness, somnolence and paresthesia being the mostly frequently reported AEs.

The healthy subjects will not derive any medical benefits from study participation.

1.5 Dose Rationale

Lasmiditan 200 mg has been tested and shown to be safe and well tolerated in both healthy subjects and in patients with acute migraine. In preclinical toxicology studies, adequate margins of safety have been established for lasmiditan 200 mg. This study will further evaluate the pharmacokinetics and safety of lasmiditan 200 mg both alone and when co-administered with sumatriptan (Imitrex) 100 mg.

1.6 Conduct of the Study

This study will be conducted according to the protocol and in compliance with current principles of Good Clinical Practices (GCP) and ICH. Further information on the ethical conduct of the study is provided in Section 11.

2. TRIAL OBJECTIVES

2.1 Primary Objective

The primary objective is to compare and contrast the pharmacodynamics of lasmiditan 200 mg and sumatriptan (Imitrex) 100 mg administered together to the pharmacodynamics of single doses of either drug administered alone.

2.2 Secondary Objective

Secondary objectives are to:

- Compare and contrast the pharmacokinetics of lasmiditan 200 mg and sumatriptan (Imitrex) 100 mg administered together to the pharmacokinetics of single doses of either drug administered alone.

- Evaluate the safety and tolerability of lasmiditan 200 mg and sumatriptan (Imitrex) 100 mg administered together to the safety and tolerability of single doses of either drug administered alone.

- Compare and contrast the subjective drug effects of lasmiditan 200 mg and sumatriptan (Imitrex) 100 mg administered together to the subjective drug effects of single doses of either drug administered alone.

3. OVERALL DESIGN AND PLAN OF THE STUDY

3.1 Overview

This is a randomized, double-blind, three-period, cross-over study to investigate the effect of single doses of sumatriptan (Imitrex) 100 mg on the pharmacodynamics of single doses of lasmiditan 200 mg. The study will last approximately 6 weeks including up to 3 weeks for screening and 22 days on study. Screening will be conducted within approximately 21 days of the first dose of study medication. Each dosing period will last 3 days (Day -1, Day 1, and Day 2). A wash-out period of 6 days will take place between each dose. The End of Study Visit (EoS) will take place 5 (+/- 2) days after the third dosing period is completed.

Study Day	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Period 1	-1	1	2																			
Wash-out 1																						
Period 2								-1	1	2												
Wash-out 2																						
Period 3															-1	1	2					
EoS																						

3.2 Schedule of Events

The overall Schedule of Events for the study is provided in Table 1. The detailed schedule for Days 1 and 2 in each period is provided in Table 2.

3.3 Assessments by Study Visit

3.3.1 Screening (Day –21 to -1)

The following procedures and assessments will be performed up to 21 days prior to study drug administration during the screening period. The results will be documented in the CRF and source documents

- Informed consent
- Eligibility criteria
- Demographics
- Height/weight/calculate BMI
- Medical history
- Complete physical examination
- Urine drug screen

- Breathalyzer test
- Serology (HIV 1 and 2, HBsAg and hepatitis C)
- Serum pregnancy test (for all women)
- Safety 12-lead ECG
- Vital signs (BP, HR, oral temperature, and RR)
- Orthostatic vital signs (BP and HR)
- Safety clinical laboratory evaluations (hematology, chemistry and urinalysis)
- C-SSRS: Screening
- Prior medications

3.3.2 Clinical Pharmacology Center (CPC) Admission (Day -1 of each dosing period)

- CPC admission on Day -1
- Confirm eligibility criteria
- Review medical history and update if necessary
- Targeted physical exam, if applicable
- Urine drug screening
- Breathalyzer test
- Urine pregnancy test
- Vital signs (BP, HR, oral temperature, and RR)
- Safety clinical laboratory evaluations (hematology, chemistry and urinalysis)
- Training on VAS scales
- C-SSRS: Since the last visit
- Adverse events
- Prior / concomitant medications

3.3.3 Day 1 of each dosing period

3.3.3.1 Pre-Dose

Prior to the start of the dosing on Day 1 of each period, the following procedures and assessments will be performed:

- Targeted physical exam, if applicable
- Safety 12-lead ECG within 75 minutes of dosing

- Vital signs within 60 minutes prior to dosing
- Orthostatic vital signs within 60 minutes prior to dosing
- DEQ-5 within 60 minutes prior to dosing
- Bipolar Drug liking, Bipolar High, and Unipolar Sedation, Unipolar Overall drug liking and Unipolar Take drug again VAS scales within 60 minutes prior to dosing
- Collection of Adverse Events throughout the study
- Documentation of concomitant medication begins and will continue throughout the day
- PK sample collection within 60 minutes prior to the start of dosing

Additionally, in Period 1 only, subjects will be randomized to one of six treatment sequences.

Upon completion of the pre-dose procedures and assessments, each dosing period will be initiated according to the subjects' randomly assigned dosing sequence.

- Dosing at approximately the same time in each dosing period. Subjects will fast for 10 hours before and 4 hours after dosing.

3.3.3.2 Post-Dose

After initiating dosing in each period at 0 minutes, the following procedures and assessments will be performed during the remainder of Day 1:

- Targeted physical exam as needed
- Safety 12-lead ECG at 1, 1.5, 2, 2.5, 4 and 8 hours after dosing
- Vital signs at 1, 2, 4, and 8 hours after dosing
- Orthostatic vital signs at 1 and 2 hours after dosing
- DEQ-5 at 1, 2, 4, and 8 hours after dosing
- Bipolar Drug liking, Bipolar High, and Unipolar Sedation VAS scales at 1, 2, 4, and 8 hours after dosing
- Adverse event assessment will continue throughout study participation (i.e., through EoS or early termination)
- Documentation of concomitant medication use will continue throughout study participation (i.e., through EoS or early termination).\
- Post dose PK sampling at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, and 16 hours after dosing.

3.3.4 Day 2 of each dosing period

The following procedures and assessments will be performed during the remainder of Day 2:

- Targeted physical exam as needed and at 30 hours after dosing
- Safety 12-lead ECG at 24 hours after dosing
- Vital signs at 24 hours after dosing
- Unipolar Overall drug liking and Unipolar Take drug again VAS scales at 24 hours after dosing
- DEQ-5 at 24 hours after dosing
- C-SSRS: Since the last visit at 30 hours after dosing
- Adverse event assessment will continue throughout study participation (i.e., through EoS or early termination).
- Documentation of concomitant medication use will continue throughout study participation (i.e., through EoS or early termination).
- Post dose PK sampling at 24 and 30 hours after dosing.
- For Periods 1 and 2, upon completion of all protocol-specified procedures and assessments, exit from the Phase 1 unit on Day 2 and continuation of the wash-out period until the return to the Phase 1 unit on Day -1 of the next period. The wash-out period will be 6 days between each dose. For Day 2 of Period 3, upon completion of all protocol-specified procedures and assessments, exit from the Phase 1 unit on Day 2. The subjects will return for the EoS on Day 21 (+/- 2 days).

3.3.5 End-of-Study/Early Termination

The subjects are asked to return to the Phase 1 unit for the EoS assessments on Day 21 (+/- 2 days). The following procedures and assessments will be performed:

- Complete physical exam
- Serum pregnancy test (for all women)
- Safety 12-lead ECG
- Vital signs
- Safety clinical laboratory evaluations (hematology, chemistry and urinalysis)
- C-SSRS: Since the last visit.
- Adverse events
- Concomitant medications

- The subject's participation in the study is complete.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Inclusion Criteria

Subjects may be included in the study only if all the following criteria are met:

1. Male or female aged 18-60 years, inclusive.
2. Able and willing to give written informed consent.
3. BMI between 18 and 32 kg/m^2, inclusive.
4. Subjects must be able to refrain from consuming xanthine, quinine and caffeine containing beverages, and must refrain from prolonged intensive physical exercise during the study (from 72 hours prior to dosing until the last study visit).
5. Women must be:
   - not pregnant
   - not breast-feeding
   - not planning to become pregnant during the study
6. All females must have a negative serum pregnancy test at screening and a negative urine pregnancy test at check-in on Day -1 of each period. All women must agree to use an adequate method of contraception during the study and for 30 days following the end-of-study visit. Accepted methods of contraception include: mechanical products (e.g., intrauterine device) or double-barrier methods (e.g., diaphragm, condoms, cervical cap) with spermicide, hormonal contraceptives (i.e., oral, implanted or injectable contraceptive hormones) or be surgically sterile (i.e hysterectomy, bilateral tubal ligation, bilateral oophorectomy). The subject's understanding of this requirement must be documented by the Investigator or designee.
7. Male subjects must agree to utilize a highly effective method of contraception (condom plus spermicide) during heterosexual intercourse from clinic admission until 30 days following the end of study visit.
8. Male subjects must agree to refrain from sperm donation from clinic admission until at least 30 days following the end of study visit.
9. Subjects must be able to swallow multiple pills simultaneously.
10. Subjects must be able to understand the requirements of the study and must be willing to comply with the requirements of the study

4.2 Exclusion

Subjects are excluded from the study if any of the following criteria are met:

1. Any medical condition, clinical laboratory test or other reason which in the judgment of the Investigator or designee makes the subject unsuitable for the study.

2. Any clinically significant abnormalities (as determined by the Principal Investigator or designee) in hematology, blood chemistry and/or urinalysis lab tests at screening or at Period 1 D-1.
3. Known hypersensitivity to lasmiditan, sumatriptan (Imitrex), or to any excipient of lasmiditan or sumatriptan (Imitrex) oral tablets.
4. Use of any prescription medication, including MAO-A inhibitors and other drugs associated with serotonin syndrome, within 14 days prior to dosing (except hormonal contraceptives) except for 5-HT1 (serotonin) agonists and selective serotonin reuptake inhibitors which are restricted as noted in the table below. Any exceptions must be approved by the Investigator and Medical Monitor. Use of over-the-counter medications, including vitamins and herbal or dietary supplements within 7 days prior to dosing unless approved by the Investigator and Medical Monitor. Acetaminophen for symptomatic relief of pain is allowed until 24 hours prior to dosing in each period.

