H8H-CD-LAHK

A **S**tudy of Three Doses of Lasmiditan (50 mg, 100 mg and 200 mg) Compared to **P**lacebo in the **A**cute T**R**ea**T**ment of Migr**A**i**N**e: A randomized, double-blind, placebo-controlled parallel group study (**SPARTAN**)

NCT02605174

Approval Date: November 30, 2015

16.1 Study Information

16.1.1 Protocol and protocol amendments

Document	Date
Original clinical study protocol	30 November 2015

CoLucid
pharmaceuticals, inc.

Clinical Protocol

A **S**tudy of Three Doses of Lasmiditan (50 mg, 100 mg and 200 mg) Compared to **P**lacebo in the **A**cute T**R**ea**T**ment of Migr**A**i**N**e: A randomized, double-blind, placebo-controlled parallel group study (**SPARTAN**)

Protocol No. COL MIG-302

FINAL V1.0
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STUDY PERSONNEL

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30Nov2015

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Signature

11-30-15

Date

Investigator statement

Protocol Number: COL MIG-302

Protocol Title:
A **S**tudy of Three Doses of Lasmiditan (50 mg, 100 mg and 200 mg) Compared to **P**lacebo in the **A**cute T**R**ea**T**ment of Migr**A**i**N**e: A randomized, double-blind, placebo-controlled parallel group study (**SPARTAN**)

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-302, and will conduct the trial in accordance with Good Clinical Practice (GCP) and applicable regulatory requirements.

_____
Site Name

_____
Site Address

_____
Investigator's Printed Name

_____ _____
Investigator's Signature Date

1. SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor Company:
CoLucid Pharmaceuticals, Inc.</td><td>Drug Under Study: Lasmiditan (COL-144)</td></tr>
<tr><td colspan="3">Title of Protocol: A <u>S</u>tudy of Three Doses of Lasmiditan (50 mg, 100 mg and 200 mg) Compared to <u>P</u>lacebo in the <u>A</u>cute T<u>R</u>ea<u>T</u>ment of Migr<u>A</u>i<u>N</u>e: A randomized, double-blind, placebo-controlled parallel group study (SPARTAN)</td></tr>
<tr><td>Protocol Number:
COL MIG-302</td><td>Phase: 3</td><td>Indication: Migraine - Acute Treatment</td></tr>
<tr><td colspan="3">Primary Objective: To evaluate the efficacy at 2 hours of lasmiditan 50 mg, of lasmiditan 100 mg and of lasmiditan 200 mg compared to placebo on migraine headache pain and the Most Bothersome Symptom (MBS), as identified by the individual from the associated symptoms of nausea, phonophobia and photophobia.

Secondary Objectives: To explore the time course and effect of lasmiditan 50 mg, of lasmiditan 100 mg and of lasmiditan 200 mg on relief of pain and on the MBS.

Additional Objectives: To explore the effect and time course of a second dose of lasmiditan 50 mg, of lasmiditan 100 mg and of lasmiditan 200 mg compared to placebo on relief of pain and MBS when used for rescue and for recurrence of migraine. To explore resource utilization during the study compared to pre-study in terms of cardiovascular events and in terms of migraine episodes.

Safety Objective: To explore the safety and tolerability of lasmiditan 50 mg, of lasmiditan 100 mg and of lasmiditan 200 mg, as the first dose and as a second dose, in terms of adverse events (AEs), physical examinations, vital signs, clinical laboratory evaluations, and 12-lead electrocardiograms (ECGs).</td></tr>
<tr><td colspan="3">Study Endpoints

Primary Endpoint: The proportion of subjects headache pain free at 2 hours post dose (defined as moderate or severe headache pain becoming none)

Key Secondary Endpoint: The proportion of subjects who are MBS free at 2 hours post dose (defined as the associated symptom present and identified as MBS prior to dosing being absent at 2 hours).</td></tr>
<tr><td colspan="3">Study Design:
This is a prospective randomized, double-blind, placebo-controlled study in subjects with disabling migraine (Migraine Disability Assessment (MIDAS) score ≥ 11). Subjects will be stratified (yes or no) for use of concomitant medications that reduce the frequency of migraine episodes.

Subjects will be asked to treat a migraine attack with study drug on an outpatient basis. Subjects will be provided with a dosing card containing a dose for initial treatment and a second dose to be used for rescue or recurrence of migraine. Each subject's study participation will consist of a screening visit (Visit 1) with a telephone contact within 7 days to confirm eligibility, a Treatment Period of up to 8 weeks, and an End-of-Study (EoS) visit (Visit 2) within one week (7 days) of treating a single migraine attack. The total time on study is approximately 11 weeks.

At the Screening visit (Visit 1) subjects will provide written informed consent and authorize Health Insurance Portability and Accountability Act (HIPAA). Study eligibility will be assessed on the basis of medical history including migraine history, baseline physical examination (including height and weight), vital signs, clinical laboratory tests, 12-lead ECG and responses to the MIDAS questionnaire. Subjects will be asked about any concomitant medication use as well as any cardiovascular (CV) events in the last 6 months and/or related resource utilization such as visits to cardiologists, procedures, hospitalizations, new treatments or treatment</td></tr>
</table>

adjustments for CV disease. A Columbia Suicide Severity Rating Scale (C-SSRS) will be completed. Subjects will be given an electronic diary and be trained on its use to record information about their migraine, dosing their migraine and post-dose assessments. Subjects will be randomized, dispensed study drug and instructed not to treat an attack until their eligibility has been confirmed by telephone once all screening evaluations are complete. Subjects will be randomly assigned to one of 7 treatment sequences to receive lasmiditan 50 mg (L50 mg), lasmiditan 100 mg (L100 mg) or lasmiditan 200 mg (L200 mg) or placebo (P) for the first dose (in a 1:1:1:1 ratio) and the second dose, if needed for rescue or recurrence of migraine as follows:

First dose for treatment of migraine	Second dose for rescue or recurrence of migraine (if needed)
L50 mg	L 50 mg
	L 50 mg
	placebo
L100 mg	L100 mg
	L100 mg
	placebo
L200 mg	L200 mg
	L200 mg
	placebo
placebo	placebo

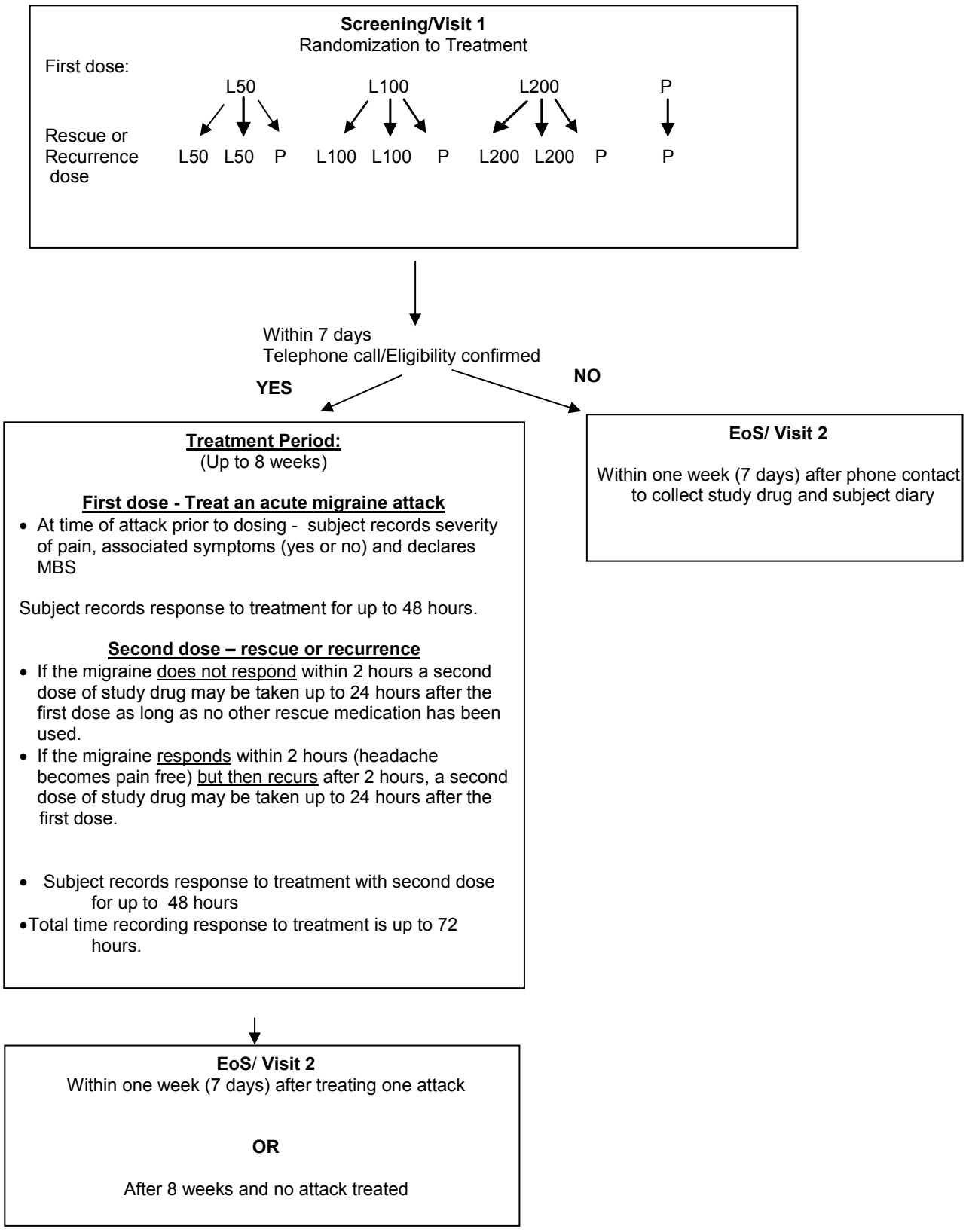
Telephone Contact: Within 7 days of **Visit 1** a phone contact must be made by study staff to the subject confirming eligibility in the trial. The subject will be reminded on the use of the diary and on dosing a migraine with study drug. Once eligibility is confirmed, subjects will begin the **Treatment Period.** Subjects considered not eligible will be advised not to take the study drug and an appointment for an **EoS/Visit 2** and the collection of study drug and the diary will be scheduled within one week (7 days) of the confirmation of eligibility phone call.

- **Treatment Period:** Subjects will be asked to treat their next migraine attack within 4 hours of onset providing that the headache severity is at least moderate at that time and not improving. Subjects will record their response to the first dose over the next 48 hours using an electronic diary. Subjects will be asked not to use rescue medication until at least 2 hours after dosing with study drug and completing the 2 hour assessments. If the migraine does not respond at 2 hours, a second dose of study drug may be taken up to 24 hours after the first dose as long as no other rescue medication has been used. If the migraine does respond within 2 hours (headache becomes pain free) but then recurs after 2 hours a second dose of study drug may be taken up to 24 hours after the first dose. Subjects will record their response to a second dose, taken for either rescue or recurrence, for 48 hours in the electronic diary. The total time for recording response to study drug is up to 72 hours depending on whether or not a second dose is used. Subjects are to contact the clinic to schedule **EoS/Visit 2** within one week (7 days) after 1 attack has been treated, or after 8 weeks have passed without treating an attack. The total time on study is approximately 11 weeks.

Subject Population: Adult patients with a history of migraine with or without aura.

Number of Subjects: Approximately 2968 subjects screened and randomized (742 per treatment arm based on the first dose) to ensure that at least 2280 subjects (570 per treatment arm based on the first dose) complete the Treatment Period	**Number of Centers:** Up to 150 centers in the US and rest of world (Western EU,)
Test Product and Doses: lasmiditan 50 mg, lasmiditan 100 mg**;** lasmiditan 200 mg and matching placebo	**Route of Administration:** Oral

Study schema:



Criteria for Inclusion/Exclusion:

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

1. Able and willing to give written informed consent and authorize HIPAA.
2. Patients with migraine with or without aura fulfilling the International Headache Society (IHS) diagnostic criteria 1.1 (migraine without aura) or 1.2.1 (migraine with aura) (International Headache Classification (ICHD)-2004).
3. History of disabling migraine for at least 1 year.
4. MIDAS score ≥11.
5. Migraine onset before the age of 50 years.
6. History of 3 – 8 migraine attacks per month (< 15 headache days per month).
7. Male or female, aged 18 years or above.
8. Females of child-bearing potential must be using or willing to use a highly effective form of contraception (e.g. combined oral contraceptive, intrauterine device (IUD), abstinence or vasectomized partner).
9. Able and willing to complete an electronic diary to record details of the migraine attack treated with study drug.

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

1. Any medical condition or clinical laboratory test which in the judgment of the Investigator makes the subject unsuitable for the study.
2. Pregnant or breast-feeding women.
3. Women of child-bearing potential not using or not willing to use highly effective contraception.
4. Known hypersensitivity to lasmiditan or to any excipient of lasmiditan oral tablets or any sensitivity to a ditan.
5. History or evidence of hemorrhagic stroke, epilepsy or any other condition placing the subject at increased risk of seizures.
6. History of recurrent dizziness and/or vertigo including benign paroxysmal positional vertigo (BPPV), Meniere's disease, vestibular migraine, and other vestibular disorders.
7. History of diabetes mellitus with complications (diabetic retinopathy, nephropathy or neuropathy).
8. History within the previous three years or current evidence of abuse of any drug, prescription or illicit, or alcohol.
9. History of orthostatic hypotension with syncope.
10. Significant renal or hepatic impairment.
11. Subject is at imminent risk of suicide (positive response to question 4 or 5 on the C-SSRS) or had a suicide attempt within six months prior to the screening visit.
12. Previous participation in this clinical trial.
13. Participation in any clinical trial of an experimental drug or device in the previous 30 days.
14. Known Hepatitis B or C or HIV infection.
15. History, within past 12 months, of chronic migraine or other forms of primary or secondary chronic headache disorder (e.g. hemicranias continua, medication overuse headache) where headache frequency is ≥15 headache days per month.
16. Use of more than 3 doses per month of either opiates or barbiturates.
17. Initiation of or a change in concomitant medication to reduce the frequency of migraine episodes within three (3) months prior to **Screening/Visit 1.**
18. Subjects who are employees of the sponsor.
19. Relatives of, or staff directly reporting to, the Investigator.

