Statistical Analysis Plan 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

NCT03076970

Approval Date: 24-May-2017

COLUCID PHARMACEUTICALS INC

Statistical Analysis Plan

PROTOCOL: COL-MIG-118

Version: Final 1.0

Date: 24/May/2017

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
ATC	Anatomic-Therapeutic-Chemical
AUC	Area Under the Plasma Concentration Versus Time Curve
$AUC_{(0\text{-last})}$	Area under the plasma concentration versus time curve from time 0 to last post-dose
$AUC_{(0\text{-}\infty)}$	Area under the plasma concentration versus time curve from time 0 to infinity
BMI	Body Mass Index
BQL	Below Quantification Limit
CBC	Complete Blood Count
C_{max}	Maximum Measured Plasma Concentration
CPK	Creatine Phosphokinase
CRU	Clinical Research Unit
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of Variation
CYP3A4	Cytochrome P450 3A4, an enzyme
DDI	Drug-Drug Interaction
DEQ-5	Drug Effects Questionnaire
ECG	Electrocardiogram
eGFR	Glomerular Filtration Rate
EOS	End of Study
eCRF	Electronic Case Report Form

Abbreviation	Definition
EW	Early Withdrawal
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
IMP	Investigational Medicinal Product
LDL	Low-Density Lipoprotein
LOQ	Limit of Quantification
LS	Least-Squares
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamic
PK	Pharmacokinetic
PKE	Pharmacokinetic Evaluation
RBC	Red Blood Cell
SAP	Statistical Analysis Plan
TEAE	Treatment Emergent Adverse Event
t1/2	Apparent terminal elimination half-life
THC	Tetrahydrocannabinol
T_{max}	Time to Reach Maximum Measured Plasma Concentration
VAS	Visual Analog Scale
Vd/F	Apparent Volume of Distribution
WBC	White Blood Cell
WHO	World Health Organization
λ_z	Apparent First-Order Terminal Elimination Rate Constant

1. INTRODUCTION

Lasmiditan is being developed as a novel acute therapy for migraine. 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. Five Phase 1 studies have been completed in Europe using intravenous (IV), sublingual, and oral formulations of Lasmiditan. This study is designed to 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.

The purpose of this statistical analysis plan (SAP) is to provide all details and specifications for the analysis of the study COL MIG-118, **"**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' **"** as set forth in the clinical study protocol version 1.0 dated 17 February 2017.

2. STUDY DETAILS

2.1 Study Objectives

The study objectives are:

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 Objective-

- 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.

2.2 Study Design

This is a Phase 1, single-center, 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. A total of 42 subjects will be enrolled to ensure at least 36 subjects complete the study with approximately 60% females.

The three dosing periods are as follows-

- 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

Subjects are randomized using the William square design into one of the six treatment sequences ABC, ACB, BAC, BCA, CAB, CBA.

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.

3. DATA ANALYSIS CONSIDERATIONS

3.1 Determination of Sample Size

The sample size calculation for this study is based on the proportion of adverse events in the two treatment groups namely the combination therapy (Lasmiditan + Sumatriptan) vs a single drug (Lasmiditan). The calculation is performed using a test for two proportions in a repeated measures design. To ensure that at least 36 subjects complete, 42 subjects (approximately 60% female) will be enrolled.

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 variance.

4. STUDY ENDPOINTS

4.1 Pharmacodynamic (PD) Endpoint

Adverse Event and Vital Signs are considered as the pharmacodynamic endpoints in this study. All other PD endpoints will be considered under safety.

4.2 Pharmacokinetic (PK)Endpoints

Pharmacokinetic endpoints will include:

- C_{max} - maximum measured plasma concentration
- T_{max} - time to reach maximum measured plasma concentration
- $AUC_{(0\text{-}tlast)}$ - area under the plasma concentration versus time curve from time 0 to last measurable concentration.

- $AUC_{(0-\infty)}$- area under the plasma concentration versus time curve from time 0 to infinity
- $t_{1/2}$ - terminal phase half-life.
- CL/F- Apparent total clearance of the drug from plasma.
- Vz/F- Apparent volume of distribution during terminal phase.
- λ_z - terminal rate constant.

These PK parameters will be derived from Lasmiditan plasma concentration, Sumatriptan plasma concentration as well as the combination of Lasmiditan and Sumatriptan versus time curves following dosing on Day 1 (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).