Drug Class	Brands (examples provided)	Restricted prior to Day -1 in all periods for:
5-HT1 (serotonin) agonists	Frova	6 weeks
Selective serotonin reuptake inhibitors (SSRI)/Serotonin norepinephrine reuptake inhibitors (SNRI)/tricyclic antidepressants (TCA)	Prozac	2.5 months
	Vivactil	3 weeks
Any other prescription medication(s)		14 days
Over-the-counter medications, including vitamins and herbal or dietary supplements	--	7 days

5. History, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes including but not limited to angina pectoris, myocardial infarction, silent myocardial ischemia (Ischemic cardiac syndromes), stroke, transient ischemic attacks (cerebrovascular syndromes), and ischemic bowel disease (peripheral vascular disease).
6. History, symptoms, or signs of vasospastic coronary artery disease.
7. History, symptoms, or signs of arrhythmia or Wolff Parkinson White (WPW) syndrome that could affect the subject's safety in the opinion of the Investigator or designee.
8. History, symptoms, or signs of severe hepatic impairment.
9. History, symptoms, or signs of diabetes.
10. History within the previous 3 years or current evidence of abuse (according to DSM-IV criteria) of any drug, prescription or illicit, or alcohol; a positive urine screen for drugs of abuse or breathalyzer alcohol test.
11. Positive urinary test for drugs of abuse and/or alcohol breath test at Screening

and/or at check-in on Day -1 of each Period. Cotinine will be included at screening only.

12. History of orthostatic hypotension with or without syncope.
13. Supine systolic blood pressure (BP) > 135 mm Hg, diastolic BP > 85 mm Hg, respiratory rate >20 breaths per minute, pulse >90 beats per minute, or temperature >37.5° at Screening. Low values on any vital sign measurement will be assessed at the discretion of the Investigator or designee. For orthostatic vital signs, any decrease in systolic and/or diastolic blood pressure great than 20 mmHg. Any other changes will be assessed at the discretion of the Investigator or designee.
14. ECG changes including QT interval prolongation and congenital long QT syndrome.
15. Electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, or other medicinal products that lead to QT prolongation.
16. Any clinically significant alanine aminotransferase (ALT), alkaline phosphatase (AP), aspartate aminotransferase (AST), or bilirubin abnormalities judged by the Investigator or designee at Screening.
17. Treatment with centrally active drugs or those affecting peripheral cholinergic transmission within 3 months of study entry.
18. Consumption of grapefruit, grapefruit juice, Seville oranges, Seville orange juice, or beverages containing any of these juices or consumption of members of the mustard green family (including kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, and mustard (i.e. seeds, greens, spice or the condiment)) within 72 hours of dosing.
19. Tobacco or nicotine users except subjects who stopped using tobacco or nicotine 1 year or more before signing the informed consent.
20. Subject is at imminent risk of suicide or had a suicide attempt within 6 months prior to the screening visit.
21. Participation in any clinical trial of an experimental drug or device in the previous 30 days.
22. Positive Hepatitis C antibody, Hepatitis B surface antigen, or positive human immunodeficiency virus (HIV) antibody.
23. Subjects who donated plasma in the 7 days or blood in the 3 months preceding study drug administration.
24. Subjects with an inability to communicate well with the Investigator or designee and study staff (i.e., language problem, poor mental development or impaired cerebral function).
25. Inability to fast or consume the food provided in the study.

26. Relatives of or staff directly reporting to the Investigator.

Subjects must give written informed consent for participation in the study before any study-specific screening tests or evaluations.

Subjects with test results which do not meet the above inclusion/exclusion criteria may have the relevant test repeated once if it is thought to represent a laboratory error, a reversible, clinically insignificant intermittent condition, or is not consistent with the subject's historical values. If inclusion/exclusion criteria are not met after the repeat test, the subject should be considered a screen failure and should not be enrolled in the study. Subjects may be rescreened once.

4.3 Protocol Exceptions and Deviations

Exceptions to the above eligibility criteria will not be granted. It is expected that subjects will meet all eligibility criteria. Departures from the protocol should be avoided unless required for the safety of the subject. Protocol deviations will be documented by the study monitor and will be included in the final clinical study report. Protocol deviations should be submitted to the Institutional Review Board (IRB) in accordance with the site's IRB requirements.

4.4 Subject Withdrawal Criteria

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

If such withdrawal occurs or if the subject fails to return for EoS, the Investigator or designee should determine the primary reason for a subject's premature withdrawal from the study and record the reason in the subject's study records.

Premature withdrawal may occur for any of the following reasons:

- Non-compliance with the protocol requirements
- Pregnancy
- Death
- AE
- Subject request
- Investigator or designee request
- Sponsor request

If a subject withdraws or is withdrawn after randomization and administration of study drug under the above criteria or for any other reason, study staff should make every effort to complete the full panel of assessments scheduled until 4 hours after study drug administration. The reason for subject withdrawal must be documented.

If a subject withdraws or is withdrawn from the study due to an adverse event (clinical or laboratory), the subject will be instructed to return to the clinic for, at a minimum, the evaluations scheduled for EoS. If the adverse event has still not resolved, additional follow-up will be performed as appropriate and documented. As a minimum requirement, AEs should be followed for at least 1 week after the subject's dose of study medication.

For subjects who are lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the Investigator or designee should show "due diligence" by documenting in the source documents all steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc.

Any subject who discontinues from the study between Screening and dosing in Dosing Period 1 may be replaced.

5. TREATMENT OF SUBJECTS

5.1 Subject Identification and Randomization

At screening, each subject will be assigned a unique three-digit subject number starting with 001. Numbers will be assigned by the study site personnel in ascending sequential order to each unique subject screened. If a subject is rescreened, the reason for rescreening will be noted and the subject will be assigned a new screening number. If a subject fails to be enrolled, the reason should be documented on the enrollment log. The subject will be considered a screen failure.

On Dosing Period 1/Day 1 subjects will be assigned a treatment sequence by a three digit randomization number starting with 101. The number is only for identifying a subject with their assigned treatment and not for subject identification.

5.2 Description of Study Drug

There are three study drugs: lasmiditan 200 mg oral tablet, lasmiditan 200 mg placebo oral tablet, and sumatriptan (Imitrex) 100 mg oral tablet. For purposes of the study all are referred to as study drug.

5.3 Concomitant Medications

Use of any prescription medication, including MAO-A inhibitors and other drugs associated with serotonin syndrome, within 14 days prior to dosing (except hormonal contraceptives) except for 5-HT1 (serotonin) agonists and selective serotonin reuptake inhibitors which are restricted as noted in the table below. Any exceptions must be approved by the Investigator and Medical Monitor. Use of over-the-counter medications, including vitamins and herbal or dietary supplements within 7 days prior to dosing unless approved by the Investigator or designee and Medical Monitor. Acetaminophen for symptomatic relief of pain is allowed until 24 hours prior to dosing in each period.

Drug Class	Brands (examples provided)	Restricted prior to Day -1 in all periods for:
5-HT1 (serotonin) agonists	Frova	6 weeks
Selective serotonin reuptake inhibitors (SSRI)/Serotonin norepinephrine reuptake inhibitors (SNRI)/tricyclic antidepressants (TCA)	Prozac	2.5 months
	Vivactil	3 weeks
Any other prescription medication(s)		14 days
Over-the-counter medications, including vitamins and herbal or dietary supplements	--	7 days

Prior medications are medications that were being taken within 30 days of signing the informed consent and finished prior to administration of the study drug. Concomitant medications are medications started prior to the start of the study and continued after

administration of study drug or started during the study after administration of study drug. Prior and concomitant medication use will be collected from Screening to EoS.

It is not anticipated that the healthy volunteers participating in this study will be taking any prescription medications for any disorder.

If intake of a drug should become necessary for any reason during the course of the study, the subject is required to inform the Investigator or designee immediately. The Investigator or designee will record the drug, the dose, and the time of intake in the subject's CRF.

5.4 Restrictions

5.4.1 Dietary and Fluid Restrictions

Subjects will fast for at least 10 hours prior to dosing and will continue to fast until at least 4 hours after dosing in each period. Meals during each dosing period will be standardized. All subjects will consume the same food during each meal. The composition of each meal may vary from day to day and between dosing periods. Subjects will fast at least 8 hours prior to any blood draw for clinical laboratory assessments.

The study drugs will be taken with 240 mL of water. Subjects will be allowed to drink non-sparkling water ad libitum, except for the time from 1 hour prior to dosing until 1 hour post-dose.

The consumption of grapefruit, grapefruit juice, Seville oranges, Seville orange juice, or beverages containing any of these juices or consumption of members of the mustard green family (including kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts, and mustard (i.e. seeds, greens, spice or the condiment)) is prohibited within 72 hours of dosing.

The consumption of alcohol is prohibited beginning 72 hours prior to dosing (**Day 1**) in each dosing period until discharge from the unit. During all other times, the maximum intake of alcohol is limited to 1 unit per day (or 7 units per week; 1 unit of alcohol corresponds to 250 mL beer, 125 mL of wine, or 25 mL of spirits).

The consumption of tobacco is not allowed during the study.

Subjects are to refrain from consumption of caffeine-containing food or beverages (e.g. coffee, tea, cola, cocoa, chocolate) and of energy drinks for 72 hours before **Screening** and in each dosing period from 72 hours before each administration of the study drug until discharge (**Days -1** to **2**).

5.4.2 Other Restrictions

Subjects will be confined to the Phase 1 unit for each dosing period from **Day -1 to Day 2.** Subjects will be discharged after the last assessment has been performed within that period (at least 30 hours post-dose for PK sample). In case of persisting adverse events, the subject may remain in the unit at the discretion of the Investigator or designee.

5.5 Treatment Compliance

Study medication will be administered in the Phase 1 unit under supervision. A mouth and hand check will be conducted for each subject after each dose to ensure compliance and proper ingestion.

5.6 Randomization and Blinding

This is a randomized, double-blind, three-period, cross-over, study to investigate the effect of single doses of sumatriptan (Imitrex) 100 mg on the pharmacodynamics of a single dose of lasmiditan 200 mg. The dosing periods are:

- A: Lasmiditan 200 mg co-administered with lasmiditan 200 mg placebo
- B: Sumatriptan (Imitrex) 100 mg co-administered with lasmiditan 200 mg placebo
- C: Lasmiditan 200 mg co-administered with sumatriptan (Imitrex) 100 mg

The study will be conducted at a single center. Subjects will be randomized using a Williams square design to one of six treatment sequences, as follows:

ABC	ACB
BAC	BCA
CAB	CBA

Seven of the planned 42 subjects will be included in each treatment sequence. The design is balanced for period and first order carryover effects.

Double-blinding will be accomplished as follows:

- Dosing staff, comprised of an unblinded pharmacist or designee (who prepared the medication), an unblinded dosing assistant, and an unblinded registered nurse (RN) will administer all study medications. They will have no other role in the trial and will not communicate their activities in the trial to other staff involved in the trial in any way.
- Investigational product, prepared in the Pharmacy by an unblinded Pharmacist or designee, will be dispensed from the Pharmacy in an amber medication vial (with a subject specific label blinded to the identity of the investigational product) to the unblinded dosing staff and dosed to the subject directly from the amber vial to the subject's mouth.
- Prior to dosing, each subject will be blind-folded and will remain blind-folded until the hand and mouth check has been completed. Curtains will be drawn around the bed prior to dosing and will remain in place until the hand and mouth check has been completed. No one will enter the curtained space other than the subject, the unblinded RN, and the unblinded dosing assistant.