Criteria for Evaluation:

Efficacy/Pharmacodynamics:

- Headache pain (4 point scale: none (0), mild (1), moderate (2), severe (3))
- Most bothersome symptom (selected from a list of associated symptoms present at predose)
- Nausea, phonophobia or photophobia (yes or no)
- Headache response within 24 hours - time to headache relief and time to pain free
- 24 and 48 hour sustained pain free response
- Presence of vomiting (yes or no)
- Disability (4 point scale: not at all (0), mild interference (1), marked interference (2), completely, needs bed rest (3))
- Requirement for rescue medication between at 2 hours and between 2- 24, and 24-48 hours (yes or no)
- Requirement for recurrence medication between 2- 24, and 24-48 hours (yes or no)
- Patient global impression of change (7 point scale)
- Headache pain after a second dose of lasmiditan for rescue or recurrence of migraine
- Time to headache relief and time to pain free after a second dose of lasmiditan for rescue or recurrence of migraine
- MBS free after a second dose of lasmiditan for rescue or recurrence of migraine

Safety:

- Adverse events (spontaneously reported)
- Physical examination
- Vital signs
- 12-lead electrocardiograms
- Clinical laboratory parameters

Resource utilization:

- Any CV events in the 6 months prior to screening and/or related resource utilization such as visits to cardiologists, procedures, hospitalizations, new treatments or treatment adjustments for CV disease compared to on study Visit 1 through Visit 2.
- Any visits to an emergency room or physician's office for treatment of migraine in the 3 months prior to screening compared to on study Visit 1 through Visit 2, excluding study specific visits.
- Concomitant medications for the treatment of migraine and/or pain for 3 months prior to screening compared to concomitant medications for migraine and/or pain Visit 1 through Visit 2.
- Missed days of work and/or school.

Statistical Analysis:

Efficacy:

This multi-center, randomized, double-blind, parallel-group, placebo-controlled clinical study is designed to evaluate the efficacy and safety of lasmiditan 50 mg, of lasmiditan 100 mg and of lasmiditan 200 mg vs. placebo in the acute treatment of migraine based on the first dose. Subjects will be stratified (yes or no) for use of concomitant medications that reduce the frequency of migraine episodes.

Efficacy will be assessed using the primary endpoint of the proportion of subjects headache pain free at 2 hours, defined as moderate or severe headache pain becoming none and the key secondary endpoint of the proportion of subjects MBS free at 2 hours defined as the associated symptoms (nausea, phonophobia or photophobia) present prior to dosing and identified by the subject to be MBS becoming absent.

The primary analyses will compare the proportion of subjects who are headache pain free and the proportion of subjects who are MBS free at 2 hours in the lasmiditan 200 mg and placebo groups in the modified Intent-to-Treat (mITT) population. Each of these two analyses will be carried out using logistic regression Wald Chi-square test with region included in the model and will be conducted using a one-sided test at the alpha=0.025 level of significance.

If both primary analyses are statistically significant (one-sided, $p<0.025$), additional confirmatory hypotheses will

be tested in the mITT population in the following sequential order:

- Proportion of subjects who are headache pain free at 2 hours in the lasmiditan 100 mg and placebo group.
- Proportion of subjects who are MBS free at 2 hours in the lasmiditan 100 mg and placebo group.
- Proportion of subjects who are headache pain free at 2 hours in the lasmiditan 50 mg and placebo group.
- Proportion of subjects who are MBS free at 2 hours in the lasmiditan 50 mg and placebo group.

All of the above analyses will be completed using one-sided tests at the alpha=0.025 level of significance. If an analysis is not statistically significant, then all subsequent analyses will be conducted but are designated as exploratory rather than confirmatory.

Additional analyses will explore the time course and effect of the first dose of lasmiditan 200 mg and of lasmiditan 100 mg and of lasmiditan 50 mg on features of migraine including: headache response (a reduction in headache pain from moderate or severe to mild or none), vomiting, disability, headache recurrence and the use of recurrence medication, the use of rescue medication, patient global impression of change, time to headache relief, and time to headache pain free. Descriptive analyses will be performed on the proportion of subjects who are nausea free at 2 hours, the proportion who are phonophobia free 2 hours and the proportion who are photophobia free at 2 hours. Exploratory second dose (for rescue or recurrence of migraine) comparisons between treatment groups will be performed.

Sample Size Rationale

This Phase 3 study is designed to demonstrate that lasmiditan is effective in the treatment of acute migraine in adult patients with and without aura. The sample size was estimated based on the 2 hour headache pain free and associated symptoms (nausea, phonophobia, or photophobia) free response rates observed in the Phase 2 study COL MIG-202.

Dose	Pain free	Nausea free	Phonophobia free	Photophobia free
Placebo	7.4%	59.3%	51.9%	34.6%
50 mg	13.9%	68.4%	58.2%	53.2%
100 mg	13.6%	74.1%	75.3%	67.9%
200 mg	18.8%	63.8%	59.4%	58.0%

For the primary endpoint of the proportion of patients pain free at 2 hours a sample size of 570 evaluable subjects per arm provides power of >90% for the 50 mg dose, the 100 mg dose and the 200 mg dose.

In order to estimate sample size for the key secondary endpoint of proportion of patients MBS free at 2 hours, simulation was performed in SAS on the conditional probability of being free from any one symptom defined as MBS under 4 different scenarios. For each symptom or combination of symptoms, the likelihood of an individual symptom being the MBS was estimated. In the most conservative scenario (scenario 1) it was assumed that nausea would always be declared the MBS if it was present, regardless of the presence of other symptoms (phonophobia or photophobia). The other 3 scenarios assumed lower likelihoods of nausea to be considered the MBS and allowed for the other symptoms (either phonophobia or photophobia) to be considered the MBS at a higher rate. This resulted in power estimates of > 95% for MBS at a sample size of 570 for the lasmiditan 50 mg dose and >99% for MBS at sample sizes of 450 to 570 per arm for the 100 mg dose across all 4 scenarios. For the 200 mg dose, an average power of 71% was estimated across five seeds under the most conservative scenario 1. In contrast, the 3 scenarios that did not declare nausea to be the default MBS if it was present estimated a greater average power of 82.6% to 91%.

Group	Scenario	Variable	Seed				
			55405	74951	82002	82377	90075
Placebo vs D50	1	Power (MBS)	96.90%	95.90%	96.10%	95.60%	96.80%
		Sample Size	570	570	570	570	570
	2	Power	93.70%	94.30%	94.80%	93.90%	93.90%
		Sample Size	450	450	450	450	450
	3	Power	90.40%	90.40%	90.10%	91.00%	91.40%
		Sample Size	575	575	575	575	575
	4	Power	93.70%	94.30%	94.80%	93.90%	93.90%
		Sample Size	450	450	450	450	450
Placebo vs D100	1	Power (MBS)	>99.99%	>99.99%	>99.99%	>99.99%	>99.99%
		Sample Size	570	570	570	570	570
	2	Power	99.90%	>99.99%	>99.99%	>99.99%	>99.99%
		Sample Size	450	450	450	450	450
	3	Power	>99.99%	>99.99%	>99.99%	>99.99%	>99.99%
		Sample Size	575	575	575	575	575
	4	Power	99.90%	>99.99%	>99.99%	>99.99%	>99.99%
		Sample Size	450	450	450	450	450
Placebo vs D200	1	Power	70.87%	70.87%	72.97%	71.17%	68.47%
		Sample Size	570	570	570	570	570
	2	Power	84.40%	85.00%	85.80%	85.90%	85.80%
		Sample Size	450	450	450	450	450
	3	Power	83.50%	83.20%	81.30%	83.40%	81.80%
		Sample Size	575	575	575	575	575
	4	Power	90.20%	90.50%	92.50%	91.40%	90.40%
		Sample Size	450	450	450	450	450

[1] Mean rate is the freedom from MBS at 2 hours post dose.
P=placebo, L = lasmiditan

It is expected for a one-sided, two-sample comparison of proportions at the 2.5% level of significance, a sample size of 570 subjects per treatment arm (as defined by the first dose) provides >90% power to detect a difference in headache pain free response rates for assumed true rates of 7.4% and 18.8% (placebo and 200 mg), 7.4% and 13.6% (placebo and 100 mg) and 7.4% and 13.9% (placebo and 50 mg) >90 % power for MBS for both the 50 mg dose arm and the 100 mg dose arm and very near or higher than 80% power for MBS in the 200 mg dose arm.

Safety:
Adverse events will be summarized, and event rates will be presented by treatment arm and dose (initial dose and second dose for rescue or recurrence or use of alternative rescue medication). Physical examinations, vital signs, ECG parameters and clinical laboratory data, will be summarized by treatment arm and dose in terms of change from baseline status.

Resource Utilization:
Resource utilization such as visits to cardiologists, procedures, hospitalizations, new treatments or treatment adjustments for CV disease as well as visits to the emergency room or a physician's office for the treatment of migraine will be summarized by treatment arm in terms of information reported at **Screening/Visit 1** compared to information reported at **EoS/Visit 2**. Concomitant medication use for migraine and/or pain and missed days of work and/or school will be summarized by treatment arm.

Schedule of Assessments

Assessment	**Visit 1** Screening and Baseline	**Telephone Contact** Within 7 days after Visit 1	**Treatment** Treatment of an attack within 8 weeks	**EoS/Visit 2** Within 7 days after treatment **OR** After 8 weeks and no attack treated[1]
Obtain informed consent/HIPAA	**X**			
Document migraine characteristics per IHS criteria	**X**			
Review inclusion / exclusion criteria	**X**			
Complete MIDAS	**X**			
Review migraine history including prior treatment	**X**			
Review medical history and concomitant medication	**X**			
Review resource utilization (visits to specialists, emergency rooms, etc)	**X**			**X**
Physical examination and vital signs (heart rate, blood pressure)	**X**			**X**
Weight and height	**X**			
12-lead ECG	**X**			**X**
Clinical laboratory[2]	**X**			**X**
Columbia Suicide Severity Rating Scale	**X**			**X**
Randomization	**X**			
Dispense study drug, study diary, and provide detailed instructions	**X**			
Confirm eligibility[3]		**X**		
Migraine attack (electronic diary) documentation by subject			**X**	
Documentation of rescue/recurrence medication			**X**	
Documentation of adverse events and concomitant medication	**X**	**X**	**X**	**X**
Collect unused/empty study drug pack.				**X**[1]

1 Subjects that do not treat a migraine for any reason during the 8 weeks should attend an **EoS visit** to return unused study drug and the e-diary. No other assessments are required.

2 Clinical laboratory tests include hematology, biochemistry, lipid profile, urinalysis, and pregnancy test for women of childbearing potential.

3 The confirmation of eligibility is made by telephone contact by the site study staff to the subject. Final eligibility is based on the laboratory results. If a subject is considered not eligible, he/she will be advised not to take the study drug and an appointment for a follow-up visit (Visit 2/EoS) for collection of study drug and diary will be scheduled. No assessments are required.

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

>	Greater than
≥	Greater than or equal to
<	Less than
5-HT	5-Hydroxytryptamine
βHCG	Beta human chorionic gonadotropin
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
AMPP	American Migraine Prevalence and Prevention
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
BP	Blood pressure
bpm	Beats per minute
BPPV	Benign paroxysmal positional vertigo
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CBC	Complete blood count
CD	Compact disc
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract research organization
CS	Clinically significant
C-SSRS	Columbia Suicide Severity Rating Scale
DBP	Diastolic blood pressure
DVD	Digital video disc
ECG	Electrocardiogram
EoS	End of study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEENT	Head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICHD	International Headache Classification
IHS	International Headache Society
IRT	Interactive Response Technology
IUD	Intrauterine Device
IV	Intravenous
ITT	Intent-to-treat
L	Lasmiditan
MBS	Most Bothersome Symptom
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MIDAS	Migraine disability assessment
mITT	modified Intent-to-treat
mL	milliliter

mmHg	millimeters of mercury
NCS	Not clinically significant
P	Placebo
PP	Per protocol
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
TEAE	Treatment emergent adverse events
WBC	White blood cells
WHO	World Health Organization
WOCBP	Women of child-bearing potential
WNL	Within normal limits

4. INTRODUCTION

Migraine is a common neurological disorder and was ranked by the World Health Organization (WHO) in their 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 study by the American Migraine Prevalence and Prevention (AMPP) 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 treatment for acute 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, and those who respond poorly to their current prescription medication for acute migraine. The current mainstay migraine therapies are chemical analogs of sumatriptan ('triptans'), developed for their potent cranial vasoconstrictor properties.[4] Triptans are selective 5-$HT_{1B/1D}$ receptor agonists and mediate their vasoconstrictor activity via 5-HT_{1B} receptors expressed on vascular smooth muscle.[5] As large numbers of patients were exposed to triptans, it was established through post-marketing surveillance that their vasoconstrictor mechanism of action also conferred a risk of serious cardiovascular adverse events, some fatal.[3] Consistent with their common pharmacology, sumatriptan, zolmitriptan, rizatriptan, eletriptan and naratriptan all induced comparable dose-dependent contraction of isolated human coronary arteries.[5,6,7] Because of the liability of triptans to cause coronary vasospasm, they are contraindicated in patients with known coronary artery disease (CAD), and it is strongly recommended that they are not prescribed to patients with risk factors for undiagnosed CAD (e.g., hypertension, hypercholesterolemia, smoker, obesity, diabetes, strong family history of CAD, female with surgical or physiological menopause, male over 40 years of age) without first undergoing a thorough cardiovascular evaluation.

