

H8H-CD-LAHL(D)/COL MIG-305 v4

An Open-label, Long-term, Safety Study of Lasmiditan (100 mg and 200 mg) in the Acute Treatment Of Migraine (GLADIATOR)

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Approval Date: 09-Nov-2018

**Protocol COL MIG-305 (H8H-CD-LAHL)
An Open-label, Long-term, Safety Study of Lasmiditan (100 mg and
200 mg) in the Acute Treatment Of Migraine (GLADIATOR)**

EudraCT No. 2015-005674-37

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Lasmiditan (LY573144)

Eli Lilly and Company
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Protocol (COL MIG-305 v1) Signed and Approved by CoLucid: 17 June 2015
Amendment (COL MIG-305 v1.1) Signed and Approved by CoLucid: 08 December 2015
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15 September 2017
Amendment H8H-CD-LAHL(D)/COL MIG-305 v4 Electronically Signed and Approved by Lilly on
date provided below.

Approval Date: 09-Nov-2018 GMT

INVESTIGATOR STATEMENT

Protocol Number: H8H-CD-LAHL(D)/COL MIG-305 v4

Protocol Title:

An Open-label, Long-term, Safety Study of Lasmiditan (100 mg and 200 mg) in the Acute Treatment Of Migraine (GLADIATOR)

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 Eli Lilly and Company (Lilly), and the Institutional Review Board/Ethics Committee before they can be implemented, except when necessary to eliminate immediate hazards to the subjects.

I confirm that I have read this protocol amendment H8H-CD-LAHL(D)/COL MIG-305 v4, I understand it, and I will work according to this protocol amendment. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and the applicable laws and regulations. I will accept the monitor's overseeing of the trial. I will abide by the publication plan set forth in my agreement with Eli Lilly and Company (or subsidiary). I confirm that if I or any of my staff are members of the ethics review board, we will abstain from deliberation and voting on this protocol amendment.

Site Name

Site Address

Investigator's Printed Name

Investigator's Signature

Date

1. SYNOPSIS

Name of Sponsor Company: Eli Lilly and Company		Drug Under Study: Lasmiditan (COL-144; LY573144)
Title of Protocol: An Open-label, Long-term, Safety Study of Lasmiditan (200 mg and 100 mg) in the Acute Treatment of Migraine		
Protocol Number: H8H-CD-LAHL/COL MIG-305	Phase: 3	Indication: Migraine - Acute Treatment
<p>Primary Objective: To evaluate the safety and tolerability of long-term intermittent use of lasmiditan 100 mg and of lasmiditan 200 mg, as the first dose and as a second dose, for the acute treatment of migraine.</p> <p>Secondary Objectives: To explore the long-term efficacy of lasmiditan 100 mg and lasmiditan 200 mg in terms of headache response over time.</p> <p>Additional Objectives: To compare patient reported resource utilization during the study to patient reported information from COL MIG-301 or COL MIG-302 in terms of cardiovascular events and in terms of migraine episodes.</p>		
<p>Study Endpoints</p> <p>Primary Endpoint: The proportion of patients and the proportion of attacks associated with any adverse event and with specific adverse events.</p> <p>Secondary Endpoint: The proportion of migraine attacks treated with lasmiditan 100 mg and with lasmiditan 200 mg which respond at 2 hours, calculated for each 3 month period.</p>		
<p>Study Design: This is a prospective, randomized, open-label study in subjects with migraine who have completed the Phase 3 studies, COL MIG-301 or COL MIG-302. Subjects will be stratified (yes or no) for use of concomitant medications that reduce the frequency of migraine episodes.</p> <p>Subjects will be asked to treat all migraine attacks with study drug on an outpatient basis for up to 12 months. Each patient's study participation will consist of a screening visit (Visit 1) and a treatment period of up to 12 months during which the subject will treat all migraine attacks with either lasmiditan 200 mg or lasmiditan 100 mg (with a second dose of study drug permitted between 2 and 24 hours (h) for recurrence of migraine only for subjects randomized to lasmiditan 100 mg). During the treatment period subjects will return to the clinic at 1, 3, 6, 9 and 12 months. There will be an early termination (ET) visit within two weeks (14 days) of treatment discontinuation for all subjects that discontinue between scheduled visits. The End-of-Study (EoS) visit will be at 12 months or at any scheduled visit when the subject's participation in the study is ended. Participation in the study for 12 months will be defined as completing Month 12/Visit 6.</p> <p>At Screening/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 completing study COL MIG-301 or COL MIG-302. The EoS/Visit 2 of COL MIG-301 or COL MIG-302 can be the same day as Screening/Visit 1. Assessments required for this visit can be the same assessments obtained at the EoS/Visit 2 of COL MIG-301 or COL MIG-302 as long as that visit occurred on the same day or no more than two weeks prior to signing informed consent and HIPAA for participation in COL MIG-305 as outlined in the Schedule of Assessments (Table 1). Regardless of the timing of</p>		

signing of informed consent for COL MIG-305, medical history, migraine history and concomitant medication use will be reviewed and any changes or updates since enrolling in COL MIG-301 or COL MIG-302 will be noted. All subjects will complete the MIDAS questionnaire. If **Screening/Visit 1** is not the same day as **EoS/V2** of COL MIG-301 or COL MIG-302 but within 2 weeks, a complete physical examination, vital signs and urine pregnancy test will also be done. Subjects that are consented more than two weeks after **EoS/Visit 2** of COL MIG-301 or COL MIG-302 will undergo the following assessments: a complete physical examination, vital signs, clinical laboratory tests (including urine pregnancy test on women of child-bearing potential (WOCBP)) and 12-lead ECG. A Columbia Suicide Severity Rating Scale (C-SSRS) will be completed. All subjects will be randomized and dispensed study drug and instructed to use lasmiditan as the first treatment for each migraine attack. Subjects will be randomly assigned in a 1:1 ratio, to receive lasmiditan 100 mg (L100 mg) or lasmiditan 200 mg (L200 mg). Subjects randomized to lasmiditan 100 mg will be allowed to take a second dose of study drug if needed for recurrence of migraine.

Treatment Period: Subjects will be asked to use lasmiditan as the first treatment for each new migraine attack within 4 hours of onset providing that the headache severity is at least moderate at that time and not improving. Subjects should not exceed a total dose of 200 mg of lasmiditan in a 24-hour period. Subjects will record their response to the first dose over the next 48 hours using an electronic diary. If the migraine responds 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 only for subjects randomized to lasmiditan 100 mg. Subjects will record their response to a second dose, taken for 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 of study drug is used (for subjects randomized to lasmiditan 100 mg). Subjects using an alternate medication other than a second dose of study drug for the treatment of migraine rescue or recurrence will report the use of medication and continue to record their responses in the electronic diary up to the 48 hour timepoint.

Subjects will be asked to return to the clinic at months 1, 3, 6, 9 and 12 (Visits 2, 3, 4, 5 and 6). At each visit a brief physical examination based on adverse events (AEs), vital signs and a urine pregnancy test on all WOCBP will be obtained. Blood and urine samples for clinical laboratory parameters (hematology, serum chemistry and urinalysis) will be obtained at **Month 1/Visit 2, Month 6/Visit 4 and Month 12/Visit 6 (EoS/ET)**. A 12-lead ECG will be obtained at **Month 6/Visit 4 and Month 12/Visit 6 (EoS/ET)**. C-SSRS will be completed at each visit. The MIDAS questionnaire will be completed at **Month 3/Visit 3, Month 6/Visit 4, Month 9/Visit 5 and Month 12/Visit 6 (EoS/ET)**. At each visit, resource utilization, AEs, use of concomitant medication, use of study drug and patient diary compliance will be assessed; subjects who are continuing will be dispensed study drug. Subjects who decide to withdraw at a scheduled visit should confirm the date of the visit is 7 days (\pm 2 days) from their last migraine treated with study drug. Subjects who decide to discontinue between scheduled visits are asked to contact the clinic to schedule an **ET /Visit 6** within two weeks (14 days) after discontinuation of dosing. The total time on study is up to 54 weeks (a maximum of 378 days).

Subject Population: Adult patients with a history of migraine who have completed COL MIG-301 or COL MIG-302.

Number of Subjects: Approximately 2580 subjects (combined from COL MIG-301 and COL MIG-302) will be enrolled, with the goal of having at least 300 patients dose an average of 2 migraines per month for 6 months and 100 patients dose an average of 2 migraines per month for 12 months.