6. STUDY DRUG MATERIAL AND MANAGMENT

6.1 Lasmiditan

Lasmiditan drug product is a tablet containing 200 mg of lasmiditan (as free base). The tablet is white, film coated, and round with no markings. Lasmiditan drug product is for oral administration.

Lasmiditan hemisuccinate active pharmaceutical ingredient (API) was manufactured by Produits Chimiques Auxillaires et de Synthèse (PCAS), 19 route de Meulan, F-78520 Limay (France). The drug product was manufactured by Patheon 111 Consumers Drive, Whitby, Ontario L1N 5Z5 Canada, or by Patheon 2100 Syntex Court, Mississauga, Ontario L5N 7K9, Canada and contains the following inactive excipients: purified water, microcrystalline cellulose PH102, Starch 1500, sodium croscarmellose, sodium lauryl sulphate, magnesium stearate (non-bovine) and Opadry II White (film coating).

6.2 Lasmiditan Placebo

Lasmiditan matching placebo contains purified water, microcrystalline cellulose PH102, Starch 1500, sodium croscarmellose, sodium lauryl sulphate, magnesium stearate (non-bovine) and Opadry II White (film coating). The placebo tablets match the active tablets in size, shape, and appearance.

Placebo was manufactured by Patheon 111 Consumers Drive, Whitby, Ontario L1N 5Z5 Canada, or by Patheon 2100 Syntex Court, Mississauga, Ontario L5N 7K9, Canada.

6.3 Lasmiditan and Lasmiditan Placebo Packaging and Labelling

Lasmiditan 200 mg matching placebo oral tablets will be delivered as bulk supplies in high-density polyethylene (HDPE) bottles from Catalent Pharma Solutions, Kansas City, Missouri, US.

All packaging and labeling will be performed according to Good Manufacturing Practice (GMP) and GCP rules. The lot number and date of manufacture for the clinical lot used in the study will be provided to the clinical site and will be reported in the Clinical Study Report. All study drug will be labeled with:

- Protocol number
- Sponsor's name and address
- Investigational New Drug statement
- Instructions for use and storage

6.4 Storage of Lasmiditan and Lasmiditan Placebo

All lasmiditan and its matching placebo should be stored by the study site at controlled room temperature of 25°C (77°F); excursions are permitted to +/- 15°C (59°F-104°F).

6.5 Lasmiditan and Lasmiditan Placebo Administration

Double blinding will be accomplished as described in Section 5.6.

Investigational site staff will dispense lasmiditan 200 mg or its placebo according to the dosing plan. Lasmiditan will be co-administered with either sumatriptan (Imitrex) or lasmiditan placebo. The two study drugs will be swallowed simultaneously with 240 ml of water.

After dosing and rinsing with water, a hand and mouth check will be performed. Subjects will receive study drug in a sitting position on the bed. For the first 4 hours after each dose, the subjects will continue to fast and must remain seated on their bed at an angle of approximately 45° except to use the bathroom. They may then move freely within the Phase 1 unit per Institution policy, but should refrain from engaging in any strenuous activity throughout the study period.

6.6 Sumatriptan (Imitrex)

Sumatriptan (Imitrex) 100 mg will be supplied by the Investigator (or designee) as tablets for oral administration. Branded Imitrex is planned to be used in this study. In the event that it becomes unavailable, a generic substitute may be used.

6.7 Sumatriptan (Imitrex) Administration

Investigational site staff will dispense sumatriptan (Imitrex) 100 mg according to the dosing plan. Sumatriptan (Imitrex) will be co-administered with either lasmiditan or lasmiditan placebo. The two study drugs will be swallowed simultaneously with 240 ml of water.

After dosing and rinsing with water, a hand and mouth check will be performed. Subjects will receive study drug in a sitting position on the bed. For the first 4 hours after each dose, the subjects will continue to fast and must remain seated on their bed at an angle of approximately 45° except to use the bathroom. They may then move freely within the Phase 1 unit per Institution policy but should refrain from engaging in any strenuous activity throughout the study period.

6.8 Sumatriptan Storage

Sumatriptan (Imitrex) tablets should be stored according to manufacturer's instructions.

6.9 Drug Accountability, Dispensing and Destruction

Under supervision of the Investigator or designee, the study pharmacist or designee will be responsible for drug accountability. The pharmacist or designee will keep an accurate inventory of both study drugs and dispensing using a drug dispensing log. The pharmacist or designee must keep study drug inventory available for inspection by the Sponsor, an agent for the Sponsor, and regulatory authorities.

The Investigator or designee will administer the study drugs only to the identified subjects of this study, following the procedures described in this study protocol.

If any unused study drug remains at the site at study completion, the pharmacy will be instructed how to dispose of or return the material to the Sponsor after the Sponsor's representative has performed accountability. The Sponsor's representative will complete authorization forms for disposal or return with the responsible pharmacist or designee. Copies of these forms should be included with the returned material. The original form should be maintained in the pharmacy within the site study files.

The study drugs supplied for this study are only intended for use by subjects in this study. They must not be diverted for use by other subjects or personnel.

7. METHODS OF ASSESSMENT

So that data capture can be standardized, all assessments should be performed as indicated. In cases where blood sampling for PK analysis and other assessments (vital signs or ECGs) are scheduled to occur at the same time, the order of procedures will be: 5 minutes supine rest, ECG, supine vitals followed by standing vitals, and PK blood draw. This does not apply to screening procedures.

Every effort should be made to collect the PK samples at the exact times as specified (Table 2). Samples taken pre-dose and up to and including 8 hours post-dose will be taken ±5 minutes of the nominal time. Samples taken after 8 hours post-dose will be taken ±10 minutes of the nominal time.

7.1 Informed Consent

The ICF must be executed prior to performing any study-related activities associated with the study. The ICF must be approved by the reviewing IRB prior to being given to any subject. Informed consent will be obtained for all subjects participating in the study. Subjects may withdraw consent at any time. Participation in the study may be terminated at any time without the subject's consent as determined by the Investigator or designee.

7.2 Inclusion/Exclusion Criteria

Eligibility screening of healthy subjects will be completed within 21 days prior to administration of the study drug in the first period and will be documented on the CRF. Confirmation of eligibility will be performed after check-in of each dosing period.

Screen failures and the reason for failure to meet the study eligibility requirements will be documented in the study site source documents but not entered into the study database.

7.3 Demographics

During Screening, subject initials, date of birth, age, gender, race and ethnicity will be recorded on source documents and on the CRF. Name, address, phone number, and emergency contact information will be documented in the source documents only.

7.4 Medical History

General and relevant medical history will be recorded during Screening on the source document and CRF and will include information relating to any prior or existing medical conditions involving the following disease types or systems: allergic, endocrine, musculoskeletal, dermatologic, eyes, ears/hearing, nose/throat , reproductive, respiratory, cardiovascular, gastrointestinal, genitourinary, neurological, immune system, blood disorders, cancer and psychiatric. History of hospitalization, history of surgery, pre-planned future surgeries (e.g., elective procedures for preexisting

conditions that did not worsen) will be recorded. History of tobacco/nicotine/alcohol/caffeine/drug use will also be recorded.

Prior medication used in the last 30 days to treat any medical conditions will be recorded on the CRF.

7.5 Physical Examination

A complete physical examination will be completed and recorded at Screening and EoS. The examination will be done at the nominal time +/- 10 hours.

A complete physical examination will include the following: general appearance, skin, HEENT, heart, lymph nodes, lungs, abdomen, extremities/joints, neurological systems, and mental status.

A brief, targeted (symptom-related) physical examination will be performed if indicated by an AE during each dosing period.

Height, Weight (without shoes) and BMI calculation will be performed at Screening only.

7.6 Vital Signs

Vital signs, measured after at least 5 minutes supine, will include supine systolic blood pressure (SBP), supine diastolic blood pressure (DBP), heart rate (HR), respiration rate (RR), and oral body temperature. All vital sign measurements will be performed by appropriately qualified and authorized study personnel, using appropriate equipment.

BP and HR will be measured if possible in the same arm at each visit by using automated devices. BP results will be recorded in millimeters of mercury (mmHg). HR will be measured in the humeral artery in the dominant arm for approximately 30 seconds and will be recorded as beats per minute (bpm). RR will be measured and recorded in breaths per minute. Oral body temperature will be measured in degrees Celsius.

At Screening and for interim and study exit vital signs, subjects who have a supine systolic BP > 135 mm Hg or < 90 mm Hg or who have a supine diastolic BP > 85 mm Hg or < 50 mm Hg will undergo at least one BP reassessment within 15 minutes of the original. Subjects who have a heart rate > 90 bpm or < 50 bpm will undergo at least one heart rate reassessment within 15 minutes of the original. All out of range results will be assessed by the PI, Sub-Investigator, or designee.

If interim BP or heart rate values are deemed clinically significant, subjects should be monitored by study staff and if deemed necessary from a safety standpoint, the patient will be discontinued.

Vital signs will be taken at Screening and at EoS. During each dosing period, they will be taken at check-in on Day -1, on Day 1 within 60 minutes of dosing and 1, 2, 4, and 8 hours after dosing, and on Day 2, 24 hours after dosing. Assessments will be performed at the nominal times +/- 15 minutes.

7.7 Orthostatic Vital Signs

Orthostatic vital signs will be measured after at least 5 minutes supine then at least 2 minutes standing and will include systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). Any subjects experiencing a decrease in systolic and/or diastolic blood pressure great than 20 mmHg will undergo at least one reassessment within 15 minutes of the original. All out of range results will be assessed at the discretion of the PI, Sub-Investigator, or designee. If interim results are deemed clinically significant, subjects should be monitored by study staff and if deemed necessary from a safety standpoint, the patient will be discontinued.

Orthostatic vital signs will be taken at Screening. During each dosing period they will be taken at Day 1 within 60 minutes of dosing and 1 and 2 hours after dosing. Assessments will be performed at the nominal times +/- 15 minutes.

7.8 ECG

A standard, digital 12-lead ECG with a 10-second rhythm strip will be used to assess cardiac function after subjects have been at least 5 minutes supine.

ECGs will be taken at Screening and at EoS. During each dosing period they will be taken on Day 1 within 75 minutes prior to dosing and 1, 1.5, 2, 2.5, 4, and 8 hours after dosing, and on Day 2 at 24 hours after dosing. Assessments will be performed at the nominal times +/- 15 minutes.