Treatment of migraineurs with known cardiovascular disease and cardiovascular risk factors is particularly challenging because the incidence of myocardial infarction, stroke, claudication, diabetes, hypertension and hypercholesterolemia are all higher in individuals with migraine compared with the general population.[8] Many migraineurs who were previously eligible for triptan therapy may become ineligible as they age and develop cardiovascular disease and/or associated risk factors. For these patients, there is a pressing need for an effective migraine therapy with a non-vascular mechanism of action.

This study is a Phase 3 multicenter study in subjects with acute migraine. The study is designed to determine the efficacy and safety of lasmiditan 200 mg compared to placebo and lasmiditan 100 mg compared to placebo given as a first dose for the treatment of a migraine attack. A second dose of study drug is included in the study design to investigate the safety and efficacy of lasmiditan 200 mg compared to placebo and lasmiditan 100 mg compared to placebo when taken for rescue or when taken for recurrence of migraine. In addition to safety assessments, information will be obtained on the different dose levels of lasmiditan. Patients with cardiovascular risk factors will be eligible to participate in this clinical trial. Data from this study

will be used to further investigate and confirm the safety and efficacy of lasmiditan in the treatment of acute migraine in patients with risk factors for cardiovascular disease.

4.1 Background

Lasmiditan is a highly selective and potent 5-HT_{1F} receptor agonist with ≥ 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.[9,10,11] Unlike triptans, lasmiditan did not constrict rabbit saphenous vein,[9] an assay predictive of human coronary artery constriction.[12] Lasmiditan is under development as a neurally acting treatment for migraine without the vasoconstrictor liability of triptans.

4.2 Clinical Studies to Date

Five Phase 1 studies have been completed in Europe using intravenous (IV), sublingual, and oral formulations of lasmiditan. Two European Phase 2 studies have been completed with lasmiditan in the acute treatment of migraine.

Lasmiditan was well tolerated in healthy volunteers following 20 minute IV infusions at dose levels of 0.1 to 20 mg with few AEs reported (clinical study H8H-BD-LACA). There was a clear increase in the number of AEs reported following 20 minute IV infusions of 30 and 60 mg of lasmiditan, although most were rated as mild. The number of AEs reported following 60 mg of lasmiditan decreased significantly when the rate of infusion was reduced from 3 to 1 mL/min and the infusion time was increased to 60 minutes, although the number of subjects reporting AEs was similar. All subjects receiving 60 minute IV infusions of 120 and 180 mg of lasmiditan reported AEs with a similar overall frequency at each dose level. 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 intravenous lasmiditan 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.

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 400 mg lasmiditan. 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), including also the assessment of safety and tolerability. 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 ICH E14 guidance,[13] the primary objective was to assess the effect of 100 mg lasmiditan and 400 mg lasmiditan on cardiac de- and re-polarization. The statistical evaluation of the primary variable revealed that 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. [13]

The bioavailability of lasmiditan 200 mg administered orally as a tablet formulation under fed and fasted conditions was investigated (clinical study COL MIG-104). A slight delay in the time to reach maximum plasma concentration was observed in the fed state. As in other Phase 1 studies, lasmiditan was well tolerated. The most common AEs across both conditions were somnolence, dizziness, orthostatic hypotension (with and without dizziness) and paresthesia.

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.

During the clinical development of lasmiditan there were no deaths and no subjects were 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 200 mg lasmiditan, and resolved without sequelae.

More details on the preclinical and clinical experience with lasmiditan are given in the Clinical Investigator's Brochure. [14]

4.3 Minimization of Risk

The dose levels of lasmiditan (50 mg, 100 mg and 200 mg) have previously been tested and shown to be safe and well tolerated in healthy subjects and in patients with acute migraine.

Lasmiditan given orally at doses up to 400 mg has been well tolerated, with no clinically significant effects on vital signs, ECG or clinical laboratory parameters. The most frequent adverse events have been somnolence, dizziness, fatigue, and paresthesia. These were transient and usually of mild or moderate severity.

Since somnolence, dizziness and fatigue have been seen, patients participating in this study will be advised not to drive or operate machinery for 12 hours after treatment.

Rescue medication will be permitted after completion of the 2 hour assessments if the migraine does not respond (subject is not headache pain free). A second dose of randomized study drug may be taken up to 24 hours after the first dose as long as no other rescue medication has been used.

If the migraine responds within 2 hours (headache becomes pain free) but then recurs after 2 hours, a second dose of randomized study drug may be taken up to 24 hours after the first dose.

To insure standardization, all adverse events will be assessed using WHO Toxicity Criteria (Appendix 1).

4.4 Potential Benefit

Migraine is a common disorder with a prevalence of 11.7% (17.1% of women and 5.4% of men) based on a large population survey of US households. Nearly a third of sufferers experience three or more migraine attacks a month, and over half report that the attacks cause severe disability or require bed rest. [15] Despite the substantial functional impairment caused by the disease, it is estimated that less than half of all migraineurs use prescription medication to manage their disease, indicating a substantial unmet medical need. [16]

In the completed Phase 2 studies, lasmiditan was effective in alleviating migraine attacks when given by the IV or oral routes of administration. This study will recruit patients meeting the internationally recognized diagnostic criteria for migraine set by the International Headache

Society (IHS). Patients that complete COL MIG-302 will be eligible to be enrolled and randomized into the open-label, long-term, safety study of lasmiditan 100 mg and lasmiditan 200 mg (COL MIG-305).

4.5 Dose Rationale

The dose levels of lasmiditan to be used in this study (50 mg, 100 mg and 200 mg) have been tested and shown to be safe and well tolerated in both healthy subjects and in patients with acute migraine. In a Phase 2 study, both doses were effective in alleviating the symptoms of migraine. In preclinical toxicology studies, adequate margins of safety have been established for lasmiditan 50 mg, 100 mg and 200 mg and its major human metabolites. This study will further evaluate the safety and efficacy of lasmiditan 50 mg, 100 mg and 200 mg with the primary analysis performed on the first dose taken for treatment of a new acute migraine attack.

The inclusion of a second dose of either lasmiditan 50 mg or 100 mg or 200 mg or placebo as randomly assigned for treatment of rescue or recurrence of migraine is to evaluate the safety and efficacy of a second dose of lasmiditan and further establish the dosing profile for the use of lasmiditan in the treatment of acute migraine.

4.6 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 International Conference on Harmonization (ICH). Further information on the ethical conduct of the study is in Section 13.

5. TRIAL OBJECTIVES AND PURPOSE

5.1 Primary objective

To evaluate the efficacy at 2 hours of lasmiditan 50 mg, of lasmiditan 100 mg and of lasmiditan 200 mg compared to placebo on migraine headache pain and the Most Bothersome Symptom (MBS), as identified by the individual from the associated symptoms of nausea, phonophobia and photophobia.

5.2 Secondary objectives

To explore the time course and effect of lasmiditan 50 mg, of lasmiditan 100 mg and of lasmiditan 200 mg on relief of pain and on the MBS.

5.3 Additional Objectives

To explore the effect and time course of a second dose of lasmiditan 50 mg, of lasmiditan 100 mg and of lasmiditan 200 mg compared to placebo on relief of pain and MBS when used for rescue and for recurrence of migraine. To explore resource utilization during the study compared to
pre-study in terms of cardiovascular events and in terms of migraine episodes.

5.4 Safety objectives

To explore the safety and tolerability of lasmiditan 50 mg, of lasmiditan 100 mg and of lasmiditan 200 mg, as the first dose and as a second dose, in terms of adverse events (AEs), physical examinations, vital signs, clinical laboratory evaluations, and 12-lead electrocardiograms (ECGs).

5.5 Overall Study Design and Plan: Description

This is a prospective randomized, double-blind, placebo-controlled study in patients with disabling migraine (MIDAS score ≥11). Approximately 2968 subjects will be screened and randomized (742 per treatment arm based on the first dose) to ensure that approximately 2280 subjects (570 per treatment arm based on the first dose) treat a migraine attack and complete the Treatment Period. Subjects will be stratified (yes or no) for use of concomitant medications that reduce the frequency of migraine episodes.

Subjects will be asked to treat a migraine attack with study drug on an outpatient basis. Subjects will be provided with a dosing card containing a dose for initial treatment and a second dose to be used for rescue or recurrence of migraine. Each subject's study participation will consist of a screening visit (**Visit 1**) with a telephone contact within 7 days to confirm eligibility, a **Treatment Period** of up to 8 weeks, and an **EoS** visit (**Visit 2**) within two weeks (14 days) of treating a migraine attack. The total time on study is approximately 12 weeks.

At the **Screening visit (Visit 1)** subjects will provide written informed consent and authorize HIPAA. Study eligibility will be assessed on the basis of medical history including migraine history, baseline physical examination (including height and weight), vital signs, clinical laboratory tests, 12-lead ECG and responses to the MIDAS questionnaire. Subjects will be asked about any concomitant medication use as well as any cardiovascular (CV) events in the last 6 months and/or related resource utilization such as visits to cardiologists, procedures, hospitalizations, new treatments or treatment adjustments for CV disease. A C-SSRS will be completed. Subjects will be given an electronic diary and be trained on its use to record information about their migraine, dosing of their migraine and post-dose assessments. Subjects will be randomized, dispensed study drug and instructed not to treat an attack until their eligibility has been confirmed by phone once all screening evaluations are complete. Subjects will be randomly assigned treatment as described in Section 5.5.1.

Telephone contact. Within 7 days of **Visit 1** a phone contact must be made by study staff to the subject confirming eligibility in the trial. At this point, ineligible subjects are instructed to return to the clinic to be discontinued and eligible subjects begin the **Treatment Period**. During the call, the subject will be reminded on the use of the diary and on dosing a migraine with study drug.

Treatment Period: Subjects will be asked to treat their next migraine attack within 4 hours of onset providing that the headache severity is at least moderate at that time and not improving. Subjects will record their response to the first dose over the next 48 hours using an electronic diary. Subjects will be asked not to use rescue medication until at least 2 hours after dosing with study drug and completing the 2 hour assessments. If the migraine does not respond at 2 hours, a second dose of study drug may be taken up to 24 hours after the first dose as long as no other rescue medication has been used. If the migraine does respond within 2 hours

(headache becomes pain free) but then recurs after 2 hours a second dose of study drug may be taken up to 24 hours after the first dose. Subjects will record their response to a second dose, taken for either rescue or recurrence, for 48 hours in the electronic diary. The total time for recording response to study drug is up to 72 hours depending on whether or not a second dose is used. Subjects are to contact the clinic to schedule **EoS/Visit 2** within one week (7 days) after 1 attack has been treated, or after 8 weeks have passed without treating an attack. The total time on study is approximately 11 weeks.

5.5.1 Treatment Arms

Subjects will be centrally randomized to one of 7 treatment sequences to receive lasmiditan 50 mg (L50 mg), lasmiditan 100 mg (L100 mg) or lasmiditan 200 mg (L200 mg) or placebo (P) for the initial dose (in a 1:1:1:1 ratio) and the second dose, if needed for rescue or recurrence of migraine as follows:

First dose for treatment of migraine	Second dose for rescue or recurrence of migraine (if needed)
L50 mg	L 50 mg
	L 50 mg
	placebo
L100 mg	L100 mg
	L100 mg
	placebo
L200 mg	L200 mg
	L200 mg
	placebo
placebo	placebo

5.5.2 Schedule of Assessments

- **Screening/Visit 1:** The screening examinations to determine subject eligibility are performed. Subjects are randomized and provided with a dosing card.

- **Telephone call, confirmation of eligibility**: Within 7 days after screening, a telephone contact must be made between the site study staff and subject to confirm study eligibility based on clinical laboratory results. If a subject is considered not eligible, he/she will be advised not to take the study drug. An appointment for a follow-up visit (**EoS/Visit 2**) and collection of study drug and diary will be scheduled.

- **EoS/Visit 2: The end of study visit**
  - The subject will return to the clinic for post-treatment follow-up one week (7 days) after a subject completes treatment (treats one migraine attack within 8 weeks)

  - If a subject has not treated a migraine attack within 8 weeks after **Screening/Visit 1** the subject will be contacted to return to the clinic. In this case, this visit will only be used to return the study drug and e-diary.

The overall Schedule of Assessments for the study is provided in Table 1.