4.3 Safety Endpoints

Safety will be assessed by physical examinations, standard 12-lead ECGs, clinical laboratory tests (clinical chemistry panel, CBC, and urinalysis), Columbia Suicide severity rating scale (C-SSRS), DEQ-5, Visual Analogue scales (VAS) and collection of adverse events.

5. DEFINITIONS

$AUC_{(0-tlast)}$

Area under the concentration-time curve from time zero (pre-dose) to time t of the last quantifiable concentration of each dose of Lasmiditan, Sumatriptan or (Lasmiditan+Sumatriptan) calculated by means of the mixed log-linear trapezoidal rule.

$AUC_{(0-\infty)}$

Area under the plasma concentration vs. time curve from time 0 to infinity, calculated as AUC = AUC0–t + AUCextra. AUCextra represents an extrapolated value obtained by C /λz, where C is the predicted concentration at time t at or above LOQ, and λz is the estimated apparent terminal rate constant.

%AUCextrap

Area under the plasma concentration-time curve extrapolated from time t to infinity as a percentage of total AUC.

C_{max}

Maximum concentration in plasma following each dose of Lasmiditan, Sumatriptan or (Lasmiditan+Sumatriptan), obtained directly from the observed concentration versus time data.

λ_z

Apparent terminal elimination rate constant, determined from the slope of the log-transformed plasma concentration curve.

CL/F

Apparent total clearance of the drug from plasma.

Vz/F

Apparent volume of distribution during terminal phase.

$t_{1/2}$

Apparent terminal elimination half-life , is determined as $\ln(2)/\lambda_z$.

T_{max}

Time to maximum plasma concentration.

Study Day

This is the number of days from the date of the first study drug administration:

Study Day = (Target Date - Date of the first study drug administration) + 1 if target date is greater than or equal to the date of the first study drug administration or

Study Day = (Target Date - Date of the first study drug administration) if target date is less than date of the first study drug administration.

Baseline

Baseline is defined as the latest assessment prior to the first study drug administration within each period unless otherwise specified. If the assessment occurs on the same date as the dose administration, then the time of assessment should be compared to the time of dose administration. If time is not available, protocol schedule of events should be considered.

6. STATISTICAL METHODOLOGY

6.1 General Considerations

All pharmacokinetic evaluations will be performed using non-compartmental methods in Phoenix® WinNonlin® version 6.4 or higher (Pharsight Corporation, Mountain View, California, USA). All statistical evaluations will be conducted using SAS® version 9.3 or higher (SAS® Institute, Cary, North Carolina). All tables, figures and listings will be produced in landscape format.

The term "study drug" may refer to either Lasmiditan or Sumatriptan (or both Lasmiditan and Sumatriptan together).

In general, all data will be listed by subject, period, treatment and visit/time point where appropriate. The total number of subjects in the study group (N) under the stated population will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum. In case of $n<2$, where n indicates the number of evaluable subjects at the particular time point, the standard deviation will be empty. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data, whereas the standard deviation will be presented to two more decimal places than the original data.

In summary tables of categorical variables, counts and percentages will be used. The count [n] indicates the actual number of subjects with a particular value of a variable or event, which should always be less than or equal to the total number of subjects with non-missing value of the variable or event in the respective study group [M].

Percentage will be obtained by: % = (n/M)*100. Unless otherwise stated, all percentages will be expressed to one decimal place.

The closest non-missing measurement (whether from scheduled or unscheduled visit) taken prior to the first study drug administration within each period will be considered as the baseline value. The change from baseline values will be derived for each subject as the post-baseline evaluation minus the baseline evaluation within each period.

All dates will be displayed in DD/MMM/YYYY format.

6.2 Analysis Populations

The analysis populations defined in this study are as follows:

6.2.1 Safety Population

Safety population will consist of all subjects who received any amount of study medication (Lasmiditan or Sumatriptan). The safety population will be used for all safety analyses.

6.2.2 PD Population

Pharmacodynamic (PD) population will consist of all subjects who received a single dose of study medication (Lasmiditan or Sumatriptan) and have completed at least one treatment period.

6.2.3 PK Population

Pharmacokinetic (PK) population will consist of all subjects who completed at least one treatment period without any protocol violations, 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.

The reason for excluding a subject from the PK population will be documented.