Number of Centers: Up to 240 centers in US and ex-US (all COL MIG-301 and COL MIG-302 centers will be included)

Test Product and Doses:
lasmiditan 100 mg and lasmiditan 200 mg

Route of Administration: Oral

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. Completed COL MIG-301 or COL MIG-302 within the last 12 weeks. Subjects that completed COL MIG-301 prior to COL MIG-305 being available will be allowed to enroll as long as enrollment occurs within 4 weeks of COL MIG-305 activation at their site. Subjects discontinued due to administrative hold will be allowed to re-enroll in the study.
3. 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).
4. Able and willing to complete an electronic diary to record details of all migraine attacks 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. Subject is at imminent risk of suicide (positive response to question 4 or 5 on the C-SSRS).
6. Initiation of or a change in concomitant medication to reduce the frequency of migraine episodes since completing COL MIG-301 or COL MIG-302.
6. Participation in any clinical trial of an experimental drug or device since completing **EoS/Visit 2** of COL MIG-301 or COL MIG-302.
7. Subject did not dose a migraine during the allotted time while enrolled in COL MIG-301 or COL MIG-302 or was evaluated to be noncompliant with the e-diary requirements (particularly recording their migraine and post-dose assessments).

Criteria for Evaluation:

Safety:

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

Efficacy/Pharmacodynamics (for each attack unless otherwise specified):

- Headache pain (4 point scale: none (0), mild (1), moderate (2), severe (3))
- Most bothersome symptom (MBS) (selected from a list of the associated symptoms of migraine (nausea, phonophobia or photophobia) 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 (5 point scale: none (0), mild (1), moderate (2), severe (3) or very severe (4))
- Requirement for rescue medication between 2, 24, and 48 hours (yes or no)
- Requirement for recurrence medication between 2, 24, and 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
- Total number of migraine attacks and attacks treated with study medication over each 3 month

period

Resource utilization:

- Any CV events and/or related resource utilization such as visits to cardiologists, procedures, hospitalizations, new treatments or treatment adjustments for CV disease as collected in study COL MIG-301 or COL MIG-302 compared to on study **Visit 1** through **Visit 6/EoS/ET**.
- Any visits to an emergency room or physician's office for treatment of migraine as collected in study COL MIG-301 or COL MIG-302 compared to on study **Visit 1** through **Visit 6/EoS/ET** excluding study specific visits.
- Concomitant medications for the treatment of migraine and/or pain as collected in study COL MIG-301 or COL MIG-302 compared to concomitant medications for migraine and/or pain **Visit 1** through **Visit 6/EoS/ET**.
- Missed days of work and/or school or daily activities based on responses to MIDAS questionnaire.

Statistical Analysis:

Safety:

Adverse events will be summarized in terms of the proportion of patients and the proportion of attacks associated with any adverse event and with specific adverse events. Physical examinations, vital signs, clinical laboratory parameters (hematology, serum chemistry and urinalysis) and ECG parameters will be summarized in terms of change from baseline status at 1, 3, 6, 9 and 12 months or early termination.

Efficacy:

This is an open-label study with no control group. Efficacy data will be summarized using descriptive statistics. The proportion of attacks treated with study medication which respond at 2 hours will be calculated for each 3 month period.

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 patient reported information recorded in study COL MIG-301 or COL MIG-302 compared to information reported at **Visits 2, 3, 4, 5, and EoS/ET/6**. Concomitant medication use for migraine and/or pain and missed days of work and/or school or daily activities based on responses to MIDAS questionnaire will be summarized by treatment arm.

Sample Size Rationale

The sample size was chosen to provide an appropriate long-term safety database. It is not based on statistical hypothesis.

Schedule of Assessments

Assessment	Visit 1 Screening and Baseline	Visit 2, 3, 4 and 5 (Months 1, 3, 6 and 9)	Visit 6/EoS/ ET¹
Obtain informed consent/HIPAA	X		
Review inclusion / exclusion criteria	X		
Review migraine history, medical history and concomitant medications	X		
MIDAS questionnaire	X	X	X
Review resource utilization (visits to specialists, ERs, etc.)	X	X	X
Complete physical examination	X		
Vital signs (heart rate, blood pressure)	X ²	X	X
Brief physical examination based on AE(s)	X ²	X	X
Weight	X		X
12-lead ECG	X ³	VISIT 4 ONLY	X
Clinical laboratory ⁴	X ³	VISIT 2 and 4	X
Urine pregnancy for women of child-bearing potential	X ^{5,6}	X ⁶	X ⁶
Columbia Suicide Severity Rating Scale	X ³	X	X
Randomization	X		
Dispense study drug, study diary, and provide detailed instructions	X	X	
Collect empty dosing card(s) and unused study drug. Review dosing compliance and diary		X	X
Migraine attack (electronic diary) documentation by subject		X	
Documentation of rescue/recurrence medication		X	X
Documentation of adverse events and concomitant		X	X

1. **ET** is for subjects that discontinue the study between scheduled visits. The patient should return to the clinic within 14 days of the decision to withdraw from the study. **EoS** is the designation for any scheduled visit that the subject discontinues at or Visit 6 (month 12).
2. Brief physical examination based on AE (s) and vital signs will be the values obtained from **EoS/Visit 2** of COL MIG-301 or COL MIG-302 only if subject signs consent and enrolls in COL MIG-305 on the same day.
3. Laboratory tests, ECG and C-SSRS will be the values obtained from **EoS/Visit 2** of COL MIG-301 or COL MIG-302, as long as the subject signs consent and enrolls in COL MIG-305 on the same day or within two weeks (14 days) of **EoS/Visit 2**.
4. Clinical laboratory tests include hematology, biochemistry, lipid profile and urinalysis. In the event of clinically significant laboratory findings, including but not limited to hepatic laboratory abnormalities, repeat or additional laboratory testing may be required outside of a scheduled clinic visit.
5. A urine pregnancy test for women of childbearing potential is required unless Visit 1 is same day as EoS/Visit 2 of COL MIG-301 or COL MIG-302.

6. If urine pregnancy test is positive a confirmatory serum β HCG test must be performed. The confirmatory test may be run in the local clinical laboratory. The subject should be told not to dose with study drug until the confirmatory test results are obtained. If serum test is positive the subject is to be discontinued from the study.

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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
ALP	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
CPK	Creatine phosphokinase
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
ET	Early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
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
Ig	Immunoglobulin
IHS	International Headache Society
INR	International Normalised Ratio
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
RBC	Red blood cell
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
TBL	Total bilirubin
TEAE	Treatment emergent adverse events
ULN	Upper limit of normal
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 evaluate the safety and tolerability of long-term intermittent use of lasmiditan 200 mg and lasmiditan 100 mg given as a first dose for the treatment of a migraine attack. A second dose of study drug is allowed to investigate the safety of lasmiditan 200 mg and lasmiditan 100 mg when taken for rescue or when taken for recurrence of migraine. In addition to safety assessments, the efficacy of long term intermittent use of lasmiditan will be evaluated. 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 μ M) 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 μ M). 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 (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, including in Phase 3 studies COL MIG-301 and COL MIG-302.

All doses of lasmiditan were associated with driving impairment in a study of healthy volunteers on a computer-based driving simulator. Patients should restrict their driving, operation of heavy machinery, or other similar activities after taking study drug, as described in the informed consent form (ICF).

Rescue medication (other than study drug) will be permitted after completion of the 2 hour assessments if the migraine does not respond (subject is not headache pain free).

For subjects randomized to lasmiditan 100 mg, if the migraine responds 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.

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 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) who complete Phase 3 studies COL MIG-301 or COL MIG-302.

4.5 Dose Rationale

The dose levels of lasmiditan to be used in this study (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, including in Phase 3 studies COL MIG-301 and COL MIG-302. This study will further evaluate the safety and efficacy of the long-term intermittent use of lasmiditan 100 mg and 200 mg.

The allowance of a second dose of either lasmiditan 100 mg or 200 mg for treatment of rescue or recurrence of migraine is to further evaluate the safety and efficacy of a second dose of lasmiditan and 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 safety and tolerability of long-term intermittent use of lasmiditan 100 mg and of lasmiditan 200 mg, as the first and as a second dose, in the acute treatment of migraine.

5.2 Secondary objectives

To explore the long-term efficacy of lasmiditan 100 mg and lasmiditan 200 mg in terms of headache response over time.

5.3 Additional Objectives

To compare patient reported resource utilization during the study to patient reported information from COL MIG-301 or COL MIG-302 in terms of cardiovascular events and in terms of migraine episodes.

5.4 Overall Study Design and Plan: Description

This is a prospective, randomized, open-label study in subjects with migraine who have completed CoLucid Phase 3 study, COL MIG-301 or COL MIG-302. 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 all migraine attacks with study drug on an outpatient basis for up to 12 months. Each patient's study participation will consist of a screening visit (Visit 1) and a treatment period of up to 12 months during which the subject will treat all migraine attacks with either lasmiditan 200 mg or lasmiditan 100 mg (with a second dose of study drug permitted between 2 and 24 hours (h) for recurrence of migraine only for subjects randomized to lasmiditan 100 mg). During the treatment period subjects will return to the clinic at 1,3,6,9 and 12 months. There will be an early termination (ET) visit within two weeks

(14 days) of treatment discontinuation for all subjects that discontinue between scheduled visits. The End-of-Study (EoS) visit will be at 12 months or at any scheduled visit when the subject's participation in the study is ended. Participation in the study for 12 months will be defined as completing **Month 12/Visit 6**.