Trained study staff will perform the ECGs and all ECG results must be reviewed at the site by the Investigator or a medically qualified designee for clinical management of the subject. ECG values of HR, RR, PQ/PR, QRS, QT QTcF and QTcB, calculated by the Fridericia formula ($QTc = QT/(RR)^{0.33}$ and Bazett formula ($QTc = QT/(RR)^{0.5}$, respectively will be presented. The Investigator or a designee will evaluate whether the ECG is normal or abnormal. Abnormal findings will be identified as either clinically significant (CS), or not clinically significant (NCS). CS findings that emerge after dosing in all periods are to be reported as AEs by the Investigator or designee.

The clinical significance of ECG changes will be determined by the Investigator or designee after review of the ECG report with relation to the subject's medical history, physical examination, and concomitant medications.

ECGs may be repeated for quality reasons and the repeat used for analysis. Additional ECGs may be collected by the Investigator or designee for safety reasons. The electronic version of the ECG is regarded as source data. The conduct and evaluation of ECG recordings will be carried out according to the Institution's procedures.

If treatment-related abnormal ECG changes occur, subjects may be treated with medications such as nitroglycerin, aspirin, or may be given supplemental oxygen.

7.9 VAS scales

VAS scales will be administered following dosing according to the schedules in Table 1 and Table 2. These scales are 100 mm scales. The subject chooses the point along the scale that is consistent with their current state. They will be administered by paper. Subjects will be trained on Day -1 of each dosing period as described in Section 7.9.6. Scoring of the scales will be done by trained staff.

7.9.1 Bipolar Drug liking

Subjects will rate "At this moment, my liking for the drug is" on the bipolar drug liking scale. Anchors will be

- 0: Strong disliking
- 50: Neither liking nor disliking
- 100: Strong liking

The bipolar drug liking VAS will be completed during each dosing period on Day 1 within 60 minutes prior to dosing and at 1, 2, 4, and 8 hours +/- 20 minutes after dosing.

7.9.2 Bipolar High VAS

Subjects will rate "I am feeling high" on the bipolar drug high scale using the anchors:

- 0: Definitely not
- 50: Neutral
- 100: Definitely so

The bipolar high VAS will be completed during each dosing period on Day 1 within 60 minutes prior to dosing and at 1, 2, 4, and 8 hours +/- 20 minutes after dosing.

7.9.3 Unipolar Sedation

Subjects will rate "At this moment, I am feeling..." with the anchors:

- 0: Alert
- 100: Drowsy

The unipolar sedation VAS will be completed during each dosing period on Day 1 within 60 minutes prior to dosing and at 1, 2, 4, and 8 hours +/- 20 minutes after dosing.

7.9.4 Unipolar Overall drug liking VAS

Subjects will rate "Overall, my liking for the drug is ..." on the unipolar overall drug liking scale using the anchors:

- 0: Strong disliking
- 100: Strong liking

The unipolar overall drug liking VAS will be completed on Day 1 within 60 minutes prior to dosing and on Day 2 at 24 hours +/- 20 minutes after dosing.

7.9.5 Unipolar Take drug again VAS

Subjects will rate "I would take this drug again' on the unipolar scale using the anchors:

- 0: Definitely not
- 100: Definitely so

The unipolar take drug again VAS will be completed on Day 1 within 60 minutes prior to dosing and on Day 2 at 24 hours +/- 20 minutes after dosing.

7.9.6 Training on VAS scales

Subjects will be trained on the VAS scales on Day -1 of each period. Training will include a brief review of how the scales are completed and the completion of three training scales. The same three scales will be used for every period.

The training scales will be:

- Bipolar: "Last night, I slept..." using the anchors 0: Very badly, 50: Neither well nor badly, and 100: Very well.
- Bipolar: "My dinner last night was..." using the anchors 0: the worst I have ever had, 50: neither good nor bad, and 100: the best I have ever had.
- Unipolar: "The weather yesterday was great" using the anchors 0: Definitely not and 100: Definitely so.

7.9.7 Drug Effects Questionnaire (DEQ-5)

The standardized Drug Effects Questionnaire (DEQ-5) [11] is composed of five DEQ constructs: Feel, High, Dislike, Like, and More. Studies have demonstrated that it reliably shows differences in subjects' subjective experience of substances and placebo and that it has convergent, concurrent, and predictive validity.

The DEQ-5 will be completed during each dosing period on Day 1 within 60 minutes prior to dosing and at 1, 2, 4, and 8 hours after dosing and on Day 2 at 24 hours +/- 20 minutes after dosing.

7.10 C-SSRS

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

At Screening, the Screening version of the C-SSRS will be used. The 'Since the last visit' version will be used in each dosing period at check-in on Day -1 and on Day 2 at 30 hours +/- 10 hours after dosing and at EoS.

If present, suicidal ideation will be classified in 5 classes (1-5), the intensity of suicidal ideation will be classified in 5 dimensions, and any suicidal behavior will be classified in

6 classes (actual attempt, interrupted attempt, aborted attempt, preparatory acts towards and attempt, suicidal behavior, suicide).

7.11 Clinical Laboratory

7.11.1 Laboratory Parameters

Laboratory testing (hematology with differential, serum chemistry and urinalysis) will be performed using standard methods.

All subjects must fast at least 8 hours prior to any clinical laboratory assessment blood draw.

The urine screen for drugs of abuse will be performed at Screening and on Day -1 of each dosing period at check-in. Hepatitis B/C and HIV serology will be performed at Screening. Serum pregnancy testing will be done on all female subjects at Screening and EoS. Urine pregnancy testing will be completed on all female subjects on Day -1 of each dosing period at check-in. Clinical laboratory testing (CBC, chemistry, and urinalysis) will be performed at Screening, Day -1 of each dosing period, and EoS.

Table 3: List of Laboratory Tests

Hematology	Serum Chemistry	
RBC Hematocrit Hemoglobin Mean corpuscular hemoglobin (MCH) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin concentration (MCHC) Platelet count WBC count (with differential) Neutrophils (granulocytes) Lymphocytes Monocytes Basophils Eosinophils	Creatinine Potassium (K+) Sodium (Na+) Chloride (Cl-) Magnesium (Mg++) Glucose Urea Bilirubin (Total) Bilirubin (direct)	eGFR AST ALT AP Total Protein Albumin CO_2
Urinalysis: Macroscopic examination routinely including specific gravity, pH, protein, glucose, ketones, blood and urobilinogen. A microscopic examination will be performed if warranted based on macroscopic results.		
Urine drug screen: A urine sample will be collected and analyzed (positive or negative) for drugs of abuse including amphetamine, opiate, cocaine, barbiturates benzodiazepines, and marijuana (tetrahydrocannabinol [THC]). For the Screening visit only, cotinine will be included in the urine drug screen panel.		
Serology: Testing for HbsAg, Hepatitis C antibody and HIV 1 and 2 will be performed at the screening visit only. Results of each serology test will be reported as either positive or negative.		
For females: A serum_hCG test at the screening visit and EoS, urine_hCG test on the day of Phase 1 unit admission for each of the three treatment periods (Day -1 of each dosing period).		
AST: aspartate aminotransferase; ALT: alanine aminotransferase; AP: alkaline phosphatase; HbsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; HIV: human immunodeficiency virus; RBC: red blood cell; WBC: white blood cell		

7.11.2 Clinical Laboratory Sample Collection, Storage, and Shipping

Detailed instructions for laboratory sample collection, processing, and shipping instructions will be provided in the Laboratory Manual.

Biological material will be stored and secured, in a way that assures that unauthorized access is prohibited and the samples are not lost, deteriorated or accidentally or illegally destroyed. Details for storage and shipping will be provided in the Laboratory Manual.

7.11.3 Abnormal and Clinically Significant Results

The Investigator or designee must categorize all abnormal hematology, chemistry, and urinalysis laboratory values as either CS or NCS. Clinical significance is defined as any variation in laboratory parameters which has medical consequences that result in an alteration in the subject's medical care. The Investigator or designee will use the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 as a guide when evaluating the clinical significance of all abnormal clinical laboratory results. In case of CS laboratory results, the Investigator or designee will continue to monitor the subject with additional laboratory assessments until (1) values have reached normal range and/or baseline levels, or (2) the Investigator or designee has judged that the abnormal values are not related to the administration of study drug or other protocol specific procedures.

7.12 Breathalyzer Test

A breathalyzer assessment of breath alcohol concentration will be performed. Subjects with a positive test result at Screening or Day -1 of Period 1 will be excluded from the study; subjects with a positive result at Day -1 of Period 2 or 3 will be terminated from the study.

The breathalyzer assessment will be performed will be performed at Screening and on Day -1 of each dosing period at check-in

7.13 Pharmacokinetics Samples

Blood samples will be collected within 60 minutes prior to the start of dosing and then 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24 and 30 hours following the dose at time 0 in each dosing period. Samples collected during the first 8 hours post-dosing (including the 8 hour time-point) will be collected at the nominal times +/- 5 minutes. Samples collected after the first 8 hours post-dosing will be collected at the nominal times +/- 10 minutes

Samples taken pre-dose and up to and including 8 hours post-dose will be taken ±5 minutes of the nominal time. Samples taken after 8 hours post-dose will be taken ±10 minutes of the nominal time. In cases where blood sampling for PK analysis and other assessments (vital signs or ECGs) are scheduled to occur at the same time, the

order of procedures will be: 5 minutes supine rest, ECG, supine vitals followed by standing vitals, and PK blood draw.

7.13.1.1 Sample Collection, Preparation, and Handling

Blood samples will be collected into lithium heparinized polypropylene tubes (6.0 mL). The tubes should be mixed immediately after filling by gently inverting the tubes at least 8 to 10 times and should be placed on ice after the sample is collected. Thereafter, the tubes will be centrifuged as soon as possible (within 30 minutes of collection) at a minimum of 1500 g for 15 minutes at 2°C until cells and plasma are well separated. The resulting plasma samples will be transferred into two (duplicate) 1.8 ml cryovial tubes and labeled appropriately. The samples will be frozen as soon as possible (within 24 hours) of collection and stored frozen at –60 to -80°C until time of shipment to Covance Laboratories, Inc., 3301 Kinsman Blvd. Madison, WI 53704, US for analysis.

The times of blood sample collection, pipetting and freezing will be recorded in the source documents.

7.13.1.2 Assay Methodology

Plasma samples will be analyzed for lasmiditan at Covance Laboratories, Inc., Madison, US, 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.