The PK population will be used for all PK analyses.

6.3 Coding Dictionaries Used

Adverse event and medical history verbatim terms provided by the investigator will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA, version 20.0). The resultant primary system organ class and preferred term will be used for AE summaries and medical history listing.

Prior and concomitant medication generic terms provided by the investigator will be coded per WHO Drug Insight and classified by preferred terms and ATC classes. The resultant ATC class and preferred term will be used for prior and concomitant medication listings.

6.4 Analysis Methods

6.4.1 Study Subjects Disposition

Subject disposition will be tabulated by an overall summary of the number of subjects who were randomized into the study, completed all treatment periods, were included into the safety, PK population and PD population, completed the study and prematurely discontinued (with breakdown by reason for early discontinuation). The summary will be based on all enrolled subjects.

A listing will be presented to describe whether the subject completed the study, date of completion or early withdrawal, and the reason for early discontinuation, if applicable. A listing will also be provided to describe when informed consent was obtained and if the subject meets all inclusion/exclusion criteria. The date of consent and reason for entry criteria violation, if any, will be presented.

6.4.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics such as age, sex, race, ethnicity, height (cm), weight (kg) and BMI (kg/m^2) will be summarized overall and by sequence. The summary will be based on the safety populations.

Descriptive statistics will be presented for age, height, weight and BMI. Frequency counts and percentage will be presented for sex, race and ethnicity.

The demographic and baseline characteristic data will also be presented as a data listing.

6.4.3 Medical History/ Surgical History/Hospitalization

Medical history details as collected on the eCRF such as category, description, the date of onset and stop date will be presented in a by-subject data listing. History of surgery/hospitalization might be included in the medical history or presented as a separate listing.

6.4.4 Prior and Concomitant Medications

All information on concomitant therapy (including all prescription/non-prescription medications, herbal medications and vitamin supplements) taken within 30 days prior to the informed consent and during the study must be recorded on the subject's eCRF and should include the name of the procedure or drug and duration of the treatment (start and stop dates). Concomitant treatments (non-pharmacological treatments) include any surgical or diagnostic procedures. Non-pharmacological treatments would not be listed.

Prior medications are defined as those taken only before the date of the first dose of the study medication i.e. stopped before the start of the study medication. Concomitant medications are defined as any non-study medication taken during the course of the study i.e. on or after the date of the first dose of the study medication. Additionally, the medications will be considered concomitant if the start and stop date of the medication are missing (not available).

Prior and concomitant medication information will be presented in a by-subject listing with anatomical-therapeutic-chemical (ATC) classification and WHO Drug Dictionary preferred term, start and stop date, dosage, route, frequency and indication.

6.4.5 Protocol Deviations

The study site will record all deviations occurred through the study and all protocol deviations will be listed by subject.

6.4.6 Study Drug Administration

The study medication administration details including the dosing date and time, dose, fasting status will be presented in a by-subject listing.

The number and percentage of subjects receiving each of the 3 scheduled treatments will be presented by treatment group.

6.4.7 Pharmacodynamic Analysis

Pharmacodynamic analysis will involve the analysis of all adverse events (AE) and the analysis of vital signs. All AEs and vital signs data will be listed and summarized.

Adverse Events

Adverse Events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA version 20.0) AE coding system for purpose of summarization.

An AE will be defined as treatment-emergent (TEAE) if its time of onset or worsening is on or after the time of the study drug administration.

An AE will be defined as treatment related if its relationship to the study drug is recorded as Possibly Related or Related on the eCRF.

An overall summary of number of events and number and percentage of subjects with at least one AE, TEAE, serious TEAE, treatment-related TEAE, serious treatment-related TEAE and TEAE leading to discontinuation will be presented.

A summary of the frequency (number and percentage of subjects with events) of TEAEs will be presented by system organ class, preferred term, and treatment group. Adverse events will also be analyzed by their severity (mild, moderate, severe, life threatening or fatal) and relationship to study drug (related or not related).

A subject experiencing the same AE multiple times will be counted only once for that preferred term. Similarly, if a subject experiences multiple AEs (preferred terms) within the same system organ class then that subject will be counted only once for that system organ class. When summarizing by severity and relationship, only event with highest severity or relationship will be counted. All AEs will be presented in alphabetical order of system organ classes and preferred terms.