At **Screening/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 completing study COL MIG-301 or COL MIG-302. The **EoS/Visit 2** of COL MIG-301 or COL MIG-302 can be the same day as **Screening/Visit 1**. Assessments required for this visit can be the same assessments obtained at the **EoS/Visit 2** of COL MIG-301 or COL MIG-302 as long as that visit occurred on the same day or no more than two weeks prior to signing informed consent and HIPAA for participation in COL MIG-305 as outlined in the Schedule of Assessments ([Table 1](#)). Regardless of the timing of signing of informed consent for COL MIG-305, medical history, migraine history and concomitant medication use will be reviewed and any changes or updates since enrolling in COL MIG-301 or COL MIG-302 will be noted. All subjects will complete the MIDAS questionnaire. If **Screening/Visit 1** is not the same day as **EoS/V2** of COL MIG-301 or COL MIG-302 but within 2 weeks, a complete physical examination, vital signs and urine pregnancy test will also be done. Subjects that are consented more than two weeks after **EoS/Visit 2** of COL MIG-301 or COL MIG-302 will undergo the following assessments: a complete physical examination, vital signs, clinical laboratory tests (including urine pregnancy test on women of child-bearing potential (WOCBP)) and 12-lead ECG. A Columbia Suicide Severity Rating Scale (C-SSRS) will be completed. All subjects will be randomized and dispensed study drug and instructed to use lasmiditan as the first treatment for each new migraine attack. Subjects will be randomly assigned in a 1:1 ratio, to receive lasmiditan 100 mg (L100 mg) or lasmiditan 200 mg (L200 mg). Subjects randomized to lasmiditan 100 mg will be allowed to take a second dose of study drug if needed for recurrence of migraine.

Treatment Period: Subjects will be asked to use lasmiditan as the first treatment for each new 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. For subjects randomized to lasmiditan 100 mg, 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 should not exceed a total dose of 200 mg of lasmiditan in a 24-hour period. Subjects will record their response to a second dose, taken for 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 of lasmiditan 100 mg is used. Subjects using an alternate medication other than a second dose of lasmiditan 100 mg for the treatment of migraine rescue or recurrence will report the use of medication and continue to record their responses in the electronic diary up to the 48 hour timepoint.

Subjects will be asked to return to the clinic at months 1, 3, 6, 9 and 12 (Visits 2, 3, 4, 5 and 6). At each visit a brief physical examination based on adverse events (AEs), vital signs and a urine pregnancy test on all WOCBP will be obtained. Blood and urine samples for clinical laboratory parameters (hematology, serum chemistry and urinalysis) will be obtained at **Month 1/Visit 2**, **Month 6/Visit 4** and **Month 12/Visit 6 (EoS/ET)**. A 12-lead ECG will be obtained at **Month 6/Visit 4** and **Month 12/Visit 6 (EoS/ET)**. C-SSRS will be completed at each visit. The MIDAS questionnaire will be completed at **Month 3/Visit 3**, **Month 6/Visit 4**, **Month 9/Visit 5** and **Month 12/Visit 6 (EoS/ET)**. At each visit, resource utilization, AEs, use of concomitant medication, use of study drug and patient diary compliance will be assessed; subjects who are

continuing will be dispensed study drug. Subjects who decide to withdraw at a scheduled visit should confirm the date of the visit is 7 days (± 2 days) from their last migraine treated with study drug. Subjects who decide to discontinue between scheduled visits are asked to contact the clinic to schedule an **ET /Visit 6** within two weeks (14 days) after discontinuation of dosing. The total time on study is up to 54 weeks (a maximum of 378 days).

5.4.1 Schedule of Assessments

- **Screening/Visit 1:** Screening examinations to determine subject eligibility are performed. This visit can be the same as **EoS/Visit 2** of COL MIG-301 or COL MIG-302 if occurring on the same day or within 2 weeks of completing **EoS/Visit 2** and consenting to participate in this study. Subjects are randomized and provided with a dosing card.
- **Visits 2, 3, 4 and 5 (Months 1, 3, 6 and 9):**
The subject will return to the clinic for each visit for safety assessments. The timing of the visits should be at approximately the same time of day (± 1 hour). Study drug and e-diary compliance will be reviewed. Empty dosing card(s) will be collected along with any unused study drug. Study drug will be dispensed.

Monthly visit increments are defined as follows:

- **Visit 2/Month 1** – is defined as 30 days $\pm 2d$ from Visit 1
 - **Visit 3/Month 3** – is defined as 60 days $\pm 4d$ from Visit 2
 - **Visit 4/Month 6** – is defined as 90 days $\pm 4d$ from Visit 3
 - **Visit 5/Month 9** – is defined as 90 days $\pm 4d$ from Visit 4
- **Visit 6 (Month 12)/EoS/ET: End of study visit or Early termination**
The subject will return to the clinic for **EoS** visit at month 12 for final safety assessments. Empty dosing card(s) and unused study drug will be collected. This visit should be scheduled 90 days $\pm 4d$ from Visit 5 and be one week (7 days ± 2 days) after the last migraine treated on study. If a patient decides to discontinue from the study at any of the scheduled visits the **Visit 6/EoS** assessments will be conducted.
 - **Visit 6/Month 12 (EoS)** – is defined as 90 days $\pm 4d$ from Visit 5 and 7 days ($\pm 2d$) after last migraine treated with study drug whichever is later.
 - If a subject decides to withdraw from the study at any scheduled visit, the visit should occur at the increments defined and be 7 days (± 2 days) from the last migraine treated on study.
 - For study consideration, 12 months is defined as completing **Month 12/Visit 6**.

Early termination is defined as the subject's return to the clinic between scheduled study visits to discontinue from the study for any reason. The visit should be scheduled within two weeks of the decision to discontinue. Safety assessment will be performed. Empty dosing card(s) and unused study drug will be collected.

The overall Schedule of Assessments for the study is provided in [Table 1](#).

5.5 Assessments by Study Visit

5.5.1 Screening Visit /Visit 1

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

- Explain the purpose of the study to prospective subjects and obtain written informed consent and HIPAA.
- Review inclusion/exclusion criteria (See Sections 6.1 and 6.2.).
- Review and update medical history including migraine history and prior treatment and collect demographic information (See Section 9.1.1).
- Review and update concomitant medications that the subject is taking.
- Review and update resource utilization (See Section 9.1.1.3).
- Have subject complete MIDAS questionnaire (See Section 9.1.1.2 and Appendix 2).
- Collect weight (Height will be obtained from COL MIG-301 or COL MIG-302 to calculate BMI).
- Perform a complete physical examination. (See Section 9.1.2). **IF** not the same day as **EoS/Visit 2** of COL MIG-301 or COL MIG-302.
- Obtain a brief physical examination (if indicated by an AE) from **EoS/Visit 2** of COL MIG-301 or COL MIG-302 if the same day.
- Obtain vital signs (See and 9.1.3). **IF** not the same day as **EoS/Visit 2** of COL MIG-301 or COL MIG-302. (Or from **EoS/Visit 2** of COL MIG-301 or COL MIG-302 if same day).
- Perform a 12-lead ECG (see Section 9.1.4). **ONLY** if more than two weeks from **EoS/Visit 2** of COL MIG-301 or COL MIG-302. (Otherwise ECG from **EoS/Visit 2** of COL MIG-301 or COL MIG-302 is used).
- Collect blood and urine samples for clinical laboratory tests (hematology, chemistry, and urinalysis; see Section 9.1.5). **ONLY** if more than two weeks from **EoS/Visit 2** of COL MIG-301 or COL MIG-302 (Otherwise values from **EoS/Visit 2** of COL MIG-301 or COL MIG-302 is used).
- Collect urine sample for urine pregnancy test for WOCPB (or from **EoS/Visit 2** of COL MIG-301 or COL MIG-302 if same day). If urine pregnancy test is positive a confirmatory serum β HCG test must be performed. The confirmatory test may be run in the local clinical laboratory. The subject should be told not to dose with study drug until the confirmatory test results are obtained. If serum test is positive the subject is to be discontinued from the study.
- Obtain C-SSRS (See Section 9.1.6 and Appendix 3). **ONLY** if more than two weeks from **EoS/Visit 2** of COL MIG-301 or COL MIG-302.
- 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.
- Dispense study drug as assigned.
- Provide access to electronic diary.
- Confirm timing of **Visit 2**.
- Discharge subject.