7.13.1.3 Pharmacokinetic Parameters

The following compartmental pharmacokinetic parameters will be derived from plasma concentrations of lasmiditan:

C_{max} Maximum plasma concentration as observed

$AUC_{0-\infty}$ 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

t_{max} Time to maximum plasma concentration

λ_z Apparent terminal rate constant determined from the slope of the log-transformed plasma concentration curve

$t_{1/2}$ Apparent terminal elimination half-life, calculated as $\ln(2)/\lambda_z$

7.14 Adverse Events and Serious Adverse Events

7.14.1 Adverse Events

An AE is defined as any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of a study treatment or procedure that may or may not be considered related to the study treatment or procedure. AEs are collected from the time the subject signs the informed consent form until the completion of EoS. AEs that occur prior to dosing in period 1 will be recorded as medical history. Those occurring during and/or after dosing in period 1 will be recorded as adverse events.

Adverse events will be classified according to the Common Terminology Criteria for Adverse Events (CTCAE), v4.03 published June 14, 2010, the most recent version available.[12]

The occurrence of AEs should be sought by non-directive questioning of the subject at each visit in the study. AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the subject and/or observed by the Investigator, designee, or medical staff, and
- Changes in laboratory values that are clinically relevant as assessed by the Investigator or designee and for which a medical intervention was initiated.

All AEs must be recorded in the site's study records and the AE CRF with the following information:

1. Relationship to Study Drug: The Investigator or designee must assess whether they consider an AE drug-related. In assessing this relationship, the Investigator or designee must use information about the drug as outlined in the Investigators' Brochure, the subject's pre-existent medical conditions/concurrent medication, and chronology of the event relative to drug administration. The following definitions will be used:

    - **Reasonably or possibly related** applies to those AEs that, after careful medical consideration at the time they are evaluated, are considered by the Investigator (or designee) to have at least a possible relationship to study drug.

    - **Not reasonably or not possibly related** applies to those AEs that, after careful medical consideration at the time of evaluation, are considered by the Investigator (or designee) to have no relationship, or no reasonable possibility of a relationship, to study drug.

2. Event Severity: The Investigator or designee will be asked to assess the severity of the AE using the CTCAE V4.03[12]. These criteria assign a grade of 1 through 5 to indicate the severity of AEs. For AEs that are not listed in these criteria, the Investigator or designee will use medical judgment to assess the severity of the AE. A general guideline to these grades of severity, taken from CTCAE V4.03, is:
   - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
   - Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (see CTCAE for more details).
   - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization of prolongation of hospitalization indicated; disabling; limiting self care Activities of Daily Living.
   - Grade 4: Life-threatening consequences; urgent intervention indicated.
   - Grade 5: Death related to AE.

   The following are guidelines to be used by the Investigator or designee to judge the event severity of an AE that is not in CTCAE:
   - Mild - awareness of sign or symptom, but easily tolerated
   - Moderate - discomfort enough to cause interference with usual activity
   - Severe - incapacitating with inability to work or perform usual activity
   - Life Threatening
   - Death related to AE

3. Duration: Start and end dates and times, or if continuing.

4. Action taken.

5. Whether it constitutes a SAE, per definition below.

6. Outcome: resolved, resolved/ with sequelae, continuing, death, or unknown (only for subjects that are lost to follow-up).

The Investigator (or designee) should attempt to establish a diagnosis of the AE based on signs, symptoms and/or other clinical information. In such cases, the diagnosis, and not the individual signs/symptoms or laboratory abnormalities, should be documented in the subject's source documentation and the CRF unless the etiology of the event is unknown. An assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to study drug, the interventions required to treat it, and the outcome.

7.14.2 Treatment Emergent Adverse Events (TEAE)

A TEAE will be an AE that occurred during the study after a subject ingested the dose of study drug until 48 hours post-dose or that was present prior to dosing and exacerbated after the dose of study drug. This pertains to all dosing periods.

7.14.3 Serious Adverse Events

An SAE is any AE that results in any of the following outcomes:

- Death: This includes death unrelated to the study drug (e.g. car accident). If a subject dies during the study and an autopsy is performed, autopsy results will become part of the subject's study chart and a copy should be sent to the Sponsor.
- Life-threatening experience
- Required or prolonged inpatient hospitalization: Exceptions will be hospitalizations for a) elective or preplanned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug or b) treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE and not resulting in hospital admission
- Persistent or significant disability/incapacity
- Congenital anomaly
- Important medical events that may not result in death, be immediately life threatening, or require hospitalization may be considered a SAE when, based upon medical judgment, they may jeopardize the patient and may require intervention to prevent one of the outcomes listed above.

7.14.4 Unexpected Adverse Event

An unexpected adverse event is defined as an AE, the nature or severity of which is not consistent with the information in the Investigator's Brochure for lasmiditan or in the Imitrex (sumatriptan) labeling.

7.15 Reporting Serious Adverse Events

The Investigator or designee is responsible for reporting all SAEs, **regardless of causality**, to the Sponsor or their designated representative by phone, fax or email within 24 hours of learning of the occurrence. The reporting timeframe starts when the subject signs the informed consent form and ends at EoS. At a minimum, a description of the event and the Investigator's (or designee) judgment of causality must be provided at the time of the initial report. These preliminary reports will be followed by detailed descriptions that will include copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

Complications or progression of an initial SAE must be reported as a follow-up SAE Report to the original SAE regardless of when the follow-up information is received by the Investigator or designee. A follow-up SAE Report must be submitted within 24 hours of the Investigator or designee receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new SAE.

The procedures for reporting SAEs are as follows:

- Complete the "Serious Adverse Event Report Form". The Investigator or designee may contact the Medical Monitor, Lisa Beth Ferstenberg, MD at 240-688-8572 or lbferstenberg@gmail.com.
- Email the SAE Form to the attention of the Medical Monitor within 24 hours of the Investigator's (or designee's) knowledge of the event. The Sponsor will also be notified of the SAE by phone or email.

The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the source documentation at the study site.

Follow-up information should be communicated in the same way using a new SAE Report Form stating that it is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

If the SAE was not previously documented in the Investigator's Brochure and is thought to be related to study drug, the Sponsor or their designee may urgently require further information from the Investigator or his designee for reporting to the relevant regulatory authority.

The Investigator and study personnel should institute any supplemental investigations of SAEs based on their clinical judgment of likely causative factors. This may include clinical laboratory tests not specified in the protocol, histopathologic examinations, or consultations with specialists. The Sponsor or their designee may also request the Investigator or designee to conduct supplemental assessments.

The Investigator or designee should notify the Medical Monitor of any death or SAE occurring after a subject has withdrawn from the study when such a death or SAE may reasonably be related to the study drug. However, the Investigator is not obligated to actively seek adverse events in former study participants.

7.16 Follow-up of Adverse Events

All SAEs and any non-serious adverse events or laboratory abnormalities resulting in premature discontinuation will be followed until they have resolved, returned to baseline, or are determined to be chronic or stable by the Investigator or designee. Other non-serious adverse events should be followed through the EoS.

7.17 Procedures for unblinding Investigational Product

When it is required to ensure the safety and appropriate care of the subject, the Investigator can break the blinded treatment assignment to determine which treatment a subject has received and to initiate appropriate medical care. When possible, the Medical Monitor should be notified prior to breaking the blind. If not possible in advance, the Investigator or designee will inform the Medical Monitor as soon as possible after the event. The reason for breaking the blind will be recorded in the source documents.

7.18 Reporting Safety Information to the IRB

The Investigator or designee is responsible for following all local regulations for the reporting of safety information, including the reporting of SAEs to the IRB.

The Investigator or designee must promptly report to his or her IRB all unanticipated problems involving risks to subjects. This includes death from any cause and all serious adverse events reasonably or possibly associated with the use of study drug. It is recommended that all SAEs occurring at a site, regardless of causality, be reported to the site's IRB in accordance with the IRB's requirements.

Lasmiditan has been filed under an Investigational New Drug (IND) application with the US FDA. An SAE may require safety reports to be filed to regulatory agencies if the SAE is related to the study drug and is unexpected based upon the current Investigator's Brochure. In this case, the Investigator will receive a copy of the safety report as submitted to the regulatory agencies. The Investigator or designee is responsible for submitting the safety report (initial and follow-up) or other safety information (e.g., revised Investigator's Brochure) to the IRB in accordance with the IRB's requirements and to keep a copy in their files.

7.19 Pregnancies

To ensure subject safety, each pregnancy in a subject on study drug must be reported to the medical monitor within 24 hours of learning of its occurrence. Subjects who become pregnant will be withdrawn from the study. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a subject's source documents and a Pregnancy Notification and Outcome Form and reported by the Investigator or designee to the Medical Monitor. A pregnancy, by itself, is not a SAE. Pregnancy follow-up should also be recorded and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any pregnancy-related SAE (e.g. spontaneous abortion) or any other SAE experienced during pregnancy must be recorded on a separate SAE Report Form and reported per SAE reporting procedures.

8. STATISTICAL METHODS

Before database lock, a statistical analysis plan (SAP) will be issued as a separate document, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described and justified in the final integrated clinical study report.

8.1 Sample Size

To ensure that at least 36 subjects complete, at least 42 subjects (approximately 60% female) will be enrolled.

8.2 Study Population

8.2.1 Disposition of Subjects

The number and percentage of subjects entering and completing each period of the clinical study will be presented, by dosing sequence.

8.2.2 Protocol Deviations

Deviations from the protocol, including deviations of inclusion/exclusion criteria will be assessed as "minor" or "major" in agreement with the Sponsor. Major deviations from the protocol will lead to the exclusion of a subject from the PK analysis set. Deviations will be defined before the database lock report planning meeting.

8.2.3 Analysis Populations

Pharmacodynamic population: All randomized subjects who received at least one dose of any study drug.

Safety population: All randomized subjects who received at least one dose of any study drug.

Pharmacokinetic 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.

The primary results will be based on the pharmacodynamic population. All safety analyses will be based on the safety population.

8.3 General Considerations

Continuous measurements will be summarized by means of descriptive statistics (i.e., number of observations, mean, standard deviation, minimum, median, maximum), 90% confidence intervals may be given additionally. Categorical data will be summarized using frequencies or percentages.

8.4 Pharmacodynamic Analyses

8.4.1 Adverse Events

The discrete outcome variables are the treatment emergent adverse events. A general linear random model will be used to compare and contrast the frequency difference of TEAEs in the different treatment groups, lasmiditan 200 mg co-administered with sumatriptan (Imitrex) 100 mg, lasmiditan 200 mg co-administered with lasmiditan placebo 200 mg, or sumatriptan (Imitrex) 100 mg co-administered with lasmiditan placebo 200 mg.

Adverse events will be summarized by treatment group (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 sequence, MedDRA latest version, system organ class, and preferred term.

8.4.2 Vital Signs

The continuous outcome variables, vital signs (BP, HR, RR and oral body temperature), will be summarized by treatment (lasmiditan 200 mg co-administered with sumatriptan (Imitrex) 100 mg, lasmiditan 200 mg co-administered with lasmiditan placebo 200 mg, or sumatriptan (Imitrex) 100 mg co-administered with lasmiditan placebo 200 mg) using descriptive statistics. Changes from baseline in vital signs will be summarized by descriptive statistics for each dosing sequence.