All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim term given by the investigator, preferred term, system organ class, start date, stop date, severity, outcome, action taken and drug relatedness. Separate listings will be created for Serious TEAEs and TEAEs leading to study drug discontinuation if deemed necessary.

Vital Signs/Orthostatic Vital Signs

Vital signs will be obtained at Screening, Day -1, Day1 (predose, 1hr, 2hr, 4hr, 8hr, 24hr post dose) and Day 2 of each period.

Vital signs will include body temperature, respiratory rate, heart rate and systolic and diastolic blood pressure.

Orthostatic vital signs will be obtained at Screening and Day 1 (predose, 1hr, 2hr) of each period and may or may not include all the vital parameters.

Height, weight and BMI will be measured only at the Screening Visit only.

Actual values of vital signs and changes from baseline will be summarized using descriptive statistics by treatment and time point. Only subjects with both non-missing baseline and time point values will be summarized at each time point.

6.4.8 Pharmacokinetic Analysis

Calculation of PK parameters will be performed using Phoenix® WinNonlin® version 6.4 (or later). Statistical analysis and generation of summary tables and listings will be performed in SAS.

All PK analyses will be performed on the PK population.

6.4.9 Plasma PK Concentrations

Blood samples for determination of plasma concentrations will be collected on Day1 and Day 2 for each treatment period and at the time points indicated in the following table:

Day(s)	PK Collection Time Points
Day 1	Pre-dose and 0.25, 0.5, 1, 1.5, 2, 2.5,3, 4, 6, 8, 12, and 16, hours post-dose
Day 2	24 and 30 hours following the Day 1 dose of IMP

Plasma concentrations that are below quantification limits (BQL) will be treated as follows in the pharmacokinetic analyses and clearly identified in listings.

1. If it is a leading BQL - treat as 0 (zero)
2. If it a middle BQL - treat missing value (depending on the situation)
3. If it is a tailing BQL, treat as missing valve.

Descriptive statistics of Lasmiditan, and Sumatriptan plasma concentrations will be presented for each treatment period and timepoint. The statistics will additionally include geometric mean and CV (%). All plasma concentrations will be listed.

Figures (linear and semi-logarithmic) illustrating the relationship between time after study drug administration and plasma drug concentrations will be created for each subject and for the mean results.

6.4.9.1 PK Parameter Estimation

Pharmacokinetic parameters $C_{max,}$ $T_{max,}$ $AUC_{0\text{-}tlast,}$ $AUC_{0\text{-}inf,}$ $t_{1/2}$, $\lambda_{z,}$ CL/F, Vz/F will be estimated. The exact time of sample collection, relative to time of dose, will be used in the analyses. No imputation of missing samples will occur. If a scheduled sample's concentration is missing, the pharmacokinetic analyses will be conducted as if that sample had not been scheduled for collection. The time of dosing will be considered as time 0 and the pre-dose assessment will be treated as if it occurred at time 0. Any subject with sufficient data to adequately characterize their concentration-time profile will be included in the pharmacokinetic analyses. If the terminal half-life for any case is physiologically implausible, and a suitable set of terminal concentrations cannot be selected from the semi logarithmic concentration-time plot, then no elimination parameter estimates will be reported. $t_{1/2}$ can only be estimated for those cases where the apparent elimination rate constant has been estimated.

Descriptive statistics will be presented for each PK parameter for each study medication by treatment period (Lasmiditan and, Sumatriptan). All PK parameters will be listed.

6.4.9.2 Pharmacokinetic Statistical Inference

The PK parameters, Cmax and $AUC_{0\text{-}tlast}$ and $AUC_{0\text{-}\infty}$ will be the primary PK analysis variables. An ANCOVA model will be fit for log-transformed PK parameter (C_{max} or $AUC_{0\text{-}tlast}$ $AUC_{0\text{-}\infty}$ separately) as the outcome, with the fixed effect of treatment group. From this model, least square (LS) Means for each treatment and LS Mean differences to the reference drug Lasmiditan will be estimated with the corresponding 90% confidence intervals. These estimates will then be exponentiated to produce the estimates of geometric mean ratios (Combination vs standalone PK for lasmiditan and sumatriptan) with their 90% confidence intervals. It will be concluded that the IMP has no effect on PK, if 90% confidence intervals for combination/standalone is within the 80-125% interval.