5.5.2 Treatment

Subjects will be allowed to treat all acute migraine attacks with study drug. Study migraines should be of moderate or severe intensity that is not improving. The attack is to be treated within

4 hours of onset. Subjects should not exceed a total dose of 200 mg of lasmiditan in a 24-hour period.

- **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 if a second dose of study drug is taken for recurrence of migraine (for subjects randomized to lasmiditan 100 mg) (See Section 9.1.8).
- Subjects will report any unusual symptoms not felt before with a migraine during each migraine treated with study drug as well as any concomitant medication use by way of the e-diary. Sites will receive an alert and should contact the subject within 48 hours to discuss the unusual symptoms and determine if the symptom(s) are an AE along with the duration and effect of the AE on the subject.

5.5.3 Month 1/Visit 2

This visit is to occur at approximately the same time of day (\pm 1 hour), 30 days (\pm 2d) from **Screening/Visit 1**. The following assessments will be performed:

- Collect empty dosing card and/or any unused study drug and review dosing compliance.
- Review patient diary compliance.
- Collect resource utilization (See Section 9.1.1.3).
- Have subject complete MIDAS questionnaire (See Section 9.1.1.2 and Appendix 2).
- Obtain C-SSRS (See Section 9.1.6 and Appendix 3).
- Assess for AEs and use of concomitant medications.
- 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).
- 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 β HCG test. (The confirmatory test may be run in the local clinical laboratory).
- Remind subject of study requirements.
- Return any unused drug and dispense new patient card or carton of study drug.
- Schedule next visit.
- Discharge subject.

5.5.4 Month 3, 6 and 9/Visit 3, 4 and 5

- **Visit 3/Month 3** – is defined as 60 days \pm 4d from Visit 2
- **Visit 4/Month 6** – is defined as 90 days \pm 4d from Visit 3
- **Visit 5/Month 9** – is defined as 90 days \pm 4d from Visit 4

The visits should occur at approximately the same time of day (\pm 1 hour). The following assessments will be performed:

- Collect empty dosing card and/or any unused study drug and review dosing compliance.
- Review patient diary compliance.
- Collect resource utilization (See Section 9.1.1.3).
- Have subject complete MIDAS questionnaire (See Section 9.1.1.2 and Appendix 2).
- Obtain C-SSRS (See Section 9.1.6 and Appendix 3).
- Assess for AEs and use of concomitant medications.
- 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) **MONTH 6/VISIT 4 ONLY.**
- Collect blood and urine samples for clinical laboratory tests (hematology, chemistry, and urinalysis) (See Section 9.1.5). **MONTH 6/VISIT 4 ONLY.**
- Collect urine sample for urine pregnancy test for WOCPB (or from **EoS/Visit 2** of COL MIG-301 or COL MIG-302 if same day). If urine pregnancy test is positive a confirmatory serum β HCG test must be performed. The confirmatory test may be run in the local clinical laboratory. The subject should be told not to dose with study drug until the confirmatory test results are obtained. If serum test is positive the subject is to be discontinued from the study. Remind subject of study requirements.
- Return any unused drug and dispense new patient carton of study drug if required.
- Schedule next visit.
- Discharge subject.

5.5.5 EoS/ET/Visit 6 (Month 12)

The following assessments will be performed. This EoS visit is for all subjects completing study through month 12 OR any subject concluding their participation in the study at any scheduled visit. The visit should occur at approximately the same time of day (\pm 1 hour) and 90 days (\pm 4 d) from the last visit and be at least 7 days after the last migraine is dosed. Patient completion through month 12 will be defined as completing **Month 12/Visit 6**. The ET visit is for all subjects discontinuing from the study at any time between scheduled study visits for any reason. The visit should occur within 14 days of the decision to discontinue.

- Collect empty dosing card(s) and all unused study drug and review dosing compliance.
- Review patient diary compliance.
- Collect resource utilization (See Section 9.1.1.3).
- Have patient complete MIDAS questionnaire (See Section 9.1.1.2 and Appendix 2).
- Obtain C-SSRS (See Section 9.1.6 and Appendix 3).
- Assess for AEs and use of concomitant medications.
- 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 β HCG 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. Completed COL MIG-301 or COL MIG-302 within the last 12 weeks. Subjects that completed COL MIG-301 prior to COL MIG-305 being available will be allowed to enroll as long as enrollment occurs within 4 weeks of COL MIG-305 activation at their site. Subjects discontinued due to administrative hold will be allowed to re-enroll in the study. (process outlined in [Appendix 4](#)).
3. 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).
4. Able and willing to complete an electronic diary to record details of all migraine attacks 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. Subject is at imminent risk of suicide (positive response to question 4 or 5 on the C-SSRS).
5. Initiation of or a change in concomitant medication to reduce the frequency of migraine episodes since completing COL MIG-301 or COL MIG-302.
6. Participation in any clinical trial of an experimental drug or device since completing **EoS/Visit 2** of COL MIG-301 or COL MIG-302.
7. Subject did not dose a migraine during the allotted time while enrolled in COL MIG-301 or COL MIG-302 or was evaluated to be noncompliant with the e-diary requirements (particularly recording their migraine and post-dose assessments).

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 **Visit 6/EoS/ET** 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 discontinuing from the trial before a scheduled visit regardless of cause, must be seen for **ET/Visit 6** for safety assessments and to return all unused study drug and the e-diary. Subjects that withdraw from the study prior to dosing a migraine attack should return to the clinic for **ET/Visit 6** to return all unused study drug and the e-diary. Subjects that desire to withdraw from the study at one of the scheduled visits (**Visit 2, 3, 4 or 5**) should complete the **EoS/Visit 6** study assessments and 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

Each subject will use the same seven-digit subject number from the previous Phase 3 study (COL MIG-301 or COL MIG-302). If a subject fails to be randomized, the reason for not being randomized should be documented in the source documents.

7.2 Description of Study Drug

For study purposes lasmiditan 100 mg and lasmiditan 200 mg are both referred to as study drug.

7.3 Concomitant Medications

Concomitant medications (including devices) 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 (other than study drug) will be permitted after completion of the 2 hour assessments if the migraine does not respond (subject is not headache pain free). 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 any 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 study drug may be taken up to 24 hours after the first dose (only for subjects randomized to lasmiditan 100 mg). Triptans, ergots, opioids and barbiturates **MUST NOT** be used for treatment of migraine recurrence within 24 hours of study drug administration. The use of any medication for the treatment of migraine recurrence will be recorded.

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/ET/Visit 6**:

- 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 on an outpatient basis throughout the study. Prior to discharge from **Screening/Visit 1** subjects will be given study drug to treat all migraine attacks for the first month. Information on the time and date of each dose (initial treatment along with treatment of recurrence with a second dose of study drug for subjects randomized to lasmiditan 100 mg) will be recorded by the subject in the electronic diary. Subjects will return empty dosing card(s) and any (all) unused study drug to the clinic at each visit. Unused study drug may be returned to the subject and a new patient card or carton of study drug dispensed. Subject use of study drug will be monitored to control for medication overuse.

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 will be provided in 8-tablet treatment packs.

7.7 Unblinding Procedures

7.7.1 Emergency unblinding of treatment assignment

The study is open label.

7.7.2 Unblinding for Regulatory Authorities

The study is open label.

8. STUDY DRUG MATERIALS AND MANAGEMENT

8.1 Study Drug

Study drug refers to lasmiditan 100 mg and lasmiditan 200 mg.

Lasmiditan drug product is a tablet containing 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.

CCI



Each dose of study drug will consist of one tablet for the treatment of a single migraine attack. For subjects randomized to lasmiditan 100 mg, a second dose may be used for treatment of recurrence of migraine between 2 and 24 hours after the first dose. For subjects randomized to lasmiditan 200 mg, no additional study drug is to be taken within 24 hours of the dose, as the maximum dose of lasmiditan to be taken in a 24-hour period is 200 mg.

8.2 Study Drug Packaging and Labeling

All study drug will be provided as child resistant individual dosing cards containing 8 tablets. In the card, each tablet will be contained within an individual blister pack. At the discretion of the investigator and depending on the visit and usage by the subject, subjects will receive a patient pack of two dosing cards, or a patient pack of three dosing cards.

Study drug labels will include protocol number, Sponsor's name and address, and an Investigational New Drug statement.

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 at each visit with instructions to treat all acute migraine attacks as follows:

- **Screening/Visit 1**, subjects will receive a single blister card containing 8 tablets.
- **Month 1/Visit 2** subjects continuing on study may receive a single blister card containing 8 tablets or a patient carton containing two dosing cards of 8 tablets each.
- At each subsequent visit (**Visits 3, 4 and 5/Months 3, 6 and 9**) subjects may receive a single blister card containing 8 tablets or a patient carton containing two dosing cards of 8 tablets each or a patient carton containing 3 dosing cards of 8 tablets each.