8.4.3 ECG Results

All ECG endpoints will be listed by treatment (lasmiditan 200 mg co-administered with sumatriptan (Imitrex) 100 mg, lasmiditan 200 mg co-administered with lasmiditan placebo 200 mg, or sumatriptan (Imitrex) 100 mg co-administered with lasmiditan placebo 200 mg), subject and time of assessment and summarized by descriptive statistics. Changes from baseline in ECG parameters will be summarized by descriptive statistics by dosing sequence.

8.4.4 Physical Examination Results

Subjects with any changes in the physical examination evaluation from Screening to EoS will be listed and the temporal occurrence of the change relative to the treatment (lasmiditan 200 mg co-administered with sumatriptan (Imitrex) 100 mg, lasmiditan 200 mg co-administered with lasmiditan placebo 200 mg, or sumatriptan (Imitrex) 100 mg co-administered with lasmiditan placebo 200 mg) identified. A description of the study population in terms of baseline measures and demographics will be presented.

8.5 Pharmacokinetic Analyses

All evaluable subjects will be included in the PK analysis. The evaluable PK population will include all subjects who completed at least one treatment period without any protocol violations that would likely affect the PK results, who have evaluable plasma concentration data for lasmiditan and/or sumatriptan (Imitrex), and for whom at least a subset of the designated PK parameters can be determined.

Data will be summarized using descriptive statistics (sample size, mean, median, standard deviation, minimum, and maximum) for continuous variables and using frequency and percentage for discrete variables for each treatment unless additional analysis is deemed appropriate based upon a review of the PK results.

Standard PK parameters (C_{max}, t_{max}, $t_{½}$ and AUC [$AUC_{(0\text{-last})}$ and $AUC_{(0\text{-}\infty)}$] of lasmiditan 200 mg will be used to describe the characteristics of the drug when co-administered with sumatriptan (Imitrex) or when taken alone.

The primary statistical analysis will use the paired t-test applied to log-transformed PK parameter (lasmiditan C_{max} or AUC_{30} separately) in the lasmiditan/sumatriptan (Imitrex) treatment period paired with the same subject's parameter value in the lasmiditan treatment period. From this model the means for each treatment and mean differences to the reference lasmiditan treatment will be estimated with the corresponding 90% confidence intervals. These estimates will then be exponentiated to produce the estimates of geometric mean ratios with their 90% confidence intervals. It will be concluded that sumatriptan (Imitrex) has no effect on lasmiditan PK, if 90% confidence intervals for ratios of PK parameters derived in lasmiditan/sumatriptan (Imitrex) treatment period to those derived in lasmiditan treatment period are within the 80-125% interval.

The sample size of 36 subjects will provide at least 80% power to show equivalence of the PK of lasmiditan in the absence and presence of sumatriptan (Imitrex), assuming a 25% within subject coefficient of variation.

8.6 Safety Analyses

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.

8.6.1 Adverse Events

Discussion of Adverse Event Analysis is in Section 8.4.1.

8.6.2 Clinical Laboratory

Clinical laboratory values will be summarized by descriptive statistics by treatment (lasmiditan 200 mg co-administered with sumatriptan (Imitrex) 100 mg, lasmiditan 200 mg co-administered with lasmiditan placebo 200 mg, or sumatriptan (Imitrex) 100 mg co-administered with lasmiditan placebo 200 mg). Changes from baseline in clinical laboratory values will be summarized by descriptive statistics. All clinical laboratory values outside normal range (including Screening and EoS examination) will be listed by treatment (lasmiditan 200 mg co-administered with sumatriptan (Imitrex) 100 mg, lasmiditan 200 mg co-administered with lasmiditan placebo 200 mg, or sumatriptan (Imitrex) 100 mg co-administered with lasmiditan placebo 200 mg) and subject number, including demographic information and flagging of values.

8.7 Interim Analyses

No formal interim analysis is planned for this study.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

9.1 Study Monitoring

The investigator will allow the Sponsor or a designee to:

- inspect the site, the facilities, and the material used for the study;
- meet all members of the team involved in the study;
- consult all the documents relevant to the study;
- check that the CRFs have been correctly completed;
- have direct access to source documents for comparison of data therein with the data in the CRFs;
- check that AEs have been documented; and
- verify that the study is carried out in compliance with the protocol.

This study will be monitored at regular intervals, by agreement of the Investigator.

All information dealt with during these visits will be treated as strictly confidential.

The Investigator or designee will provide the sponsor with the following:

- Progress reports at regular intervals
- Adequately completed CRFs

9.2 Data collection

The Investigational site will be supplied with instructions on completing the CRFs. Designated site staff will enter the data with respect to protocol procedures, drug administration, laboratory data, and safety data on the CRFs.

Completed and reviewed CRFs must be available for monitoring and collection by the monitor at the end of the study.

All corrections on a CRF and on source data/documents must be made in a way which does not obscure the original entry. The correct data must be inserted, dated and initialed by relevant, authorized study site personnel. If the reason for the correction is not obvious, an explanation should be provided.

The Principal Investigator must, as a minimum, sign the final CRF page to attest to the accuracy and completeness of all the data.

9.3 Audits and Inspections

If the Sponsor chooses to conduct an audit before, during, or after the study, the Investigator or designee will be informed that an audit will take place.

The Investigator will be informed that the Regulatory Agencies may also carry out an inspection. In this case, the Investigator or designee must inform the sponsor as soon as he receives the notification of inspection.

The Investigator must allow the representatives of the Regulatory Agencies and persons responsible for the audit to:

- inspect the site, facilities, and material used for the study;
- meet all members of his team involved in the study;
- have direct access to study data and source documents;
- consult all the documents relevant to the study.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator or the appointed persons agree to complete the subject's CRF at each investigation. Only the Investigator or appointed persons in his/her team may fill out or correct the CRFs. The CRFs will display the subject number corresponding to the order of inclusion in the study (3 digits) and the initials of the subject (1 letter for forename, 1 letter for middle name and 1 letter for surname).

The Sponsor or their designee will review the CRFs entered by investigational site staff for completeness and accuracy and instruct the investigational site staff to make any required corrections or additions. Queries will be sent to the investigational site. Designated investigational site staff will be required to respond to the query and make any necessary changes to the data.

All corrections and alterations of data on the CRFs must be made by the Investigator or by the appointed persons as instructed in the CRF guidelines. If corrections or alterations are required of paper source documents, corrections may be made in the following manner: strike through the datum to be corrected using a single line so that the original remains legible; correction fluid must never be used. The correction should be written to the side or above the original entry and must be initialed and dated by the Investigator or designee.

It is the responsibility of the monitor to make certain that all data are completed on the CRFs.

At the end of each study period, the Investigator and the monitor must sign and date the CRF per the CRF procedure in order to attest respectively to the:

- authenticity of the data collected in the CRF, and
- coherence between the data in the CRF and those in the source documents.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Adverse events and medical history will be coded using the MedDRA terminology.

ECGs will be processed at the Phase 1 unit. Clinical laboratory samples will be processed through the laboratory at the Phase 1 unit.

After the above actions have been completed and the database has been declared to be complete and accurate, it will be locked for data analysis. Any changes to the database after that time can only be made with the approval of CoLucid Pharmaceuticals, Inc.

The Investigator or designee will keep a log of volunteers screened for study participation as appropriate and will indicate the reason why individual volunteers did not enter the study. The log will be submitted to the Sponsor or their designee as defined in the study manual. The Investigator or designee must submit to the Sponsor or its representatives a completed CRF for each subject who receives any study drug.

If computerized medical files are used and if the computer system allows, no change made in the medical files by the Investigator or designee should obscure the original information. The record must clearly indicate that a change was made and clearly provide a means to locate and read the prior information. The Investigator or designee will save data at regular intervals.

The Investigator or designee must guarantee the safety of the study data in the medical files by implementing security measures to prevent unauthorized access to the data and to the computer system.

11. ETHICS

The study will be carried out in accordance with:

- the text of the Declaration of Helsinki adopted by the World Medical Assembly in June 1964; amended in Tokyo, October 1975; in Venice, October 1983; in Hong Kong, September 1989; in Somerset West, October 1996; and in Edinburgh, October 2000; updated with the clarification note, Washington 2002, and Tokyo 2004;
- the ICH recommendations: Good Clinical Practice (E6), applied since January 17, 1997;
- and other applicable regulations.

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

11.1 Ethics Review

11.1.1 IRB opinion

Before initiation of the study, the Investigator or designee must obtain approval or favorable opinion of the study, informed consent, privacy authorization, and any advertisement for subject recruitment from a properly constituted Institutional Review Board (IRB) before study start. A signed and dated statement that the protocol, informed consent, and advertisement (as applicable) have been approved by the IRB must be given to CoLucid Pharmaceuticals, Inc. or its designated representative(s) before study initiation. Prior to study start, the investigator is required to sign the Investigator statement page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol.

The Investigator or designee is responsible for obtaining continued review of the study at intervals not exceeding one year or otherwise specified by the IRB. The Investigator or designee must supply CoLucid Pharmaceuticals, Inc. with written documentation of continued review of the clinical study.

The Investigator or designee must promptly inform their IRB of all SAEs or other safety information reported from Sponsor.

11.2 Written Informed Consent

Subjects will be informed of the nature of the study, its aim, its possible risks and restrictions, its duration and the fee, if any, they will receive. The protocol will be explained during a meeting prior to the study and each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at

any time. At this meeting, an information sheet will be given to each subject. The subject should read the form and obtain answers to any questions prior to signing and dating the informed consent form. The process of obtaining informed consent should be documented in the subject source documents. Each Investigator or designee must retain the original signed and dated informed consent form. A copy of the signed and dated informed consent form will be given to the subject. No subject can enter the study, or have study specific assessments performed before his/her informed consent has been obtained.

A copy of the approved version must be provided to the CoLucid monitor or designated representative(s) after IRB approval.

11.3 Amendments to the protocol

To alter the protocol, amendment approvals must be received from all parties that approved the original protocol (IRB and if applicable, the local regulatory authorities) before implementation. However, in cases where an amendment is required for subject safety, an amendment may be implemented prior to IRB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator or designee is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol.

CoLucid Pharmaceuticals may make administrative changes (i.e., changes that do not significantly affect subject safety, the study's scope or scientific quality) without a formal protocol amendment.

11.4 Discontinuation of the study

CoLucid Pharmaceuticals reserves the right to discontinue this study under the conditions specified in the clinical trial agreement.