5.6 Assessments by Study Visit

5.6.1 Screening Visit /Visit 1

The following items must be completed and reviewed by the Investigator or sub-Investigator within 14 days:

- Explain the purpose of the study to prospective subjects and obtain written informed consent and HIPAA.
- Document migraine characteristics per IHS criteria (See Appendix 2).
- Review inclusion/exclusion criteria (See Sections 6.1 and 6.2.).
- Document medical history including migraine history and prior treatment and collect demographic information (See Section 9.1.1).
- Have subject complete MIDAS (See Section 9.1.1.2 and Appendix 3).
- Record concomitant medications that the subject is taking.
- Document resource utilization (See Section 9.1.1.3).
- Perform a complete physical examination (including height, weight, and vital signs) (See Sections 9.1.2 and 9.1.3).
- Perform a 12-lead ECG (see Section 9.1.4).
- Collect blood and urine samples for clinical laboratory tests (hematology, chemistry, and urinalysis; see Section 9.1.5). The laboratory tests will include serum βHCG for women of childbearing potential (WOCPB). Any woman with a positive pregnancy test will be ineligible for the study. Have subject complete C-SSRS (See Section 9.1.6 and Appendix 4).
- Review study requirements and instructions on dosing and completing electronic diary (See Section 9.1.7 and 9.1.8).
- Randomize subject through the Interactive Response Technology (IRT) system.
  - For subjects who meet initial screening criteria and are randomized, advise as to when to expect the confirmatory telephone call. Remind subject not to treat a migraine attack with study drug prior to this call.
- Dispense study drug as assigned.
- Provide access to electronic diary.
  - Starting at **Visit 1** and continuing to **EoS/Visit 2**, subjects will be asked daily, how they are feeling and about the use of any concomitant medications.
- Confirm timing of **EoS/Visit 2**.
- Discharge subject.
- A subject may be rescreened only once.

5.6.2 Phone Call

Within 7 days after screening, a phone contact must be made between site study staff and subject to confirm study eligibility based on the clinical laboratory results.

- If a subject is eligible, a review of study requirements will be performed. Subjects will update their status in the e-diary to allow them to report a migraine and record dosing and post-dose assessments. Each subject will be reminded of when to treat a migraine attack with study drug, the use of rescue medication, the treatment of recurrence and diary completion along with the need to return to the clinic for **EoS/ Visit 2**. Subjects will be asked to treat their next migraine attack providing headache severity is at least moderate and not improving.

- If a subject is considered not eligible, she/he will be instructed not to take the study drug and an appointment to return the study drug and diary must be scheduled and should occur within one week (7 days).

5.6.3 Treatment

Subjects will be allowed up to 8 weeks to treat an acute migraine attack of moderate or severe intensity that is not improving. The attack is to be treated within 4 hours of onset.

- **Prior to dosing the subject will record:**
  - Time of onset
  - Time migraine pain becomes moderate or severe and the severity ((2) moderate or (3) severe) of the pain.
  - Presence or absence (yes or no) of each of the following associated symptoms of migraine: nausea, phonophobia and photophobia.
    - From the list of associated symptoms **present** the subject will identify which **ONE** is most bothersome to them as the MBS.
  - Presence or absence (yes or no) of vomiting.
  - Degree of interference with normal activities
- **Subject will dose with study drug and record time of dosing.**
- Subject will record their response to treatment for 48 hours after dosing with study drug. Total time to record response is up to 72 hours (See Section 9.1.8).
- Subjects will be asked about any adverse events (if they are feeling anything unusual) and about the use of any concomitant medications.

5.6.4 End of Study/Visit 2

The following assessments will be performed:

- Collect any unused study drug and review dosing compliance.
- Collect resource utilization (See Section 9.1.1.3).
- Collect information on missed days of work and/or school due to migraine.
- Have subject complete C-SSRS (See Section 9.1.6 and Appendix 5).
- Review any information reported since **Visit 1** regarding AEs and use of concomitant medication and confirm/assess for AEs and use of concomitant medications not already reported.
- Perform a brief symptom-related physical examination if indicated by an AE (See Section 9.1.2.).
- Obtain vital sign readings (See Section 9.1.3).
- Perform a 12-lead ECG (See Section 9.1.4).
- Collect blood and urine samples for clinical laboratory tests (hematology, chemistry, and urinalysis) (See Section 9.1.5). The laboratory tests will include a urine pregnancy test for WOCBP. A positive urine pregnancy test will be confirmed with a serum βHCG test. (The confirmatory test may be run in the local clinical laboratory).
- Subject's participation in study is complete.

6. SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion Criteria

All subjects entered into this trial must meet the following criteria:

1. Able and willing to give written informed consent and authorize HIPAA.
2. Patients with migraine with or without aura fulfilling the IHS diagnostic criteria 1.1 and 1.2.1 (ICHD-2004, Appendix 2).
3. History of disabling migraine for at least 1 year.
4. MIDAS score ≥11 (Appendix 3).
5. Migraine onset before the age of 50 years.
6. History of 3 – 8 migraine attacks per month (< 15 headache days per month).
7. Male or female, aged 18 years or above.
8. Females of child-bearing potential must be using or willing to use a highly effective form of contraception (e.g. combined oral contraceptive, IUD, abstinence, or vasectomized partner).
9. Able and willing to complete an electronic diary to record details of the migraine attack treated with study drug.

6.2 Exclusion Criteria

Subjects will be excluded from this trial if they meet any of the following criteria:

1. Any medical condition or clinical laboratory test which in the judgment of the Investigator makes the subject unsuitable for the study.
2. Pregnant or breast-feeding women.
3. Women of child-bearing potential not using or not willing to use highly effective contraception.
4. Known hypersensitivity to lasmiditan, or to any excipient of lasmiditan oral tablets, or any sensitivity to a ditan.
5. History or evidence of hemorrhagic stroke, epilepsy or any other condition placing the subject at increased risk of seizures.
6. History of recurrent dizziness and/or vertigo including BPPV, Meniere's disease, vestibular migraine, and other vestibular disorders.
7. History of diabetes mellitus with complications (diabetic retinopathy, nephropathy or neuropathy).
8. History within the previous three years or current evidence of abuse of any drug, prescription or illicit, or alcohol.
9. History of orthostatic hypotension with syncope.
10. Significant renal or hepatic impairment.
11. Subject is at imminent risk of suicide (positive response to question 4 or 5 on the C-SSRS) or had a suicide attempt within six months prior to the screening visit.
12. Previous participation in this clinical trial.
13. Participation in any clinical trial of an experimental drug or device in the previous 30 days.
14. Known Hepatitis B or C or HIV infection.
15. History, within past 12 months, of chronic migraine or other forms of primary or secondary chronic headache disorder (e.g. hemicranias continua, medication overuse headache [Appendix 2]) where headache frequency is ≥15 headache days per month.
16. Use of more than 3 doses per month of either opiates or barbiturates.
17. Initiation of or a change in concomitant medication to reduce the frequency of migraine

episodes within three (3) months prior to **Screening/Visit 1.**
18. Subjects who are employees of the sponsor.
19. Relatives of, or staff directly reporting to, the Investigator.

Subjects with test results which do not meet the above inclusion/exclusion criteria may have the underlying 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 not be enrolled in the study.

6.3 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)/Ethics Committee (EC), in accordance with the site's IRB/EC requirements.

6.4 Subject Withdrawal Criteria

Subjects may voluntarily withdraw from the study, or be removed from the study at the discretion of the Investigator or Sponsor, at any time. The Investigator may withdraw a subject at any time if it is determined that continuing 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/Visit 2**, the Investigator 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
- Adverse event (AE)
- Subject request
- Investigator request
- Sponsor request

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 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.

All subjects prematurely discontinuing from the trial (prior to **EoS/Visit 2**), regardless of cause, must be seen for **EoS/Visit 2**. Subjects that withdraw from the study prior to dosing a single attack should return to the clinic for **EoS/Visit 2** to return all unused study drug and the e-diary. Subjects who are withdrawn from the study for any reason will not be replaced.

7. TREATMENT OF SUBJECTS

7.1 Subject numbering and enrollment status

At screening, each subject will be assigned a unique seven-digit subject number. The first three characters will be numbers that identify the study site, and will be assigned by the Sponsor. The remaining four characters identify the subject. The latter four numbers will be assigned by the study site personnel in ascending sequential order to each unique subject screened at that site. For example, the subject number for the first subject screened at Study Site 001 would be 001-2001. If a subject is rescreened, the reason for rescreening will be noted and the subject will keep the same number assigned at initial screening. If a subject fails to be randomized, the reason for not being randomized should be documented in the source documents. The subject will be considered a screen failure. If a subject is randomized but is then deemed ineligible at the telephone confirmation the subject will be considered a randomization failure. This subject will return to the clinic to be discontinued. Study drug and the patient e-diary will be collected. A subject deemed to be a randomization failure may be rescreened if the reason for ineligibility is thought to represent a laboratory error, a reversible, clinically insignificant intermittent condition, or is not consistent with the subject's historical values. The subject will be given a new screening number. In this case the subject should not be re-randomized until eligibility is confirmed. If the subject is not re-randomized he/she will be considered a screen failure.

7.2 Description of Study Drug

For study purposes lasmiditan and matching placebo are all referred to as study drug.

7.3 Concomitant Medications

Concomitant medications (including devices), for migraine or pain during the 90 days (3 months) prior to study enrollment and concomitant medication used to treat other medical conditions during the 30 days (1 month) prior to study enrollment will be recorded during **Screening/Visit 1**.

Any changes in dosage or new medications added as a result of intercurrent illness during the subject's time on study must be recorded in the CRFs.

7.3.1 Rescue Medication

Rescue medication will be permitted after completion of the 2 hour assessments if the migraine does not respond (subject is not headache pain free). If the migraine does not respond within 2 hours a second dose of randomized study drug may be taken up to 24 hours after the first dose as long as no other rescue medication has been used. The Investigator may advise each subject as to an alternative suitable rescue medication. Triptans, ergots, opioids and barbiturates MUST NOT be used for rescue medication within 24 hours of study drug administration. The use of rescue medication will be recorded in the subject diary.

7.3.2 Recurrence Medication

If the migraine responds within 2 hours (headache becomes pain free) but then recurs after 2 hours, a second dose of randomized study drug may be taken up to 24 hours after the first dose.

7.4 Prohibited Medications

Use of the following medications is prohibited for the duration of a subject's participation in the study from **Screening /Visit 1** through **EoS/Visit 2**:

- Any investigational treatment other than lasmiditan.
- All other symptom modifying treatments (e.g. antiemetics) for migraine except rescue or recurrence medication as detailed in Section 7.3.1 and 7.3.2.
- If a patient requires the initiation of migraine prophylaxis (concomitant medication to reduce the frequency of migraine episodes) or a change in ongoing migraine prophylaxis after the **Screening/Visit 1** they should be withdrawn from the study.

7.5 Treatment Compliance

Study drug will be taken by the subject at home throughout the study. Prior to discharge from **Screening/Visit 1** subjects will be given study drug to treat a single migraine attack and a second dose for rescue or recurrence. Information on the time and date of each dose (initial treatment along with the use of rescue medication or treatment of recurrence) will be recorded by the subject in the electronic diary. Subjects will be instructed to return all unused study drug to the clinic at **EoS/Visit 2**.

7.6 Randomization and Blinding

Subjects will be randomized through a central randomization process by IRT during **Screening/Visit 1**. A randomization number and study drug card number will be assigned for dosing. Lasmiditan and matching placebo will be provided in double-blinded treatment packs.

7.7 Unblinding Procedures

7.7.1 Emergency unblinding of treatment assignment

Emergency unblinding should only be performed when necessary in order to treat the subject. There is no known antidote to lasmiditan, so symptomatic and supportive management of any suspected and treatment related adverse event, if necessary, is clinically indicated.

Unblinding will result in the subject being discontinued from the study, irrespective of whether the Investigator ultimately agrees with the event being related to study drug (lasmiditan). Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. The Investigator will have the ability to break the blind for any subject through the centralized randomization system (IRT). However, the Investigator should make every effort to contact the Sponsor's medical monitor or their designee to discuss the subject's emergency situation and the need to unblind prior to unblinding any subject, but must contact the Sponsor or designee within one working day after the event occurs. The Sponsor's medical monitor or their designee will also have the ability to break the blind for the Investigator while remaining blinded via the centralized randomization system if the treating Investigator requests this The blind may be broken in the case of a pregnancy should the subject desire this information. Any subject for whom the blind is broken is to be discontinued from future study treatment. The date, time and reason for breaking the blind are to be recorded in the subject's source documents.

7.7.2 Unblinding for Regulatory Authorities

In cases where unblinding is required for the purposes of reporting expedited safety events to country specific regulatory agencies or Ethics Committees, the unblinding will be performed by

an authorized member of the Quintiles Pharmacovigilance team. A blinded version of any documents to be submitted to the authorities will be shared as appropriate with study staff and site personnel. Only the authorized person(s) within the Quintiles Pharmacovigilance and Regulatory Affairs will have access to the unblinded version of any documents. The procedures for requesting and obtaining unblinded information and for maintaining the integrity of the data and clinical trial are outlined in the Pharmacovigilance Plan for this study.

8. STUDY DRUG MATERIALS AND MANAGEMENT

8.1 Study Drug

Study drug refers to lasmiditan and matching placebo.

Lasmiditan drug product is a tablet containing 50 mg, 100 mg or 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 Aptuit (Verona) Srl Via A. Fleming, 4 37135 Verona, Italy and contains the following inactive excipients: CCI [redacted]

The placebo tablets were also manufactured by Aptuit (Verona) and contain the following inactive excipients: CCI [redacted] he placebo tablets match the active tablets in size, shape and appearance.

Each dose will consist of two tablets for the treatment of a single migraine attack and two tablets for use as rescue medication or as treatment of recurrence of migraine.

- Lasmiditan 50 mg dose – one 50 mg lasmiditan tablet and either one lasmiditan 100 mg matching placebo, or one lasmiditan 200 mg matching placebo.
- Lasmiditan 100 mg dose – one 100 mg lasmiditan tablet and either one lasmiditan 50 mg matching placebo, or one lasmiditan 200 mg matching placebo.
- Lasmiditan 200 mg dose – one 200 mg lasmiditan tablet and either one lasmiditan 50 mg matching placebo, or one lasmiditan 100 mg matching placebo
- Placebo – one 50 mg lasmiditan matching placebo and one 100 mg matching placebo, or one 50 mg lasmiditan matching placebo and one 200 mg matching placebo or one 100 mg lasmiditan matching placebo and one 200 mg matching placebo.