Subjects are to return all dosing cards (used and unused to each visit). Additional single dosing cards of 8 tablets are available in the event more study drug is needed to treat migraines during the time between visits or if a subject loses a dosing card or needs a dosing card replaced. Subject use will be monitored to control for medication overuse.

Subjects will be instructed to take one tablet 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 a second dose (one tablet) of study drug (only for those subjects randomized to lasmiditan 100 mg), if needed, with approximately 4 ounces of water for recurrence of migraine at least 2 hours after the first dose. Subjects should not exceed a total dose of 200 mg of lasmiditan in a 24-hour period.

Subjects will be instructed to treat all migraines with lasmiditan as the first treatment for each new migraine attack within 4 hours of onset.

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 and all empty dosing cards. 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 Safety and Efficacy Parameters

Safety will be monitored with physical examinations, vital signs, ECGs, clinical laboratory testing, and AE/SAE assessments.

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 medication for recurrence of migraine. 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. 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

During **Screening/Visit 1** general medical history recorded for participation in COL MIG-301 or COL MIG-302 will be reviewed. Information previously recorded will be carried over into the database for COL MIG-305. Any changes or updates to a patient's medical history from information recorded for participation in COL MIG-301 or COL MIG-302 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.

Concomitant medications or devices, for migraine or pain, and any other medication for other medical conditions will also be reviewed. Information previously recorded will be carried over into the database for COL MIG-305. Any changes from information recorded for and during participation in COL MIG-301 or COL MIG-302 will be recorded on the CRF. At each visit, the use of any concomitant medications will be reviewed and updated for any changes in frequency or dosing.

In addition, any additional information since participation in COL MIG-301 or COL MIG-302 regarding the subject's migraine history including prior treatment will be recorded.

9.1.1.1 Demographics

During **Screening/Visit 1**, subject initials, age, and date of birth will be recorded on the CRF. Gender, race and ethnicity will be carried over into the database from the information recorded for COL MIG-301 or COL MIG-302.

9.1.1.2 MIDAS

MIDAS is a 5 item questionnaire (Appendix 2) 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, Month 3/Visit 3, Month 6/Visit 4, Month 9/Visit 5** and **Month 12/Visit 6/EoS/ET**.

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** subject information reported during participation in Phase 3 study COL MIG-301 or COL MIG-302 about any CV events and/or related resource utilization such as visits to cardiologists, procedures, hospitalizations, new treatments or treatment adjustments for CV disease will be reviewed and updated as appropriate. In addition the previously reported information regarding any ER visits or visit to physician's office for migraine treatment will be reviewed and updated. The information recorded for COL MIG-301 or COL MIG-302 will be carried over into the database for the COL MIG-305. At each visit, **Month 1/Visit 2, Month 3/Visit 3, Month 6/Visit 4, Month 9/Visit 5** and **Month 12/Visit 6/EoS/ET** the subject will again be asked about resource utilization during their time on study.

9.1.2 Physical Examination

If **EoS/Visit 2** of COL MIG-301 or COL MIG-302 is the same day as **Screening/Visit 1**, only a brief physical examination if indicated by an AE will be performed (as required by the earlier studies). If the subject is not enrolling in COL MIG-305 the same day they are completing COL MIG-301 or COL MIG-302, 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. At each visit, **Month 1/Visit 2, Month 3/Visit 3, Month 6/Visit 4, Month 9/Visit 5** and **Month 12/Visit 6/EoS/ET**, a brief symptom related physical examination will be performed if indicated by an AE.

Weight will be measured at **Screening/Visit 1**. BMI will be calculated by the database using the subject's height recorded for COL MIG-301 or COL MIG-302. Weight will also be measured at **Month 12/Visit 6/EoS/ET**.

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).

Vital signs will be assessed at **Screening/Visit 1** and at **Month 1/Visit 2, Month 3/Visit 3, Month 6/Visit 4, Month 9/Visit 5** and **Month 12/Visit 6/EoS/ET**. If **Screening/Visit 1** is the same day as **EoS/Visit 2** of COL MIG-301 or COL MIG-302 the vital signs obtained will be used for both studies.

9.1.4 ECG

A standard, digital 12-lead ECG will be obtained after at least 5 minutes rest at **Screening/Visit 1** (**ONLY** if more than two weeks since **EoS/Visit 2** of COL MIG-301 or COL MIG-302) and at visit **Month 6/Visit 4**, and **Month 12/Visit 6/EoS/ET**. If **Screening/Visit 1** is the same day or within 2 weeks of **EoS/Visit 2** of COL MIG-301 or COL MIG-302, the data obtained will be used for both studies.

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** (**ONLY** if more than two weeks since **EoS/Visit 2** of COL MIG-301 or COL MIG-302) and at visit **Month 1/Visit 2, Month 6/Visit 4**, and **Month 12/Visit 6/EoS/ET**. If **Screening/Visit 1** is the same day the data will be used for both studies. If **Screening/Visit 1** is within 2 weeks of **EoS/Visit 2** of COL MIG-301 or COL MIG-302 the data obtained will be used for both studies except a urine pregnancy test for WOCBP will be performed. 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 (ALP), 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 urine pregnancy test for β -HCG will be performed at the **Screening/Visit 1** (test will count for **EoS/Visit 2** for COL MIG-301 or COL MIG-302 if visit is same day). A urine pregnancy test will be performed at each visit. If a urine pregnancy test is positive during the study the subject will be discontinued from the study after confirmation with a positive serum β HCG. A subject with a positive urine β HCG must not be dosed unless a negative serum β HCG is obtained. The confirmatory serum test may be performed at the local clinical laboratory.

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.

9.1.5.3 Hepatic Safety Monitoring

If a study subject experiences elevated ALT $\geq 3X$ ULN, AST $\geq 3X$ ULN, ALP $\geq 2X$ ULN, or elevated TBL $\geq 2X$ ULN, liver testing (Appendix 5) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected if 1 or more of the following conditions occur:

- Elevation of serum ALT to $\geq 5X$ ULN on 2 or more consecutive blood tests
- Elevation of serum AST to $\geq 5X$ ULN on 2 or more consecutive blood tests
- Elevated serum TBL to $\geq 2X$ ULN (except for cases of known Gilbert's syndrome)
- Elevation of serum ALP to $\geq 2X$ ULN on 2 or more consecutive blood tests
- Subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- Hepatic event considered to be a SAE

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.

- If **Screening/Visit 1** is the same day or within 2 weeks of **EoS/Visit 2** of COL MIG-301 or COL MIG-302 the data obtained will be used for both studies.

- The “since last visit” version will be administered at **Screening/Visit 1** (**ONLY** if more than two weeks since **EoS/Visit 2** of COL MIG-301 or COL MIG-302) and at visit **Month 1/Visit 2, Month 3/Visit 3, Month 6/Visit 4, Month 9/Visit 5** and **Month 12/Visit 6/EoS/ET**. (Appendix 3).

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 should treat all migraines with study drug.

Subjects will be asked to treat each 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 should not exceed a total dose of 200 mg of lasmiditan in a 24-hour period. Subjects will be instructed not to use rescue medication (other than study drug) until at least 2 hours after taking study drug. If the subject does not become headache pain free within 2 hours, rescue medication (other than study drug) will be permitted after completion of the 2 hour assessments. 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. For subjects randomized to lasmiditan 100 mg, if the migraine responds within 2 hours (headache becomes pain free) but then recurs after 2 hours, a second dose of 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 each 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. All migraines treated with study drug will be recorded in the diary.

For each migraine, subjects will be asked to assess their headache severity at specified time points: 0 (pre dose), 0.5, 1, 2, 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 an alternative treatment as rescue medication will be assessed between 2 and 24 hours and at 48 hours. Recurrence of pain and second dosing of study drug (only for those randomized to lasmiditan 100 mg) will be assessed between 2 and 24 hours and at 48 hours.

At the same time points, specified above, 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. The diary is to be completed for the duration of a subject's participation in the study.

9.1.8.1 Recording Use of Rescue Medication and Migraine Symptoms

Any use of a rescue medication (other than study drug) 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 time points specified above. 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. For subjects randomized to lasmiditan 100 mg, 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 time points specified above. 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 also be reviewed 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/ ET/Visit 6**. AEs reported prior to dosing will be captured and considered non-treatment emergent AEs. AEs reported 48 hours after dosing a migraine and between migraines 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. Based on the half-life of study drug (3.5-4 hours) and the varied time between dosing a migraine attack, the temporal relationship of an adverse event to time of dosing will be as assessed prior to considering the adverse event to be a TEAE. Any new AE recorded 48 hours after a dose of study drug will not be considered a TEAE.