6.4.10 Safety Analysis

All safety data will be listed and tabulated. The analysis will be performed on the Safety population.

Safety parameters include adverse events, laboratory parameters, vital signs, ECG, physical examination findings, C-SSRS and DEQ-5 and VAS.

6.4.10.1 Clinical Laboratory Parameters

The clinical laboratory tests will be obtained at Screening, Day -1 of each treatment period, and end of study. The following laboratory evaluations will be performed.

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		

Laboratory test results for Clinical Chemistry, Hematology and Urinalysis, will be listed and summarized descriptively by treatment and visit. There will be no change from baseline calculations performed for Laboratory data.

Breathalyzer Test- The breathalyzer assessment for breadth alcohol concentration will be performed at Screening and Day-1 of each dosing period. A by subject listing of the data will be generated.

All individual subject clinical laboratory test results will be presented in listings by period, subject and visit.

6.4.10.2 Electrocardiogram (ECG)

ECG will be obtained at Screening, Day 1 (predose, 1hr, 1.5hr, 2hr, 2.5hr, 4hr, 8hr) Day 2 (24hr) of each treatment period and end of study.

Standard 12-lead ECGs evaluations will include heart rate and interval information such as RR, PQ/PR, QRS, QT, QTcF and QTcB. Overall interpretation (normal, abnormal not clinically significant or abnormal clinically significant) will also be recorded.

For continuous ECG parameters, actual values and changes from baseline will be summarized using descriptive statistics by treatment and time point. For ECG interpretation, the number and percentage of subjects will be summarized by treatment and time point. Additionally, a shift table from baseline to Day 2 will be presented for each treatment.

All ECG data will be provided as a by-subject listing.

6.4.10.3 Physical Examination

Complete physical examination will be performed at Screening and end of study. A brief targeted physical examination will be performed if indicated by an AE during each dosing period.

Physical examination will include the assessment of general appearance, head, eyes, ears, nose, throat (HEENT), thyroid (endocrine), heart, chest, lungs, abdomen, skin, neurological, extremities, and back. Each body system will be assessed as normal, abnormal not clinically significant or abnormal clinically significant.

Physical examination findings will be summarized by visit and body system. The number and percentage of subjects with normal, abnormal not clinically significant and abnormal clinically significant findings will be presented for each body system.

All physical examination data will be provided in a listing.

6.4.10.4 Columbia Suicide Severity Rating Scale (C-SSRS)

C-SSRS will be performed at screening with the screening/baseline version of the form. The 'Since last visit' version would be used in each dosing period at Day-1, Day 2 and end of study. A by subject listing and summary table for C-SSRS will be generated only for positive responses to any questions in the C-SSRS. If there are no positive responses, there will be a line indicating 'None of the study subjects responded with a positive response' for the listing and summary table.

6.4.10.5 Visual Analogue Scale (VAS)

VAS scales will be administered on 100mm scales as per the protocol. The following VAS scales will be performed and subjects will be trained on Day-1 of each period.

1. Bipolar drug liking
2. Bipolar High VAS
3. Unipolar sedation
4. Unipolar overall drug liking VAS
5. Unipolar take drug again VAS

All VAS data will be provided as a by-subject listing and summarized by period, treatment and visit.

6.4.10.6 Drug Effects Questionnaire (DEQ-5)

The DEQ-5 will be completed as per the protocol. All DEQ-5 data will be provided as a by-subject listing and summarized by period, treatment and visit.

7. REFERENCES

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3. CoLucid Pharmaceuticals, Inc. Clinical Study Report: A Study of Two Doses of Lasmiditan (100 mg and 200 mg) compared to Placebo in Acute Treatment of Migraine: A randomized, double-blind, placebo-controlled parallel group study (SAMURAI).
4. CoLucid Pharmaceuticals, Inc. COL-144 Investigator Brochure, Version 8.0, 23 February 2016.
5. Morean ME, de Wit H, King AC, et al., The Drug Effects Questionnaire: Psychometric Support across Three Drug Types. Psychopharmacology (Berl) 2013; 227:177-192.
6. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, published June 14, 2010. US Department of Health and Human Services, NIH, National Cancer Institute.

8. APPENDICES

Schedule of Assessments and Procedures

	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	
Unipolar Take drug again 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)**
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. 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 1. 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.