8.2 Study Drug Packaging and Labeling

All study drug will be provided as individual dosing cards containing 2 doses. In the card, each tablet will be contained within an individual blister pack. There will be a total of 4 blisters per card. The doses will be separately designated either for initial treatment or for rescue or recurrence.

All study drug will be labeled with:

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

8.3 Study Drug Storage

All study drug should be stored at room temperature.

8.4 Study Drug Preparation

No preparation will be required.

8.5 Administration

Subjects will be screened outside a migraine attack. The study drug will be dispensed to the subject during **Screening/Visit 1** with instructions to treat an acute migraine attack only after their eligibility has been confirmed by the site. Each subject will be informed of their eligibility via a telephone call within 7 days of the screening visit.

Subjects will be instructed to take both tablets with approximately 4 ounces of water as the FIRST treatment for a new migraine attack providing that: any aura symptoms have resolved

- the headache is either moderate or severe and has been so for less than 4 hours
- no prior analgesic or acute migraine treatment has been taken to treat the current migraine attack.

Subjects will be instructed to take the second dose (two tablets) if needed with approximately 4 ounces of water for rescue or for recurrence of migraine.

8.6 Study Drug Accountability

Under supervision of the Investigator, the study pharmacist or designee will be responsible for drug accountability. The pharmacist or designee will keep an accurate inventory of test article(s) 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.

Subjects will be required to return all unused study drug. If any unused material is remaining 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.

9. TREATMENT ASSESSMENTS

9.1 Efficacy and Safety Parameters

Primary efficacy will be evaluated using subject recorded response to relief from pain and from the MBS (nausea, phonophobia or photophobia) based on the first dose, as well as use of rescue medication and/or recurrence of headache and use of recurrence medication. Efficacy of a second dose will be evaluated using subject recorded response to relief from pain and from the MBS (nausea, phonophobia or photophobia) by subjects who took a second dose for rescue or for recurrence. Safety will be monitored with physical examinations, vital signs, ECGs, clinical laboratory testing, and AE/SAE assessments.

Standardization of data capture is provided in detail in the remainder of this section. Assessments should be performed in relation to dosing as indicated.

9.1.1 Medical History

General relevant medical history will be recorded on the CRF and will include information relating to any prior or existing medical conditions involving the following disease types or systems: infectious diseases, allergic, metabolic/endocrine/nutritional, hematopoietic, musculoskeletal, dermatologic, head, eyes, ears, nose and throat (HEENT), breasts, respiratory, cardiovascular, gastrointestinal/hepatic, genitourinary/renal, neurological, and psychiatric/psychosocial.

The Investigator will exclude subjects with ongoing significant major organ disease.

Smoking history and family history of cardiovascular disease will be recorded on the CRF.

Concomitant medications or devices, for migraine or pain during the 90 days (3 months) prior to study enrollment and concomitant medication used to treat other medical conditions during the 30 days (1 month) prior to enrollment will be recorded on the CRF.

In addition, information regarding the subject's migraine history including prior treatment will be recorded.

9.1.1.1 Demographics

During **Screening/Visit 1**, subject initials, age, gender, race and ethnicity will be recorded on the CRF.

9.1.1.2 MIDAS

MIDAS is a 5 item questionnaire (Appendix 3) evaluating the impact of migraine on a patient's life over the past 3 months. The questionnaire is to be completed by each subject at **Screening/Visit 1**. A score of ≥ 11 is required for inclusion in the study.

Subjects should be given sufficient time to complete the questionnaire and it should be completed prior to any procedures (i.e. physical exam, blood draw). The questionnaire is a self-reported measure and is to be reviewed with the subject for completeness only. Subjects should not be questioned about any of the responses or given suggestions on how to answer any of the questions, however clarification of what a question is asking is allowed.

9.1.1.3 Resource Utilization

During **Screening/Visit 1** subjects will be asked specifically about any CV events in the last 6 months and/or related resource utilization such as visits to cardiologists, procedures, hospitalizations, new treatments or treatment adjustments for CV disease. In addition information regarding any ER visits or visit to physician's office for migraine treatment will be recorded. At **EoS/Visit 2** the subject will again be asked about resource utilization during their time on study.

The subject will also be asked about the number of days missed from work and/or school during the migraine treated with study drug.

9.1.2 Physical Examination

A complete physical examination will be performed during **Screening/Visit 1**. A complete physical examination of all body systems will include the following: general appearance, skin, HEENT, heart, lymph nodes, lungs, abdomen, extremities/joints, neurological systems, and mental status. For **EoS/Visit 2**, a brief symptom related physical examination will be performed if indicated by an AE.

Height and weight will be measured at **Screening/Visit 1**. BMI will be calculated by the database.

9.1.3 Vital Signs

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

Blood pressure (BP) will be measured after at least 5 minutes rest and if possible in the same arm at each visit by using an automated sphygmomanometer. The results will be recorded in millimeters of mercury (mmHg). HR will be measured in the radial artery in the dominant arm for 30 seconds and will be recorded as beats per minute (bpm).

9.1.4 ECG

A standard, digital 12-lead ECG will be obtained after at least 5 minutes rest at **Screening/Visit 1**and **EoS/Visit 2**.

A trained ECG technician 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. Abnormal findings will be identified as either clinically significant (CS), or not clinically significant (NCS). CS findings are to be reported as AEs by the Investigator. ECGs will be sent to a central reader for further evaluation.

ECG reports from the central reader will include: rhythm, rate, axis, PR, QRS, and corrected (by both Fridericia and Bazett) and uncorrected QT intervals.

9.1.5 Clinical Laboratory

Samples of blood and urine will be collected for clinical laboratory tests during **Screening/Visit 1** and **EoS/Visit 2**. Tests will be conducted as designated below:

9.1.5.1 Clinical Laboratory tests conducted

Clinical laboratory evaluations will include:
Hematology: white blood cell (WBC) count with differential (neutrophils, lymphocytes, eosinophils, monocytes, basophils), hemoglobin, hematocrit, platelet count, and red blood cell (RBC) count.

Serum Chemistry Profile: albumin, alkaline phosphatase (AP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), calcium, chloride, bicarbonate, creatinine, glucose, phosphate, potassium, sodium, total bilirubin, total protein, total cholesterol, HDL, and triglycerides.

Urinalysis: protein, glucose, nitrite, ketones, blood (hemoglobin), pH, specific gravity, microscopic bacteria, RBCs, WBCs, casts, crystals, and cells. Microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive.

For WOCBP, a serum pregnancy test for β-HCG will be performed at the **Screening/Visit 1**. If a urine pregnancy test is positive during the study the subject will be discontinued from the study after confirmation with a positive serum βHCG. A subject with a positive urine βHCG must not be dosed unless a negative serum βHCG is obtained. The confirmatory serum test may be performed at the local clinical laboratory. At **EoS/Visit 2**, a urine pregnancy test will be performed. If positive, a confirmatory serum pregnancy test will be done.

9.1.5.2 Abnormal and Clinically Significant Results

The Investigator 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 will use the WHO Toxicity Criteria (see Appendix 1) as a guide when evaluating the clinical significance of all abnormal clinical laboratory results. In case of CS laboratory results, the Investigator 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 has judged that the abnormal values are not related to the administration of study drug or other protocol-specific procedures.

9.1.6 Columbia Suicide Severity Rating Scale

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

- The screening version will be administered at **Screening/Visit 1** (Appendix 4).
- The "since last visit" version will be administered at **EoS/Visit 2** (Appendix 5).

If present, suicide 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).

9.1.7 Dosing Instructions

Study drug should be administered as the **FIRST** treatment for an acute migraine attack. If the subject has already taken any prior analgesic or acute migraine treatment, he/she is no longer eligible to treat the current migraine attack but may treat a later attack with the study drug.

Subjects will be asked to treat their migraine attack within 4 hours of onset providing that the headache severity is at least moderate at that time and not improving. Subjects will record their response over the next 48 hours using an electronic diary. Subjects will be instructed not to use rescue medication until at least 2 hours after taking study drug. If the subject does not become headache pain free within 2 hours, rescue medication will be permitted after completion of the 2 hour assessments. A second dose of randomized study drug may be taken up to 24 hours after the first dose as long as no other rescue medication has been used. The Investigator will advise each subject as to alternative suitable rescue medication. Triptans, ergots, opioids and barbiturates MUST NOT be used for rescue medication within 24 hours of study drug administration. If the migraine responds within 2 hours (headache becomes pain free) but then recurs after 2 hours a second dose of randomized study drug may be taken for up to 24 hours from the first dose.

9.1.8 Subject Diary

Subjects will be trained on the use of the electronic diary at **Screening/Visit 1**. Efficacy data will be collected in an electronic diary for an attack. Subjects will record the date and time at which their migraine headache starts and when it first becomes moderate or severe. They will also record the date and time of taking the first dose of study drug.

Subjects will be asked to assess their headache severity at specified time points: 0 (pre dose), 0.5, 1, 1.5, 2, 3, 4 and 24 and 48 hours post dose using the IHS four point headache severity rating scale (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain). The need for rescue medication and second dosing of study drug or an alternative treatment will be assessed between 2 and 24 hour and at 48 hours. Recurrence of pain and second dosing of study drug will be assessed between 2 and 24 hours and at 48 hours.

At the same time points, 0 (pre dose), 0.5, 1, 1.5, 2, 3, 4, 24 and 48 hours, subjects will grade the degree of interference with normal activities and the presence or absence (yes or no) of accompanying symptoms: photophobia, phonophobia and nausea. At time 0 (pre dose) subjects will select from the accompanying symptoms present (nausea, phonophobia or photophobia) which one is the most bothersome to them. Subjects will be asked to record the presence or absence (yes or no) of vomiting. Subjects will also be asked to record the exact time at which headache relief became meaningful to them and the time at which they become headache pain free. At 2 hours subjects will be asked to record their global impression of change using a 7-point scale (very much better, much better, a little better, no change, a little worse, much worse, and very much worse).

The diary will also be used to record any symptoms or side effects the subject is experiencing and the use of any concomitant medications from **Visit 1** through to **EoS/Visit 2**

9.1.8.1 Recording Use of Rescue Medication and Migraine Symptoms

The use of rescue medication taken because headache pain freedom is not achieved at 2 hours will be recorded. Subjects will document the date and time of dosing for rescue and any migraine symptoms they are experiencing at time of dosing and at 0.5, 1, 2, 4, 24 and 48 hours post dosing. Migraine pain will be graded as none (0), mild (1), moderate (2) or severe

(3) and other symptoms (nausea, phonophobia, or photophobia) will be recorded as yes or no. At time 0 (pre dose) subjects will select from the accompanying symptoms present (nausea, phonophobia or photophobia) which one is the most bothersome to them. Subjects will be asked to record the presence or absence (yes or no) of vomiting. Subjects will also be asked to record the exact time at which headache relief became meaningful to them and the time at which they become headache pain free.

9.1.8.2 Recording Recurrence and Migraine Symptoms

If migraine recurs within 48 hours of dosing, the subject will note the exact time when the headache returns to mild, moderate, or severe intensity after being pain free. Subjects will document the time they take the second dose of study drug and any migraine symptoms they are experiencing at the time of dosing and at 0.5, 1, 2, 4, 24 and 48 hours post dosing. Migraine pain will be graded as none (0), mild (1), moderate (2), or severe (3) and other symptoms (nausea, phonophobia, or photophobia) will be recorded as yes or no. At time 0 (pre dose) subjects will select from the accompanying symptoms present (nausea, phonophobia or photophobia) which one is the most bothersome to them. Subjects will be asked to record the presence or absence (yes or no) of vomiting. Subjects will also be asked to record the exact time at which headache relief became meaningful to them and the time at which they become headache pain free.

9.2 Adverse Events and Serious Adverse Events

9.2.1 Adverse Events

An AE is defined as any undesirable physical, psychological, or behavioral effect experienced by a subject during his/her participation in an investigational study, in conjunction with the use of the drug, whether or not product-related. During the treatment of a migraine with study drug subjects will be asked if they are feeling anything unusual that they have not felt with a migraine before. A 'yes' response will trigger an alert to the site to contact the subject and assess the AE in terms of what the subject is experiencing, how long the symptoms lasted and how much the symptom(s) impacted them. During the time between dosing, subjects will be asked how they are feeling. A response of 'not well' will trigger an alert to the site to contact the subject and assess the AE similarly to the assessment of AEs reported during treatment. 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 or medical staff, and
- Changes in laboratory abnormalities that are clinically relevant as assessed by the Investigator and for which a medical intervention was initiated.

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the product are not considered AEs after treatment unless they reoccur after the subject has recovered from the pre-existing condition or, in the opinion of the Investigator; they represent a clinically significant exacerbation in intensity or frequency. AEs are collected from the time the subject signs the informed consent form until the completion of **EoS/ Visit 2**. AEs reported prior to dosing will be captured and considered non-treatment emergent AEs. AE reported 48 hours after dosing until the completion of **EoS/Visit 2** will be captured and considered non-treatment emergent AEs.

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 must assess whether they consider an AE to be drug-related. In assessing this relationship, the Investigator must use information about the drug as outlined in the Investigator's Brochure (IB), 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 other qualified physician) 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 they are evaluated, are considered by the Investigator (or other qualified physician) to have no relationship, or no reasonable possibility of a relationship, to study drug.