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/ET/Visit 6**. 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/ET/Visit 6**.

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 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. All safety analyses will be based on the Safety Population. The efficacy analyses and baseline characteristics will be based on the Intent-to-Treat (ITT) and mITT population. The Per Protocol Population will be used to support the ITT analyses.

The primary objective of this study is to evaluate the safety and tolerability of long-term intermittent use of lasmiditan 100 mg and of lasmiditan 200 mg, as the first and as a second dose, in the acute treatment of migraine.

The secondary objective of the study is to explore the long-term efficacy of lasmiditan 100 mg and lasmiditan 200 mg in terms of headache response over time.

Summary analysis of the safety and efficacy of the use of a second dose of lasmiditan 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 summarized 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 safe in the long-term intermittent treatment of acute migraine in adult patients with and without aura. The sample size was chosen to provide an appropriate long-term safety database. It is not based on any statistical hypothesis. In accordance with ICH guidelines, the goal is at least 300 patients will treat an average of 2 migraines per month for 6 months and at least 100 patients will treat an average of 2 migraines per month for 12 months.

10.2 Randomization

This is a multicenter, randomized, open-label, parallel group study.

Subjects will be centrally randomized to one of two treatments to receive lasmiditan 200 mg (L200 mg) or lasmiditan 100 mg (L100 mg) in a 1:1 ratio. Subjects will be stratified (yes or no) for use of concomitant medications that reduce the frequency of migraine episodes. Subject will be randomized and study drug will be dispensed at each study visit.

10.3 Analysis Populations

10.3.1 Disposition

The summary of disposition, the percentage of patients who received a dose of study drug, and subject data listings will be based on the randomized population:

Randomized population	All randomized subjects. Subjects are evaluated by the drug to which they are randomized.
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10.3.2 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.
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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 any migraine attacks 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.

10.3.3 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 arm 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).

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 Exposure

Treatment exposure will be assessed in terms of the actual dose. Summary statistics will be performed on the number of subjects who took a first dose for the treatment of their migraine and the number of subjects who took both a first and second dose. The average dosage used per month in three month intervals and the cumulative doses taken over the course of the study will be summarized within each treatment arm using descriptive statistics (n, mean, SD, median, minimum, and maximum).

10.5 Safety Analyses

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

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. Adverse events will be summarized in terms of the proportion of patients and the proportion of attacks associated with any adverse event and with specific adverse events.

10.5.1 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 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 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 the next migraine is dosed 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.

10.5.2 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. Observed and change from baseline (Screening/Visit 1) values for vital signs, ECGs, and clinical laboratory test results will be summarized as appropriate by treatment arm and dose. 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 6**, as appropriate by treatment arm and dose.

10.5.3 C-SSRS

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

10.6 Efficacy Analyses

This is an open-label study with no control group. Efficacy data will be summarized using descriptive statistics. The proportion of attacks treated with lasmiditan 100 mg and with lasmiditan 200 mg which respond at 2 hours will be calculated for each 3 month period.

10.6.1 Headache Response

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 be non-responders 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:

$0 \text{ (min)} < \text{date/ time rescue medication (diary)} - \text{date/ time of dosing (diary)} < 120 \text{ (min)}$.

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 be non-responders for the mITT and ITT analysis.

10.6.2 Sensitivity Analyses of the Primary and Key Secondary Endpoints

The analyses of pain free at 2 hours and of MBS free at 2 hours 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.

10.6.3 Other Efficacy Analyses

10.6.3.1 Headache relief

The proportion of attacks treated with study medication with headache relief (moderate or severe headache at baseline, which became mild or none, or mild headache which became none) at 2 hours post dose will be evaluated. The time course to headache relief will be explored up to 48 hours.

10.6.3.2 Headache recurrence

The proportion of attacks treated with study medication 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.

10.6.3.3 Headache rescue

The requirement for rescue medication at 2 hours and between 2 and 24 hours and 24- 48 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 arm.

10.6.3.4 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. Summary statistics will be presented by treatment arm and timepoint as appropriate.

10.6.3.5 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) by treatment arm and timepoint as appropriate.

10.7 Analysis of Second dose

10.7.1 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 arm 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.

10.7.2 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 arm 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.

10.8 Resource Utilization

By-subject listings of any resource utilization will be listed and will be summarized using descriptive statistics, separated by treatment arm and visit. Days missed from work and/or school or daily activities will be tabulated from information recorded on the MIDAS scale separated by treatment arm and visit.

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 Lilly (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 Lilly.

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 Lilly 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/Lilly 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. Lilly 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 Lilly or its designated representative(s) before submission to the IRB/IEC/REB and a copy of the approved version must be provided to the Lilly 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 Lilly, 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.

Lilly 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

Lilly 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 Lilly 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 Lilly. 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 Lilly, 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 Lilly or its designated representative, and must be maintained in confidence by the Investigator.

13.7 Publication policy

The publication policy for Study H8H-CD-LAHL/COL MIG-305 is described in the Clinical Trial Agreement.

14. RETENTION OF RECORDS

Retention of records is outlined in the Clinical Trial Agreement for this study.

15. REFERENCES

1. Steiner, TJ, Stovner, LJ, Birbeck GL, Migraine: The seventh disabling. *Cephalalgia* 2013; 0:1-2.
2. Buse DC, Serrano D, Pearlman SH, Ng-Mak DS, Reed ML, Lipton RB, Examination of Unmet Treatment Needs Among Persons with Episodic Migraine: Results of the American Migraine Prevalence and Prevention Study (AMPP). Abstract 2011.
3. Dodick DW, Lipton RB, Martin V, et al. Triptan Cardiovascular Safety Expert Panel. Consensus statement: cardiovascular safety profile of triptans (5-HT agonists) in the acute treatment of migraine. *Headache* 2004; **44**:414—25.
4. Humphrey PPA, Feniuk W, Perren MJ, Beresford IJM, Skingle M, Whalley ET. Serotonin and migraine. *Ann NY Acad Sci* 1990; **600**:587—598
5. Nilsson T, Longmore J, Shaw D, et al. Characterisation of 5-HT receptors in human coronary arteries by molecular and pharmacological techniques. *Eur J Pharmacol* 1999a; **372**:49—56.
6. Maassen VanDenBrink A, Reekers M, Bax WA, Ferrari MD, Saxena PR. Coronary side-effect potential of current and prospective antimigraine drugs. *Circulation* 1998; **98**:25—30.
7. Van den Broek RWM, Maassen VanDenBrink A, de Vries R, et al. Pharmacological analysis of contractile effects of eletriptan and sumatriptan on human isolated blood vessels. *Eur J Pharmacol* 2000; **407**:165—73.
8. Bigal ME, Kurth T, Santanello N, et al. Migraine and cardiovascular disease: A population-based study. *Neurology* 2010; **74**:628—635.
9. Nelson DL, Phebus LA, Johnson KW, Waincott DB, Cohen ML, Calligaro DO, et al., Preclinical pharmacological profile of the selective 5-HT_{1F} receptor agonist lasmiditan. *Cephalalgia* 2010; **30**(10):1159-1169.
10. Shephard S, Edvinsson L, Cumberbatch M, Williamson D, Mason G, Webb J, et al., Possible antimigraine mechanisms of action of the 5HT_{1F} receptor agonist LY334370. *Cephalalgia* 1999; **19**(10):851-858.
11. Goadsby PJ, Classey JD, Evidence for serotonin (5-HT)_{1B}, 5-HT_{1D} and 5-HT_{1F} receptor inhibitory effects on trigeminal neurons with craniovascular input. *Neuroscience* 2003; **122**(2):491-498.
12. Cohen ML, Johnson KW, Schenck KW, Phebus LA, Migraine therapy: relationship between serotonergic contractile receptors in canine and rabbit saphenous veins to human cerebral and coronary arteries. *Cephalalgia* 1997; **17** (6):631-638.
13. E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs: Guidance to Industry, 2005.
14. CoLucid Pharmaceuticals, Inc. COL-144 Investigator Brochure v9.0 February 2017.

15. Lipton RB, Bigal ME, Diamond F, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology* 2007; **68**:343—49.
16. Lipton RB, Diamond S, Reed M, Diamond ML, Stewart WE. Migraine diagnosis and treatment; results from the American Migraine Study II. *Headache* 2001; **41**:638-645.

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
	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

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
	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
	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

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
	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
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

Category	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
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. 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 or 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.)