11.5 Study drug supply, storage and tracking

Study drug must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated assistants have access. Upon receipt, study drug should be stored according to the instructions specified on the drug labels. Drug labels will be in the local language and will comply with the legal requirements of the country. Clinical supplies are to be dispensed only in accordance with the protocol.

All empty packaging, partially used containers, and unused supplies may be destroyed at the site, retrieved by the study monitor, or shipped to a designated facility approved by CoLucid Pharmaceuticals according to governmental regulations at the conclusion of this study (or as appropriate during the course of the study), per the instructions of the Sponsor.

The Investigator or designee will keep an accurate accounting of all study drug dispensed, destroyed or returned. Monitoring of drug accountability will be performed by the monitor during site visits and at the completion of the trial.

11.6 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and other study personnel must not disclose such information without prior written approval from CoLucid Pharmaceuticals.

Subject confidentiality will be strictly maintained to the extent possible under the law. Subject names must not be disclosed. Subjects will be identified on the CRFs and other documents submitted to CoLucid Pharmaceuticals, or its designated representative, by their initials and/or assigned subject number. Documents that identify the subject (e.g., the signed informed consent form) will not be submitted to CoLucid Pharmaceuticals or its designated representative and must be maintained in confidence by the Investigator and designee.

11.7 Publication policy

Publication by the study site or Investigator/Institution will not be allowed without the explicit written permission of the Sponsor. The Sponsor will determine authorship of the principal study manuscript(s) in conjunction with the Investigator, in accordance with current guidelines and requirements of medical journals.

12. ADMINISTRATIVE CONSIDERATIONS

12.1 Investigator and Study Administrative Structure

The study administration structure is provided in Table 4.

Table 4: Study Administrative Structure

CPC Principal Investigator:	PPD, MD SNBL CPC 800 W. Baltimore St., 6th Floor Baltimore, Maryland 21201, USA PPD
Sponsor Contact:	PPD Head Clinical and Regulatory Operations CoLucid Pharmaceuticals, Inc. 222 Third Street, suite 1320 Cambridge, MA 02142 PPD
Medical Monitor:	PPD, MD PPD PPD
Study Monitoring (CRA):	PPD PPD PPD
PK Sample Analyses and Bioanalytical Report	PPD Senior Principal Investigator Bioanalytical Chemistry Covance Laboratories, Inc. 3301 Kinsman Boulevard Madison, WI 53704-2523 E-Mail: PPD Phone: PPD Fax: PPD
Data Management, & Statistical Analyses:	PPD 3 Independence Way Suite 106 Princeton, NJ 08540
Safety Clinical Laboratory Testing:	SNBL CPC 800 W. Baltimore St., 5th Floor Baltimore, Maryland 21201, USA
Clinical Trial Drug Supply:	PPD Catalent Pharma Solutions 10245 Hickman Mills Drive Kansas City, MO 64137 USA

12.2 Records Retention

After the study, the Investigator or designee will keep all information relevant to the study for 15 years.

13. REFERENCES

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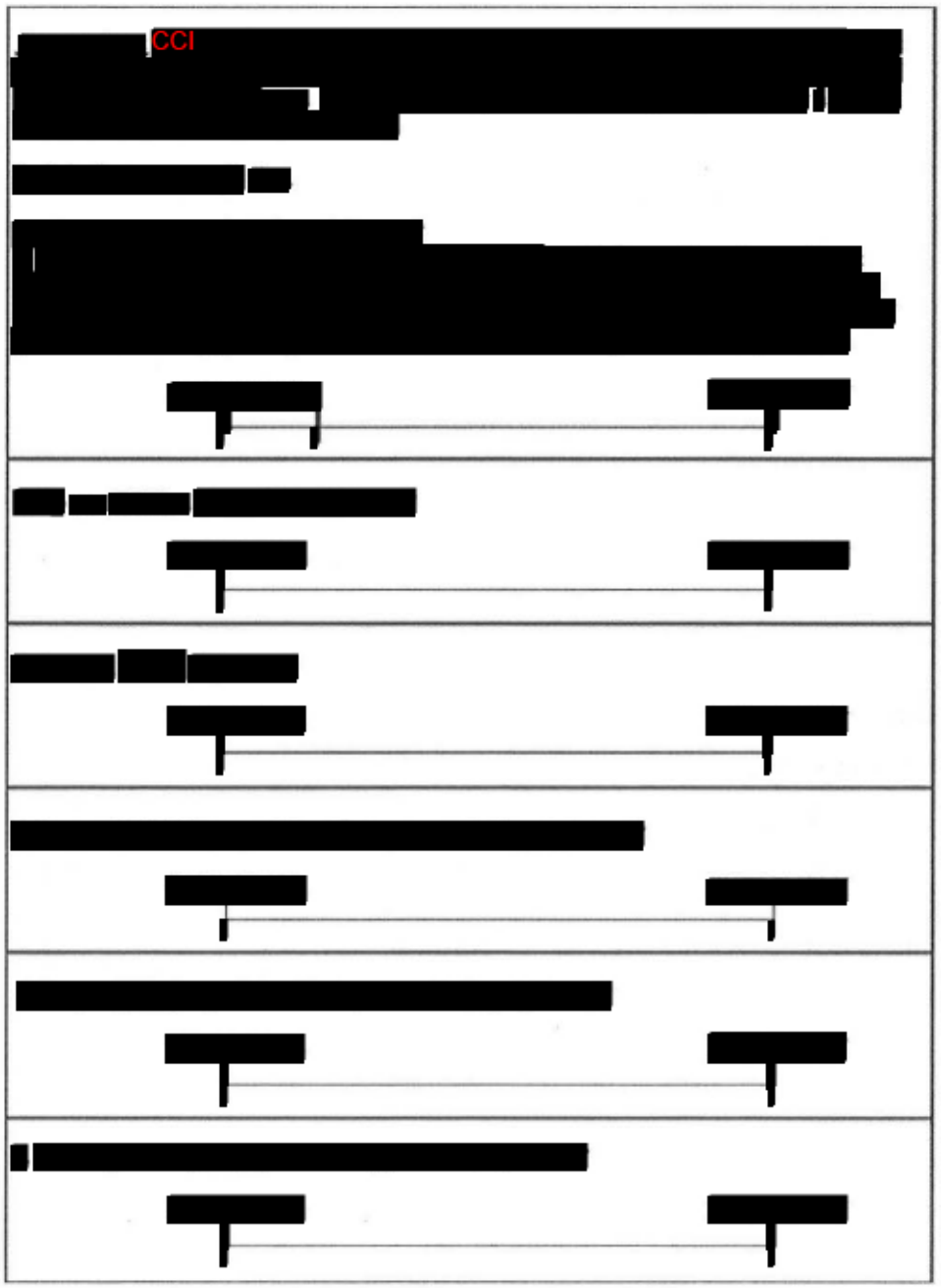
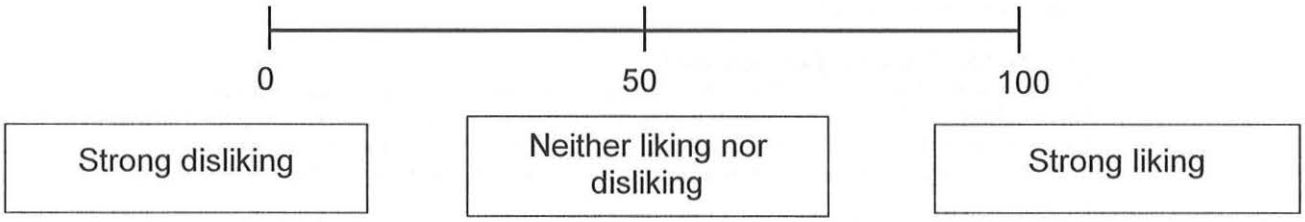
CCI [redacted]



15. Appendix 2. Visual Analogue Scales (VAS)

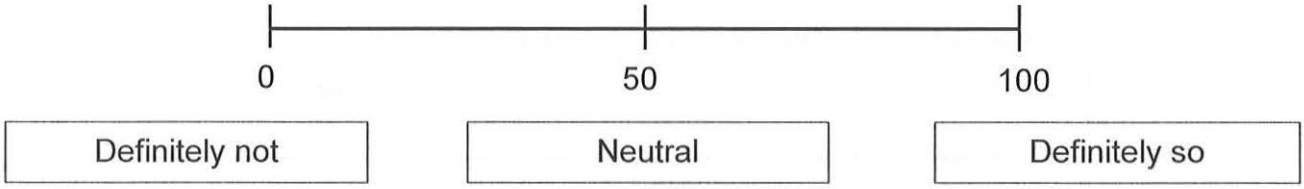
Bipolar Drug liking

At this moment, my liking for the drug is:



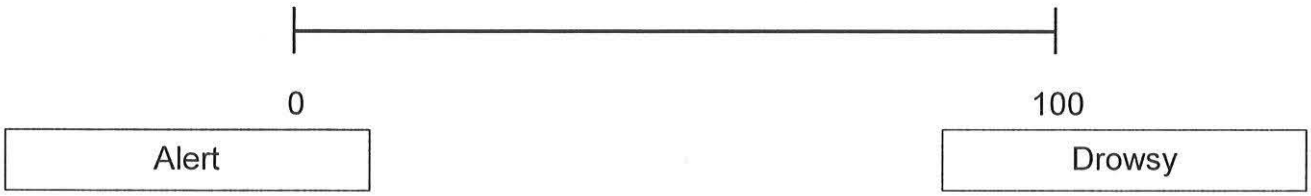
Bipolar High

I am feeling high



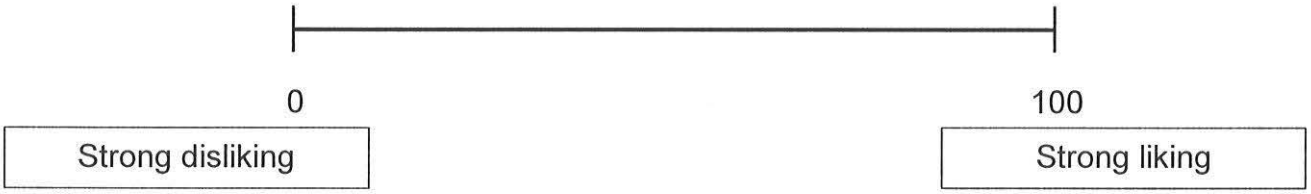
Unipolar Sedation

At this moment, I am feeling…



Unipolar Overall Drug Liking

Overall, my liking for the drug is …

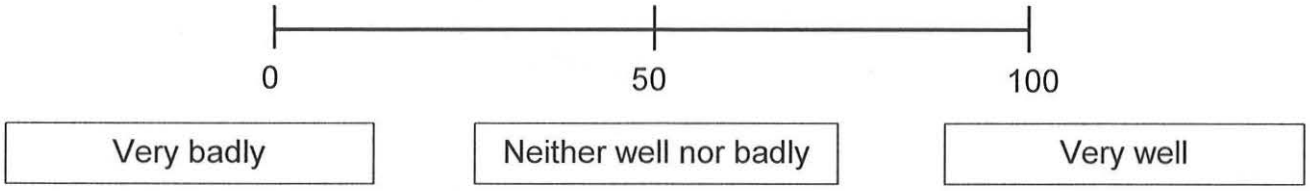


Unipolar Take drug again

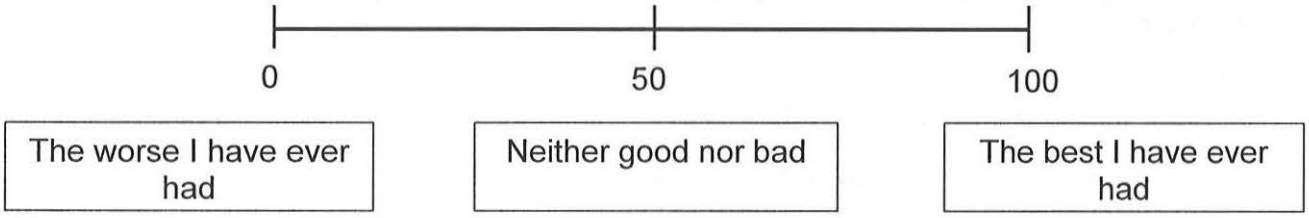
I would take this drug again

VAS Training Scales

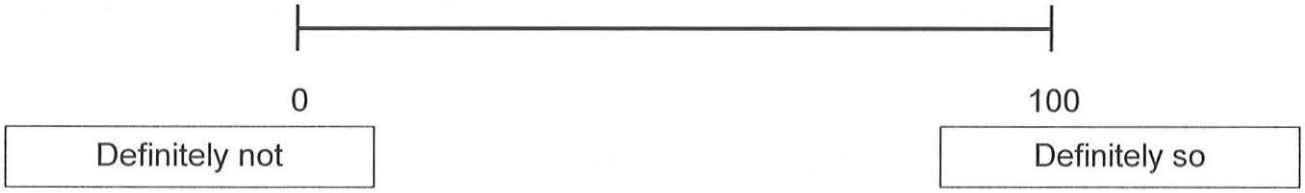
Bipolar: Last night, I slept ...



Bipolar: My dinner last night was...



Unipolar: The weather yesterday was great



CCI [redacted]

CCI [redacted]

PPD [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

PPD [redacted]

CCI [redacted]

CCI [redacted]

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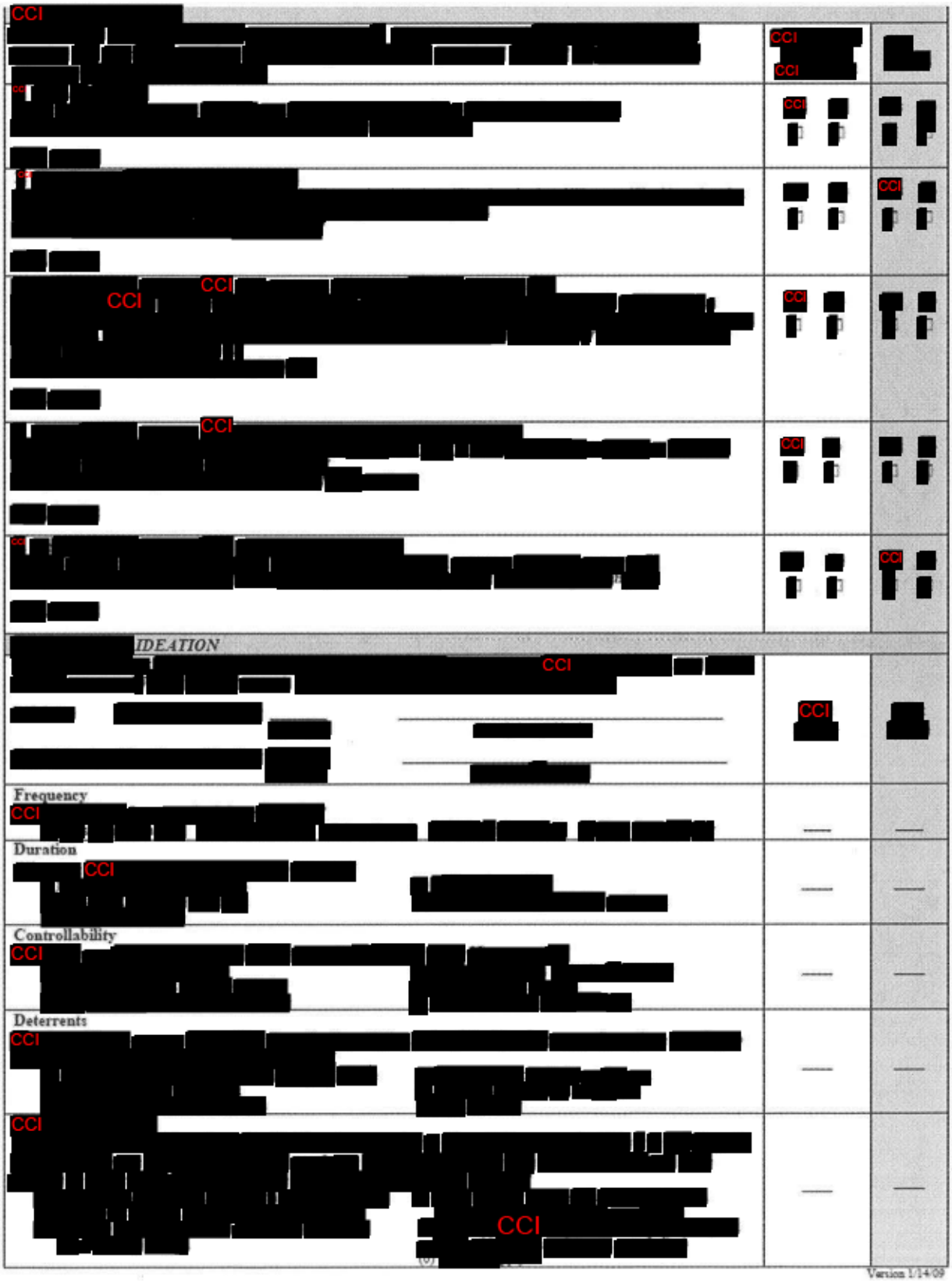
PPD [redacted]

CCI [redacted]


IDEATION
Frequency
Duration
Controllability
Deterrents
Version 1/14/09

CCI [redacted]	[redacted]	CCI [redacted]
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CCI CCI

CCI

PPD

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CCI

PPD , CCI PPD , CCI

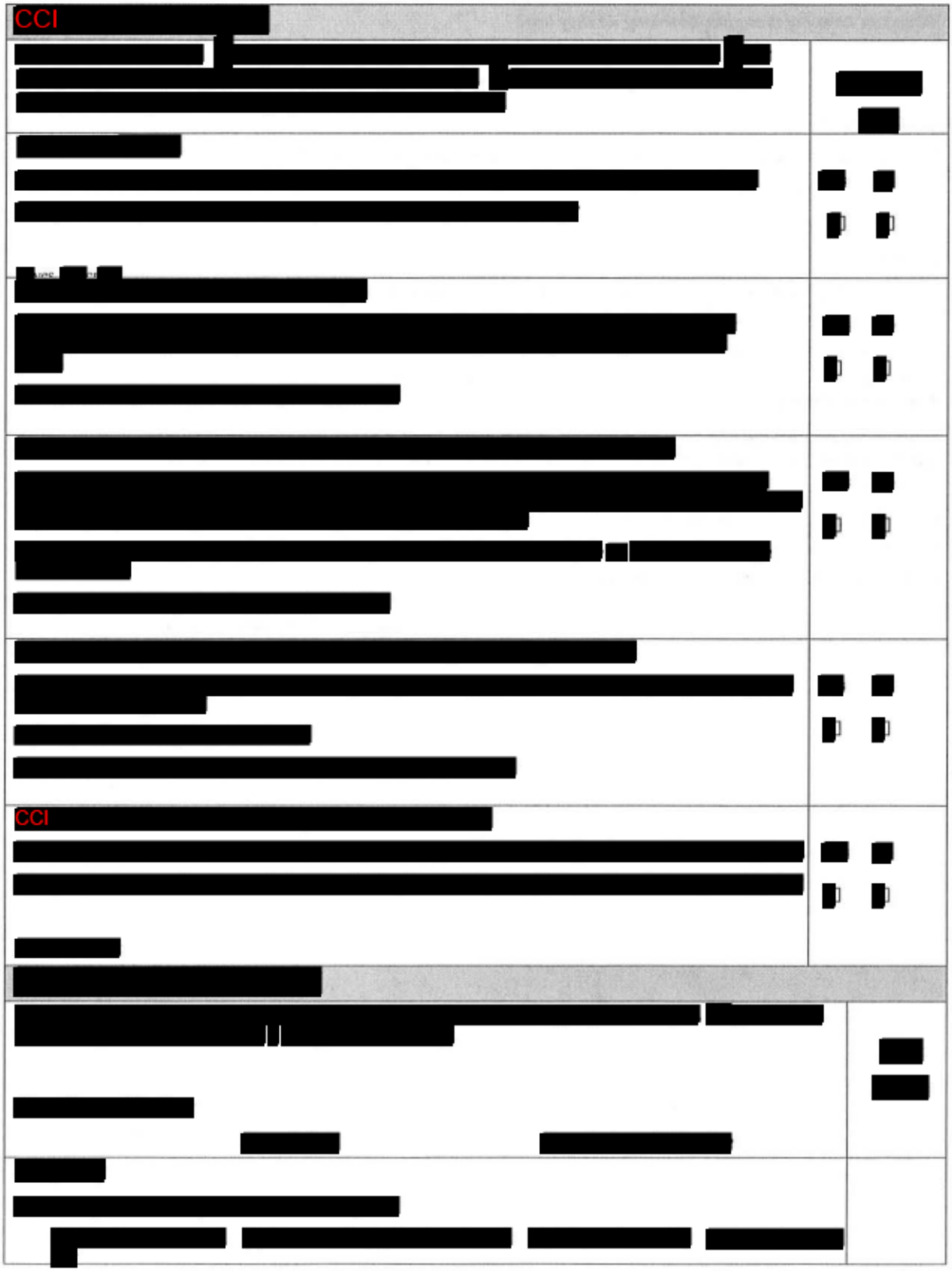
PPD CCI

CCI

CCI PPD , CCI

PPD

CCI


CCI
CCI