2. Event Severity: The Investigator will be asked to assess the severity of the AE using the WHO Toxicity Criteria, as shown in Appendix 1. The WHO criteria assign a grade of 1 through 4 to indicate the severity of AEs. For AEs that are not listed in the WHO criteria, the Investigator will use medical judgment to assess the severity of the AE.

    The following are guidelines to be used by the Investigator to judge the event severity of an AE that is not in the WHO Toxicity Criteria:
    - 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

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 the sign, symptoms and/or other clinical information. In such cases, the diagnosis, and not the individual signs/symptoms or laboratory abnormalities should be documents 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.

9.2.2 Treatment Emergent Adverse Events (TEAE)

A TEAE will be an AE that occurred during the study after the first dose of study drug or that was present prior to dosing and exacerbates after the first dose of study drug.

9.2.3 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.

9.2.4 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.

9.3 Reporting Serious Adverse Events

The Investigator is responsible for reporting all SAEs, **regardless of causality**, to the Sponsor or their designated representative by entering the information into the eCRF within 24 hours of learning of the occurrence. The reporting timeframe starts when the subject signs the informed consent form and ends following the last dose of study treatment at **EoS/Visit 2**. At a minimum, a description of the event and the Investigator's 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 de-identified 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. A follow-up SAE Report must be submitted within 24 hours of the Investigator 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.

Follow-up information should be communicated by updating the data in the SAE eCRF. 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 for regulatory authority reporting. The Sponsor may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported.

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 to conduct supplemental assessments.

The Investigator should notify Quintiles Pharmacovigilance 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.

9.4 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. Other non-serious adverse events should be followed through the **EoS/Visit 2**.

9.5 Reporting safety information to the IRB/EC

The Investigator is responsible for following all local regulations for the reporting of safety information, including the reporting of SAEs to the IRB/ EC.
The Investigator must promptly report to his or her IRB/EC 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/EC in accordance with the IRB/EC'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 is responsible for submitting the safety report (initial and follow-up) or other safety information (e.g., revised Investigator's Brochure) to the IRB/EC in accordance with the IRB/EC's requirements and keep a copy in their files.

9.6 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 to Quintiles Pharmacovigilance using the same procedure for reporting SAEs in Section 9.3. 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 in Section 9.3.

10. STATISTICS

Prior to locking and unblinding the database, a detailed statistical analysis plan will be developed before any receipt of study data and decisions will be made regarding the integrity of subject data for inclusion in the statistical analysis. The efficacy analyses and baseline characteristics will be based on the Intent-to-Treat (ITT) and mITT population. The primary analysis will be tested in the mITT population. All safety analyses will be based on the Safety Population. The Per Protocol Population will be used to support the ITT analyses.

All tests of treatment effects will be conducted at a one-sided alpha level of 0.025.

The primary objective of the study is to evaluate the efficacy of lasmiditan versus placebo at 2 hours on migraine headache pain and the MBS as identified by the individual subject based on the first dose.

Summary analysis of the efficacy and safety of the use of a second dose of lasmiditan versus placebo for either rescue or recurrence will be performed only in the subjects that actually took a second dose of study drug within 24 hours of the first dose. Analysis will be performed on the subset of subjects that dosed for rescue and on the subset that dosed for recurrence of migraine.

Data from all investigative sites will be pooled for all planned analyses. Analysis of individual site findings will be considered if necessary. For those measures that are analyzed using change from baseline scores, observed scores may also be presented descriptively.

Any changes in the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other changes to the data analysis methods described in the protocol and the justification for making the change will be described in the statistical analysis plan as well as the clinical study report. Additional exploratory analyses will be conducted as deemed appropriate. All data listings, summaries and analyses will be performed by Quintiles.

10.1 Sample Size

This Phase 3 study is designed to demonstrate that lasmiditan is effective in the treatment of acute migraine in adult patients with and without aura. The sample size was estimated based on the 2 hour headache pain free and associated symptoms (nausea, phonophobia, and photophobia) free response rates observed in the Phase 2 study COL MIG-202.

Dose	Pain free	Nausea free	Phonophobia free	Photophobia free
Placebo	7.4%	59.3%	51.9%	34.6%
50 mg	13.9%	68.4%	58.2%	53.2%
100 mg	13.6%	74.1%	75.3%	67.9%
200 mg	18.8%	63.8%	59.4%	58.0%

For the primary endpoint of the proportion of patients pain free at 2 hours a sample size of 570 evaluable subjects per arm provides power of >90% for the 50 mg dose, the 100 mg dose and the 200 mg dose.

In order to estimate sample size for the key secondary endpoint of proportion of patients MBS free at 2 hours, simulation was performed in SAS on the conditional probability of being free from any one symptom defined as MBS under 4 different scenarios. For each symptom or combination of symptoms, the likelihood of an individual symptom being the MBS was estimated. In the most conservative scenario (scenario 1) it was assumed that nausea would always be declared the MBS if it was present, regardless of the presence of other symptoms (phonophobia or photophobia). The other 3 scenarios assumed lower likelihoods of nausea to be considered the MBS and allowed for the other symptoms (either phonophobia or photophobia) to be considered the MBS at a higher rate. This resulted in power estimates of > 95% for MBS at a sample size of 570 for the lasmiditan 50 mg dose and >99% for MBS at sample sizes of 450 to 570 per arm for the 100 mg dose across all 4 scenarios. For the 200 mg dose, an average power of 71% was estimated across five seeds under the most conservative scenario 1. In contrast, the 3 scenarios that did not declare nausea to be the default MBS if it was present estimated a greater average power of 82.6% to 91%.

Group	Scenario	Variable	Seed				
			55405	74951	82002	82377	90075
Placebo vs D50	1	Power (MBS)	96.90%	95.90%	96.10%	95.60%	96.80%
		Sample Size	570	570	570	570	570
	2	Power	93.70%	94.30%	94.80%	93.90%	93.90%
		Sample Size	450	450	450	450	450
	3	Power	90.40%	90.40%	90.10%	91.00%	91.40%
		Sample Size	575	575	575	575	575
	4	Power	93.70%	94.30%	94.80%	93.90%	93.90%
		Sample Size	450	450	450	450	450
Placebo vs D100	1	Power (MBS)	>99.99%	>99.99%	>99.99%	>99.99%	>99.99%
		Sample Size	570	570	570	570	570
	2	Power	99.90%	>99.99%	>99.99%	>99.99%	>99.99%
		Sample Size	450	450	450	450	450
	3	Power	>99.99%	>99.99%	>99.99%	>99.99%	>99.99%
		Sample Size	575	575	575	575	575
	4	Power	99.90%	>99.99%	>99.99%	>99.99%	>99.99%
		Sample Size	450	450	450	450	450
Placebo vs D200	1	Power	70.87%	70.87%	72.97%	71.17%	68.47%
		Sample Size	570	570	570	570	570
	2	Power	84.40%	85.00%	85.80%	85.90%	85.80%
		Sample Size	450	450	450	450	450
	3	Power	83.50%	83.20%	81.30%	83.40%	81.80%
		Sample Size	575	575	575	575	575
	4	Power	90.20%	90.50%	92.50%	91.40%	90.40%
		Sample Size	450	450	450	450	450

[1] Mean rate is the freedom from MBS at 2 hours post dose.
P=placebo, L = lasmiditan

It is expected for a one-sided, two-sample comparison of proportions at the 2.5% level of significance, a sample size of 570 subjects per treatment arm (as defined by the first dose) provides >90% power to detect a difference in headache pain free response rates for assumed true rates of 7.4% and 18.8% (placebo and 200 mg), 7.4% and 13.6% (placebo and 100 mg) and 7.4% and 13.9% (placebo and 50 mg) >90 % power for MBS for both the 50 mg dose arm

and the 100 mg dose arm and very near or higher than 80% power for MBS in the 200 mg dose arm.

10.2 Randomization

This is a multicenter, randomized, double-blind, placebo controlled parallel group study.
Subjects will be centrally randomized to one of 7 treatment sequences to receive lasmiditan 50 mg, lasmiditan 100 mg (L100 mg) or lasmiditan 200 mg (L200 mg) or placebo (P) for the first dose (in a 1:1:1:1 ratio) and the second dose for rescue or recurrence of migraine (if needed). Subjects will be stratified (yes or no) for use of concomitant medications that reduce the frequency of migraine episodes. Study drug will be randomized and dispensed at **Visit 1** as follows:

First dose for treatment of migraine	Second dose for rescue or recurrence of migraine (if needed)
L50 mg	L 50 mg
	L 50 mg
	placebo
L100 mg	L100 mg
	L100 mg
	placebo
L200 mg	L200 mg
	L200 mg
	placebo
placebo	placebo

10.3 Analysis Populations

10.3.1 Primary efficacy – FIRST dose

The statistical analysis of the first dose will be based on the analysis populations as defined below:

Safety population All randomized subjects who use at least one dose of study drug, regardless of whether or not they undergo any study assessments. Subjects are evaluated by the drug they use, not by the drug to which they are randomized.

ITT population All randomized subjects who use at least one dose of study drug and have any post-dose assessments. Subjects are evaluated by the drug to which they are randomized.

mITT population All randomized subjects who use at least one dose of study drug to treat a qualifying migraine attack and have any post-dose assessments. Subjects are evaluated by the drug to which they are randomized.

PP population All ITT subjects will be considered per protocol (PP) if they dose a migraine attack and do not deviate from the protocol.

The following is a list of additional protocol violations which would exclude subjects from the PP population:

- Subject received excluded rescue medications or used rescue medication before 2 hour time point.
- Subject used recurrence medication before 2 hour time point.
- Subject did not receive study drug as assigned.
- Subject did not meet all inclusion/exclusion criteria.
- Subject did not treat a migraine of at least moderate severity.

10.3.2 Second Dose Analysis Populations

The analysis populations for the second dose used for rescue or for recurrence will be as defined below. Subjects **must** have taken the second dose and have been considered evaluable for the first dose and primary analysis to be included in the second dose analysis.

Safety population All randomized subjects who were considered in the safety population after the first dose and used a second dose of study drug, regardless of whether or not they undergo any study assessments. Subjects are evaluated by the drug they receive, not by the drug to which they are randomized.

ITT-2nd Dose population All randomized subjects who were considered ITT after the first dose and used a second dose of study drug and have any post-dose assessments. Subjects are evaluated by the drug to which they are randomized.

mITT-2nd Dose population All randomized subjects who were considered mITT after the first dose and used a second dose of study drug and have any post-second dose assessments. Subjects are evaluated by the drug to which they are randomized.

PP-2nd Dose population All ITT subjects will be considered per protocol (PP) if they use a second dose for rescue or recurrence of a migraine attack and do not deviate from the protocol.

The 2nd dose ITT, mITT and PP analysis populations will be further qualified by reason for second dose. Subjects will be considered in the 2nd dose rescue populations or 2nd dose recurrence populations as defined:

- **Rescue population:** All randomized subjects who did not achieve headache pain free at 2 hours, completed the 2 hour assessments and took a second dose of study drug between 2 hours and 24 hours.

- **Recurrence population:** All randomized subjects who achieved headache pain free at 2 hours, but then experienced recurrence of mild, moderate or severe migraine pain and took a second dose of study drug up to 24 hours from the first dose.

10.4 Accountability and Background Characteristics

10.4.1 Enrollment and Disposition

The number of subjects enrolled, by study population and Investigative site, will be presented by treatment. The primary reasons for discontinuation will be summarized by treatment and based on the safety population. The number and percentage of subjects with protocol deviations leading to exclusion from the PP population will be presented by reason for exclusion, stratified by treatment. All deviations will be listed.

10.4.2 Subject Characteristics

Subject characteristics will be obtained at the **Screening/Visit 1** prior to randomization and will be summarized by treatment and overall. Summaries will include descriptive statistics for continuous measures (sample size, mean, standard deviation, median, minimum, maximum) and for categorical measures (sample size, frequency and percentages). Treatments will be compared descriptively by using analysis of variance techniques for continuous data and Pearson's chi-square or Fisher's exact test for categorical data.

The results of these tests will be used in a descriptive way to highlight potential imbalances between the treatment groups. Subject characteristics may include, but are not limited to: age, gender, race/ethnicity, height, weight, BMI, and migraine history.

Subject characteristics will be summarized on all study populations.

10.4.3 Treatment Compliance

Treatment compliance will be assessed in terms of the actual dose. Treatment compliance will be used to characterize the patients and determine clinical evaluability for some analyses. Treatment compliance will be summarized within each treatment group by means of descriptive statistics (n, mean, SD, median, minimum and maximum).

10.5 Efficacy Analyses

All of the efficacy analyses will be performed on the ITT or mITT population. The primary analysis population is the mITT population. The PP population will be used as supportive analyses.

10.5.1 Primary Analysis

The treatment effect between lasmiditan and placebo will be tested first for the primary endpoint of the proportion of subjects who are headache pain free and the key secondary endpoint of the proportion of subjects who are MBS free at 2 hours in the mITT population between the lasmiditan 200 mg and placebo dose group based on the first dose. The primary analysis will be completed using logistic regression Wald Chi-square test with a basic model including treatment group and region, using a one-sided test at the alpha=0.025 level of significance.

If the primary analysis is statistically significant (one-sided, $p<0.025$), additional confirmatory hypotheses will be tested on the proportion of subjects who are headache pain free and the proportion of subjects who are MBS free at 2 hours in the lasmiditan 100 mg and placebo

groups followed by the lasmiditan 50 mg and placebo groups.