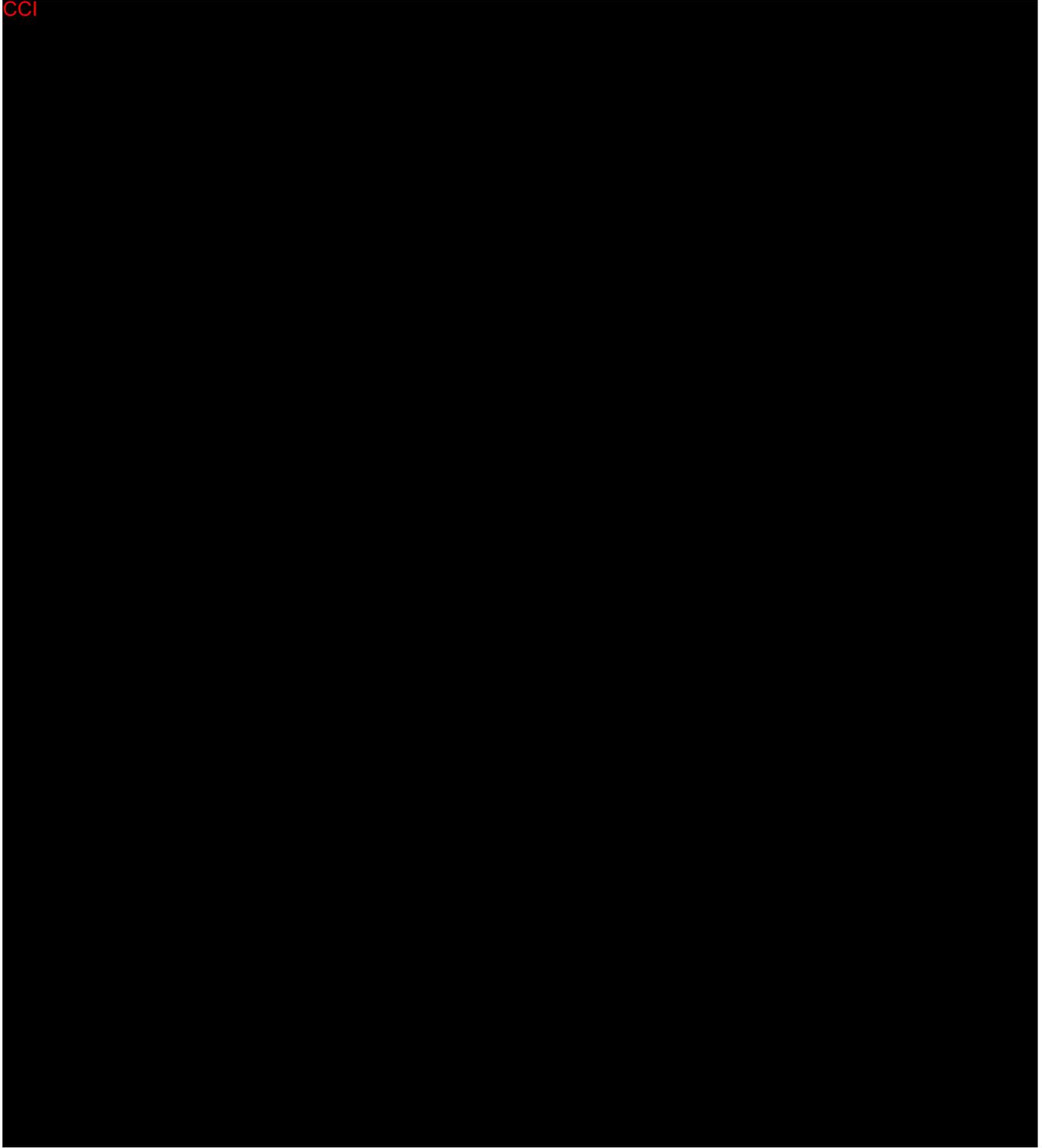
Scoring: After you have filled out this questionnaire, add the total number of days from questions 1 to 5 (ignore A and B).

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+

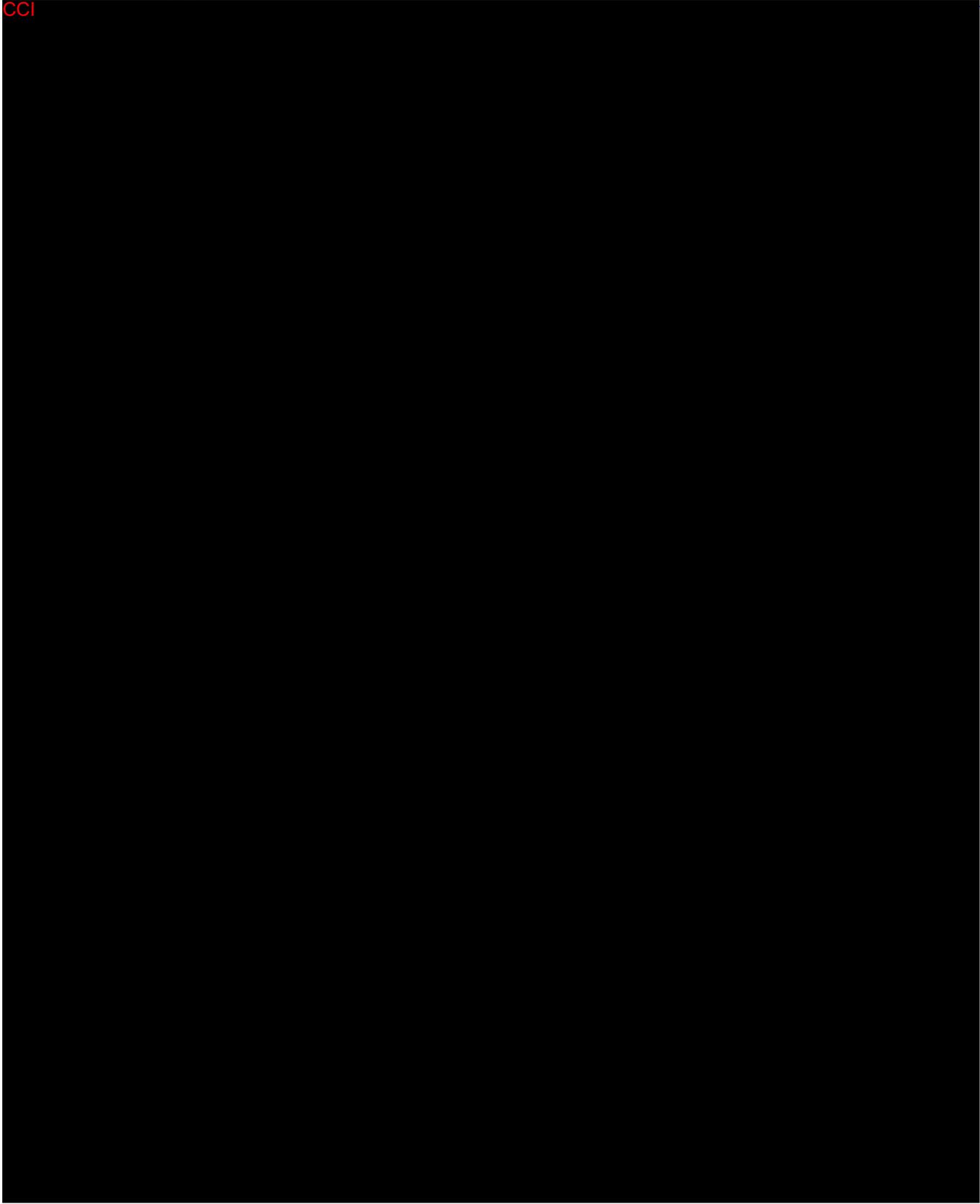
Please give the completed form to your clinician.

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.