Headache pain free at 2 hours will be defined as a reduction in headache severity from moderate (2) or severe (3) at baseline to none (0) two hours after dosing with study drug. MBS free at 2 hours will be defined as a 'no' response to the presence of the symptom (either nausea, phonophobia, or photophobia) that was identified as MBS at predose, 2 hours after dosing with study drug.

A qualifying migraine is defined as a migraine treated with study drug within 4 hours of onset.

Subjects taking rescue medication within the first two hours or who fail to record headache severity at 2 hours will be assumed to have no headache response in the mITT and the ITT analyses.

A subject is defined to have used rescue medication within the first two hours post dosing if at least one medication is documented in the rescue medication log in the subject electronic diary for which:
0 (min) < date/ time rescue medication (diary) – date/ time of dosing (diary) < 120 (min).

Subjects who do not provide a headache pain severity rating at baseline or who use other medication prior to the study drug for the study migraine attack will be assumed to have no headache response for the ITT analysis.

10.5.2 Sensitivity Analyses of the Primary and Key Secondary Endpoints

The primary endpoint of pain free at 2 hours and the key secondary endpoint of MBS free are defined as proportions. The prespecified approach for handling missing data is to assume that subjects with missing data are nonresponders. While this approach is appropriately conservative, a sensitivity analysis will be incorporated to exclude subjects with missing data.

10.5.3 Multiplicity Adjustment for Hypothesis Testing

The gatekeeping procedure will be implemented to prevent Type I error inflation for multiple comparisons among the primary and secondary analyses. The treatment effect between lasmiditan 200 mg and placebo will be tested first for the primary endpoint of the proportion of subjects who are headache pain free and the key secondary endpoint of the proportion of subjects who are MBS free at 2 hours in the mITT population.

If the primary analysis is statistically significant (one-sided, $p<0.025$), additional confirmatory hypotheses will be tested in the mITT population in the following sequential order:

1. Proportion of subjects who are headache pain free at 2 hours in the lasmiditan 100 mg and placebo group.
2. Proportion of subjects who are MBS free at 2 hours in the lasmiditan 100 mg and placebo group.
3. Proportion of subjects who are headache pain free at 2 hours in the lasmiditan 50 mg and placebo group.
4. Proportion of subjects who are MBS free at 2 hours in the lasmiditan 50 mg and placebo group.

All of the above analyses will be completed using one-sided tests at the alpha=0.025 level of significance. If one of the analyses is not statistically significant, then all subsequent analyses will be exploratory rather than confirmatory.

10.5.4 Other Efficacy Analyses

10.5.4.1 Headache relief

The proportion of subjects with headache relief (moderate or severe headache at baseline, which became mild or none) at 2 hours post dose will be evaluated. The time course to headache relief will be explored up to 48 hours. Kaplan-Meier analysis will be performed to compare time course to headache relief between lasmiditan 200 mg and placebo, lasmiditan 100 mg and placebo and lasmiditan 50 mg and placebo.

10.5.4.2 Headache recurrence

The proportion of subjects with headache recurrence (moderate or severe headache at baseline, which became pain free at 2 hours post-dose and worsened again up to 48 hours post-dose) will be evaluated based on first dose. The frequency of recurrence will be compared by the same logistic regression model used for the primary endpoint analysis. The significance level of this exploratory analysis will be a nominal one-sided 0.05.

10.5.4.3 Headache rescue

The requirement for rescue medication at 2 hours and between 2 and 24 hours and 24- 8 hours (yes or no) will be evaluated based on first dose. The information on rescue medication use will be presented descriptively by time of use and treatment group.

10.5.4.4 Associated Symptoms of Migraine

Descriptive analysis of the associated symptoms of migraine, nausea, phonophobia and photophobia, will be performed at 2 hours. Freedom from each symptom will be defined as a 'no' response to the presence of the symptom 2 hours after dosing with study drug.

10.5.4.5 Additional analyses

Summary statistics will be presented on presence of vomiting, disability (4 point scale: not at all (0), mild interference (1), moderate interference (2), completely, needs bed rest (3)), and patient global impression of change (7 point scale).

10.6 Analysis of Second dose

All of the efficacy analyses will be performed on the ITT-2nd dose or mITT- 2nd dose population. The primary analysis population is the mITT-2nd dose population. The PP-2nd dose population will be used as supportive analyses.

10.6.1 Analysis of second dose for rescue

A second dose of study drug will be considered rescue medication if taken by a subject that did not achieve headache pain free at 2 hours and completed the 2 hour assessments prior to taking the second dose.

Summary statistics will be presented by treatment sequence on relief of migraine symptoms (pain free and MBS free) along with the time course to headache relief explored up to 48 hours. Subjects that use an alternative rescue medication will not be included in the summary statistics of response to treatment for rescue.

10.6.2 Analysis of second dose for recurrence

A second dose of study drug will be considered treatment for recurrence if taken by a subject that achieved headache pain free at 2 hours, completed the 2 hour assessments, and then experienced documented recurrence of mild, moderate, or severe migraine pain prior to taking the second dose.

Summary statistics will be presented by treatment sequence on the relief of migraine symptoms (pain free and MBS free) along with the time course to headache relief explored up to 48 hours. Only subjects that used a second dose of study drug for recurrence of migraine will be included in the summary statistics of response to treatment for recurrence.

10.7 Missing Values

The primary and key secondary endpoints are defined as proportions. If a subject has a missing value for a proportion endpoint, the subject will be classified as a nonresponder for this endpoint. Subjects who have more than one symptom (nausea, phonophobia or photophobia) but do not select one as the MBS prior to dosing, will be considered inevaluable for the MBS endpoint as there is no MBS selected to evaluate. In the case of subjects that have only one symptom (nausea, phonophobia, or photophobia) at predose but do not select a MBS, the one symptom will be considered the MBS for analysis.

For subjects who do not record a symptom rating, that symptom (pain, photophobia, phonophobia or nausea) will be assumed to be present at all time points where data are missing. Subjects who do not provide a headache severity rating at baseline will be assumed to have all four symptoms (pain, nausea, photophobia and phonophobia) at all time points. If recurrence medication is taken within 24 hours post dosing, or from 24 hours to 48 hours post dosing, even if no headache is reported, headache recurrence will be assumed for the first dose analysis.

The sensitivity analysis for handling missing data is described in detail in the SAP.

10.8 Safety Analyses

Values for all safety variables will be listed by subject and time point.

Where appropriate, safety variables will be summarized by using descriptive statistics, separated by treatment arm, and dose (the first dose and the second dose for recurrence or rescue or use of alternative rescue medication), and time of assessment. Descriptive statistics for quantitative variables will include: n, mean, median, minimum, maximum, and standard deviation. Descriptive statistics for qualitative variables will include frequency counts and percentages.

10.8.1 Adverse Events

AEs will be coded by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, and all summary tables for AEs will be organized by these categories. Frequency counts and percentages will be presented for subjects with AEs within each system organ class and preferred term, separated by treatment arm and treatment sequence and dose (the first dose and the second dose for recurrence or rescue or alternative rescue medication). Both subjects ever experiencing an event as well as total events will be presented. Descriptive statistics will

also be calculated for each treatment arm and treatment sequence and dose (initial and second dose for recurrence or rescue medication) for AE relationship and AE severity. If multiple intensities are reported for a given AE for a subject, the most severe intensity will be counted. A separate, similar analysis will be conducted for TEAEs.

An AE with the date of onset on or within 48 hours after a dose of study drug, or an event that worsens in intensity within 48 hours of a dose of study drug will be considered a TEAE. An AE that occurs in the interval after 48 hours of dosing until **EoS/Visit 2** will not be considered a TEAE.

SAEs and TEAEs that resulted in termination of the study drug and withdrawal from the study will be presented.

10.8.2 Physical Examinations, Vital Signs, ECG Parameters and Clinical Laboratory Test Values,

By-subject listings of physical examinations, vital signs, ECG parameters and clinical laboratory data will include indications of values that are outside the reference ranges, and values that are clinically significant. Shift tables describing out-of-reference range shifts will be provided for vital signs, ECGs and clinical laboratory test results from the **Screening/Visit 1** to **EoS/Visit 2**, as appropriate by treatment arm and dose.

10.8.3 C-SSRS

By-subject listings of any suicidal ideation or behavior will be listed.

10.9 Resource Utilization

By-subject listings of any resource utilization will be listed and will be summarized using descriptive statistics, separated by treatment arm, and dose.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1. Study Monitoring

The investigator will allow the Sponsor or a designee:

- to inspect the site, the facilities, and the material used for the study;
- to meet all members of the team involved in the study;
- to consult all the documents relevant to the study;
- to check that the eCRFs have been correctly completed;
- to have direct access to source documents for comparison of data therein with the data in the eCRFs;
- to check that AEs have been documented; and
- to 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 will provide the sponsor with the following:

- Progress reports at regular intervals
- Adequately completed eCRFs

11.2 Data collection

Investigational sites will be supplied with instructions on accessing the web-based Electronic Data Capture (EDC) system via secure web portal. Representatives of CoLucid Pharmaceuticals, Inc. (or designee) will train designated site staff on the EDC system. Investigational site staff will not be given access to the EDC system until the required training is completed and documented. Designated site staff will enter the data required by the protocol into the electronic CRFs. Automatic validation programs check for data discrepancies in the CRFs and, by generating appropriate error messages, allow modification or verification of the entered data by the site staff. After database lock, the Investigator will receive a CD or DVD of the subject data for archiving at the investigational site.

11.3 Audits and Inspections

The Investigator will be informed that an audit will be carried out, at the request of the Sponsor, before, during, or after the study.

The Investigator will be informed that the Regulatory Agencies may also carry out an inspection. In this case, the Investigator 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; and
- to consult all the documents relevant to the study.

12. QUALITY CONTROL AND QUALITY ASSURANCE

The Investigator or the appointed persons agree to complete the subject's eCRFs, at each investigation. Only the Investigator or appointed persons in his/her team may fill out or correct the eCRFs. The eCRFs will display the subject number corresponding to the order of inclusion in the study (7 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 eCRFs 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 using an electronic data query within the EDC system. 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 eCRFs must be made by the Investigator or by the appointed persons as instructed in the eCRF 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 one of his designated team.

It is the responsibility of the monitor to make certain that all data are completed on the eCRFs. The Investigator and the monitor must sign and date the eCRF per the eCRF procedure in order to attest respectively to the:

- authenticity of the data collected in the eCRF, and
- coherence between the data in the eCRF 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 Medical dictionary for regulatory activities (MedDRA) terminology.

ECGs will be evaluated for safety through central readers and the results will be sent electronically to the study database. Clinical laboratory samples will be processed through a central laboratory and the results will be sent electronically to the study database.

Randomization codes and data about all study drugs dispensed to the subject will be tracked using a centralized randomization process. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to the study database (or a designated CRO).

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.

At the end of the study, the Investigator will receive a CD or DVD of all data submitted for subjects at that site. This CD or DVD will serve as the archival copy and must be retained per the record retention policy.

The Investigator 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 CRO or their designee as defined in the study manual. The Investigator must submit to the Sponsor or its representatives a completed eCRF 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 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 will save data at regular intervals.

The Investigator 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.

13. 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.

13.1 Ethics Review

13.1.1 IRB/EC opinion

Before initiation of the study, the Investigator 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/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent and advertisement (as applicable) have been approved by the IRB/IEC/REB 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 is responsible for obtaining continued review of the study at intervals not exceeding one year or otherwise specified by the IRB/IEC/REB. The Investigator must supply

CRO/CoLucid Pharmaceuticals, Inc. with written documentation of continued review of the clinical study.

The Investigator must promptly inform their IRB/IEC/REB of all SAEs or other safety information reported from CRO/Sponsor.

13.2 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 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. CoLucid Pharmaceuticals, Inc. or its designated representative(s) will provide to Investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the Investigator must be agreed to by CoLucid or its designated representative(s) before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the CoLucid monitor or designated representative(s) after IRB/IEC/REB approval.

13.3 Amendments to the protocol

To alter the protocol, amendments must be written by CoLucid Pharmaceuticals, Inc., and approvals must be received from all parties that approved the original protocol (IRB/IEC/REB, 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/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator 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 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.

13.4 Discontinuation of the study

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

13.5 Study drug supply, storage and tracking

Study drugs 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, all study drugs should be stored according to the instructions specified on the drug labels. Drug labels will be in the local language and comply

with the legal requirements of each country. Clinical supplies are to be dispensed only in accordance with the protocol.

Subjects will be asked to return all unused study drug and packaging at each clinic visit, at the end of the study or at the time of study drug discontinuation. All empty, partially used containers and unused supplies may be destroyed at the site, retrieved by the study monitor or shipped to a designated facility identified by CoLucid 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 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.

13.6 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. 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, or its designated representative, by their initials and/or assigned subject number. Documents that identify the subject (e.g., the signed informed consent form) should not be submitted to CoLucid or its designated representative, and must be maintained in confidence by the Investigator.

13.7 Publication policy

As is customary for multicenter trials, publication by individual study sites 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 Investigators, in abiding with current guidelines and requirements of medical journals. For such manuscript(s), masthead roles for Investigators will be determined based on subject enrollment and scientific contributions to the Study.

14. RETENTION OF RECORDS

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

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16. APPENDIX 1. WORLD HEALTH ORGANIZATION TOXICITY CRITERIA

World Health Organization (WHO) Toxicity Criteria by Grade

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hematology	WBC ($x10^3$/L)	4	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
	Platelets ($x10^3$/L)	WNL	75.0 - normal	50.0 - 74.9	25.0 - 49.9	< 25.0
	Hemoglobin (g/dL)	WNL	10.0 - normal	8.0 - 9.9	6.5 - 7.9	< 6.5
	Granulocytes/ Bands ($x10^3$/L)	2	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
	Lymphocytes ($x10^3$/L)	2	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
	Haemorrhage	none	mild, no transfusion	gross, 1 - 2 units transfusion per episode	gross, 3 - 4 units transfusion per episode	massive, > 4 units transfusion per episode
Coagulation	Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	< 0.25 x N
	Prothrombin time(Quick)	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	> 2.00 x N
	Partial thrombo-plastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	> 3.00 x N
Metabolic	Hyperglycaemia (mg/dL)	< 116	116 - 160	161 - 250	251 - 500	> 500 or ketoacidosis
	Hypoglycaemia (mg/dL)	> 64	55 - 64	40 - 54	30 - 39	< 30
	Amylase	WNL	< 1.5 x N	1.5 - 2.0 x N	2.1 - 5.0 N	> 5.0 x N
	Hypercalcaemia (mg/dL)	< 10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.4	13.5
	Hypocalcaemia (mg/dL)	> 8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	6
	Hypomagnesaemia (mg/dL)	> 1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	0.5
Gastrointestinal	Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	—
	Vomiting	none	1 episode in 24 hrs	2 - 5 episodes in 24 hrs	6 - 10 episodes in 24 hrs	> 10 episodes in 24 hrs or requiring parenteral support

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
	Diarrhea	none	increase of 2 - 3 stools / day over pre-Rx	increase of 4 - 6 stools / day, or nocturnal stools, or moderate cramping	increase of 7 - 9 stools / day, or incontinence, or severe cramping	increase of > 10 stools / day or grossly bloody diarrhea, or need for parenteral support
	Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, oedema, or ulcers but can eat solids	painful erythema, oedema, or ulcers and cannot eat solids	requires parenteral or enteral support for alimentation
Liver	Bilirubin (N = 17 µmol/L)	WNL	-----	< 1.5 x N	1.5 - 3.0 x N	> 3.0 x N
	Transaminase (SGOT, SGPT)	WNL	2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
	Alk Phos or 5 nucleotidase	WNL	≥ 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
	Liver- clinical	no change from baseline	-----	-----	pre-coma	hepatic coma
Kidney, Bladder	Creatinine	WNL	< 1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	> 6.0 x N
	Proteinuria	no change	1 (+) or < 0.3 g% or 3 g/L	2 - 3 (+) or 0.3 - 1.0 g% or ≥3 - 10 g/L	4 (+) or > 1.0 g% or > 10g/L	nephrotic syndrome
	Haematuria	negative	microscopic only	gross, no clots no Rx needed	gross and clots bladder irrigation	requires transfusion or cystectomy
	Weight gain/loss	< 5.0 %	5.0 - 9.9 %	10.0 - 19.9 %	20.00%	-----
Pulmonary	Pulmonary	none or no change	asymptomatic, with abnormality in PFTs	dyspnoea on significant exertion	dyspnoea at normal level of activity	dyspnoea at rest
Cardiac	Cardiac arrhythmias	none	asymptomatic, transient, requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring; or hypotension, or ventricular tachycardia or fibrillation
	Cardiac function	none	asymptomatic, decline of resting ejection fraction by less than 20 % of baseline value	asymptomatic, decline of resting ejection fraction by more than 20 % of baseline value	mild CHF, responsive to therapy	severe or refractory CHF
	Cardiac ischaemia	none	non-specific T- wave flattening	asymptomatic, ST and T wave changes suggesting ischaemia	angina without evidence of infarction	acute myocardial infarction
	Cardiac- pericardial	none	asymptomatic effusion, no intervention required	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage required	tamponade; drainage urgently required

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
	Hypertension	none or no change	asymptomatic, transient increase by greater than 20 mm Hg (D) or to > 150/100 if previously WNL. No treatment required.	recurrent or persistent increase by greater than 20 mm Hg (D) or to > 150/100 if previously WNL. No treatment required.	requires therapy	hypertensive crisis
	Hypotension	none or no change	changes requiring no therapy (including transient orthostatic hypo- tension)	requires fluid replacement or other therapy but not hospitalization	requires therapy and hospitalization; resolves within 48 hours of stopping the agent	requires therapy and hospitalization for > 48 hrs after stopping the agent
Neurologic	Neuro: sensory	none or no change	mild paraesthesias; loss of deep tendon reflexes	mild or moderate objective sensory loss; moderate paraesthesias	severe objective sensory loss or paraesthesias that interfere with function	-----
	Neuro: motor	none or no change	subjective weakness; no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis
	Neuro: cortical	none	mild somnolence or agitation	moderate somnolence or agitation	severe somnolence, (>50 % waking hours), agitation, confusion, disorientation or hallucinations	coma, seizures, toxic psychosis
	Neuro: cerebellar	none	slight incoordination, dysdiadochokinesia	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
	Neuro: mood	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
	Neuro: headache	none	mild	moderate or severe but transient	unrelenting and severe	-----
	Neuro: constipation	none or no change	mild	moderate	severe	ileus > 96 hrs
	Neuro: hearing	none or no change	asymptomatic, hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correctable
	Neuro: vision	none or no change	-----	-----	symptomatic subtotal loss of vision	blindness
Pain	Pain	none	mild	moderate	severe	reg. narcotics

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Skin	Skin	none or no change	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritus or other associated symptoms	generalized symptomatic macular, papular or vesicular eruption	exfoliative dermatitis or ulcerating dermatitis
Alopecia	Alopecia	no loss	mild hair loss	pronounced or total hair loss	-----	-----
Allergy	Allergy	none	transient rash, drug fever < 38°C (100.4°F)	urticaria, drug fever 38°C (100.4°F), mild bronchospasm	serum sickness, bronchospasm requiring parenteral medication	anaphylaxis
Local	Local	none	pain	pain and swelling with inflammation or phlebitis	ulceration	plastic surgery indicated
Fever of unknown origin	Fever of unknown origin	none	37.1 - 38.0°C (98.7° - 100.4°F)	38.1 - 40.0°C (100.5 - 104°F)	> 40.0°C (> 104.0°F) for less than 24hrs	> 40.0°C (>104°F) for more than 24 hrs or accompanied by hypotension
Infection	Infection	none	mild	moderate	severe	life-threatening
Additional events	Asthenia	analogous to Karnofsky index (WHO grading)				
	Chills	analogous to fever				
	Peripheral oedema	analogous to weight gain				
	Anorexia	analogous to weight loss				

17. APPENDIX 2. INTERNATIONAL HEADACHE SOCIETY DIAGNOSTIC CRITERIA

1. MIGRAINE

1.1. Migraine without aura

Description:
Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia

Diagnostic criteria:

A. At least 5 attacks[1] fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)[2;3;4]
C. Headache has at least two of the following characteristics:
    1. unilateral location[5;6]
    2. pulsating quality[7]
    3. moderate or severe pain intensity
    4. aggravation by or causing avoidance of routine physical activity (**eg**, walking or climbing stairs)
D. During headache at least one of the following:
    1. nausea and/or vomiting
    2. photophobia and phonophobia[8]
E. Not attributed to another disorder[9]

Notes:

1. Differentiating between 1.1 **Migraine without aura** and 2.1 **Infrequent episodic tension-type headache** may be difficult. Therefore at least 5 attacks are required. Individuals who otherwise meet criteria for 1.1 **Migraine without aura** but have had fewer than 5 attacks should be coded 1.6.1 **Probable migraine without aura.**
2. When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening.
3. In children, attacks may last 1-72 hours (although the evidence for untreated durations of less than 2 hours in children requires corroboration by prospective diary studies).
4. When attacks occur on ≥15 days/month for >3 months, code as 1.1 **Migraine without aura** and as 1.5.1 **Chronic migraine.**
5. Migraine headache is commonly bilateral in young children; an adult pattern of unilateral pain usually emerges in late adolescence or early adult life.
6. Migraine headache is usually frontal temporal. Occipital headache in **children**, whether unilateral or bilateral, is rare and calls for diagnostic caution; many cases are attributable to structural lesions.
7. **Pulsating** means throbbing or varying with the heartbeat.

8. In young children, photophobia and phonophobia may be inferred from their behavior.

9. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

1.2 Migraine with aura

Description:
Recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5-20 minutes and last for less than 60 minutes. Headache with the features of migraine without aura usually follows the aura symptoms. Less commonly, headache lacks migrainous features or is completely absent.

Diagnostic criteria:

A. At least 2 attacks fulfilling criterion B
B. Migraine aura fulfilling criteria B and C for one of the sub-forms 1.2.1-1.2.6
C. Not attributed to another disorder[1]

Notes:

1. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

Medication Overuse Headache
Diagnostic criteria:

A. Headache[1] present on ≥15 days/month fulfilling criteria C and D

B. Regular overuse[2] for ≥3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache[3]

C. Headache has developed or markedly worsened during medication overuse

D. Headache resolves or reverts to its previous pattern within 2 months after discontinuation of overused medication[4]

Notes:

1. The headache associated with medication overuse is variable and often has a peculiar pattern with characteristics shifting, even within the same day, from migraine-like to those of tension-type headache.

2. Overuse is defined in terms of duration and treatment days per week. What is crucial is that treatment occurs both frequently and regularly, **ie**, on 2 or more days each week. Bunching of treatment days with long periods without medication intake, practiced by some patients, is much less likely to cause medication-overuse headache and does not fulfil criterion B.

3. MOH can occur in headache-prone patients when acute headache medications are taken for other indications.

4. A period of 2 months after cessation of overuse is stipulated in which improvement (resolution of headache, or reversion to its previous pattern) must occur if the diagnosis is to be definite. Prior to cessation, or pending improvement within 2 months after cessation, the diagnosis 8.2.8 **Probable medication-overuse headache** should be applied. If such improvement does not then occur within 2 months, this diagnosis must be discarded.

Medication overuse headache (MOH) as defined by ICHD II:

- Opioids ≥ 10 days a month during the 90 days prior to screening
- Combination medications (e.g., Fiorinal®) ≥ 10 days a month
- NSAIDS or other simple medications > 14 days a month during the 90 days prior to screening
- Triptans or ergots ≥ 10 days a month during the 90 days prior to screening

18. APPENDIX 3. THE MIGRAINE DISABILITY ASSESSMENT TEST

The MIDAS (Migraine Disability Assessment) questionnaire was put together to help you measure the impact your headaches have on your life. The information on this questionnaire is also helpful for your primary care provider to determine the level of pain and disability caused by your headaches and to find the best treatment for you.

INSTRUCTIONS: Please answer the following questions about ALL of the headaches you have had over the last 3 months. Record your answer in the box next to each question. Select zero if you did not have the activity in the last 3 months

_____ 1. On how many days in the last 3 months did you miss work or school because of your headaches?

_____ 2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)

_____ 3. On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?

_____ 4. How many days in the last 3 months was your productivity in household work reduced by half of more because of your headaches? (Do not include days you counted in question 3 where you did not do household work.)

_____ 5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

_____ **Total (Questions 1-5)**

_____ A. On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day.)
_____ B. On a scale of 0 - 10, on average how painful were these headaches? (where 0 = no pain at all, and 10 = pain as bad as it can be.)

Scoring: *After you have filled out this questionnaire, add the total number of days from questions 1 to 5 (ignore A and B).*

MIDAS Grade	Grade Definition	MIDAS Score
I	Little or no disability	0-5
II	Mild disability	6-10
III	Moderate disability	11-20
IV	Severe disability	21+

Please give the completed form to your clinician.

This survey was developed by Richard B. Lipton, MD, Professor of Neurology, Albert Einstein College of Medicine, New York, NY, and Walter F. Stewart, MPH, PhD, Associate Professor of Epidemiology, Johns Hopkins University, Baltimore, MD.

19. APPENDIX 4. COLUMBIA SUICIDE SEVERITY RATING SCALE-SCREENING VISIT

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Screening Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Past X Months
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** describe:	**Yes No** ☐ ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes No** ☐ ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it."* ***Have you been thinking about how you might do this?*** describe:	**Yes No** ☐ ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** describe:	**Yes No** ☐ ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** describe:	**Yes No** ☐ ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. _____ _____ ***Most Severe Ideation:*** ***Type # (1-5) Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (4) 4-8 hours/most of day (2) Less than 1 hour/some of the time (5) More than 8 hours/persistent or continuous (3) 1-4 hours/a lot of time	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (4) Can control thoughts with a lot of difficulty (2) Can control thoughts with little difficulty (5) Unable to control thoughts (3) Can control thoughts with some difficulty (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (4) Deterrents most likely did not stop you (2) Deterrents probably stopped you (5) Deterrents definitely did not stop you (3) Uncertain that deterrents stopped you (0) Does not apply	____

Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on and end/stop the pain living with the pain or how you were feeling) (0) Does not apply	____
SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Past X Years or Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts _____ **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes No** ☐ ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** describe:	**Yes No** ☐ ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** describe:	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No**

			☐ ☐
Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

20. APPENDIX 5. COLUMBIA SUICIDE SEVERITY RATING SCALE-SINCE LAST VISIT

COLUMBIA-SUICIDE SEVERITY

RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in **The Columbia Suicide History Form**, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)

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SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	Since Last Visit

1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	
Duration ***When you have the thoughts, how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	

Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	Since Last Visit
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes No** ☐ ☐ Total # of Attempts **Yes No** ☐ ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?***	**Yes No** ☐ ☐ Total # of interrupted
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?***	**Yes No** ☐ ☐ Total # of aborted
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?***	**Yes No** ☐ ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes No** ☐ ☐

Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body;	*Enter Code*
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code*