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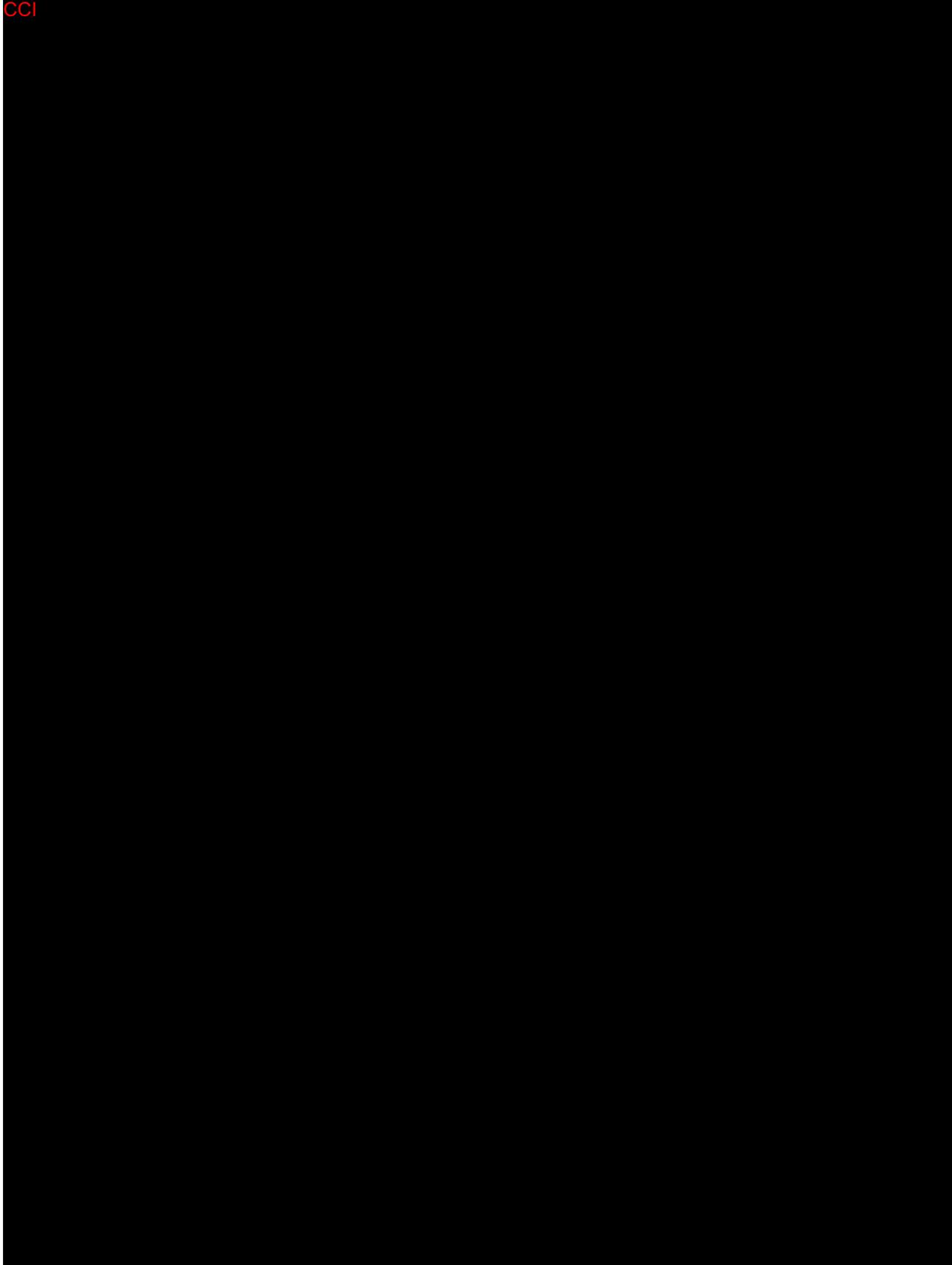
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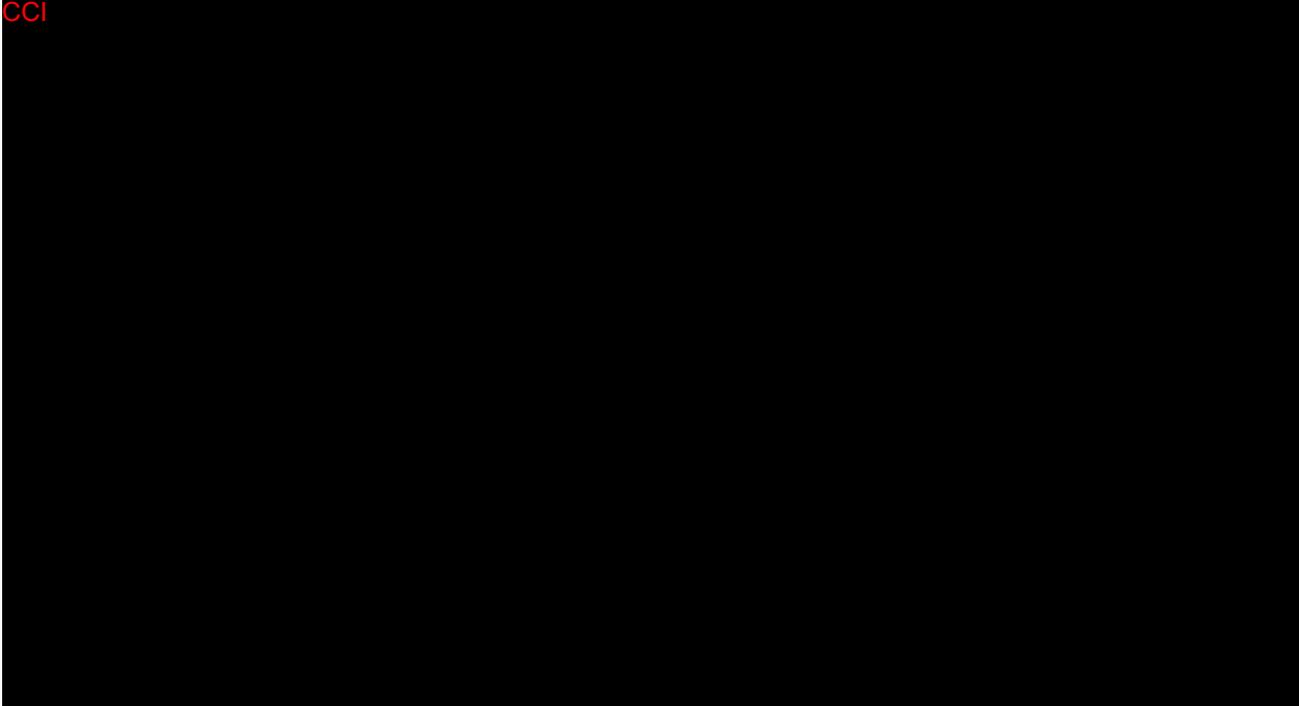
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19. APPENDIX 4. Process to Re-start subjects affected by administrative hold

The following outlines the procedures for discontinuing the subjects enrolled in GLADIATOR from October 7, 2015 to November 10, 2015 and to re-enroll those subjects that wish to continue on study.

- 1) For subjects that have **NOT dosed**:
 - a. Please contact these subjects and request them to return to the clinic and return all IP and their eDiary.
 - b. No other procedures are required since they did not dose (confirmed on returning the dosing card of 8-tablets).
 - d. Discontinue the subject in Cenduit.
 - e. Discontinue the subject in the eDiary (Refer to page 66 in the ERT Site Manual).
 - f. Discontinue subject in EDC.
 - g. **IF** the subject does not wish to be re-enrolled, subject's participation is complete.
 - h. **IF** the subject wishes to be re-enrolled:
 - Consent subject as though subject is new to the study.
 - Complete all **Visit 1** assessments as outlined in the protocol (Section 5.6.1).
 - Review the diary and re-start the subject in the diary.
 - Re-enroll the subject and dispense study drug. Please NOTE: the subject may not be randomized to the same dose as they had been previously.

- 2) For subjects who **DOSED** and already completed a Visit 2 as Visit 2 and not an ET visit:
 - a. Please contact these subjects and request them to return to the clinic and return all IP and their eDiary
 - b. Discontinue subject in Cenduit
 - c. Discontinue subject in the eDiary (Refer to page 66 in the ERT Site Manual)
 - d. Discontinue subject in EDC
 - e. **IF** the subject does **NOT** wish to be re-enrolled
 - AND at **Visit 2**, you did not collect an ECG and record weight (as required at an ET visit (**V6/ET** – Section 5.6.5) perform an ECG and record weight as part of this ET visit.
 - IF at Visit 2 you did collect an ECG and record weight the subject's participation is complete.
 - f. **IF** the subject wishes to be re-enrolled:
 - Consent subject as though subject is new to the study.
 - Complete all **Visit 1** assessments as outlined in the protocol (Section 5.6.1).
 - Review the diary and re-start the subject in the diary.
 - Re-enroll the subject and dispense study drug. Please NOTE: the subject may not be randomized to the same dose as they had been previously.

- 3) For patients who dosed and who haven't had a visit yet
 - a. Please contact these subjects and request them to return to the clinic and return all IP and their eDiary
 - b. Discontinue the subject in Cenduit
 - c. Discontinue the subject in eDiary (Refer to page 66 in the ERT Site Manual)
 - d. Discontinue subject in EDC
 - e. **IF** the subject does NOT wish to be re-enrolled

- Complete ALL **Visit 6/ET** assessments as outlined in the protocol (Section 5.6.5).
- The subject's participation is complete.
- f. **IF** the subject wishes to be re-enrolled:
 - Consent subject as though subject is new to the study.
 - Complete all **Visit 1** assessments as outlined in the protocol (Section 5.6.1).
 - Review the diary and re-start the subject in the diary.
 - Re-enroll the subject and dispense study drug. Please NOTE: the subject may not be randomized to the same dose as they had been previously

Note – all data collected from the subjects enrolled from October 7, 2015 to November 10, 2015 and affected by this administrative hold will be reported. Dosing information as well as safety data (AEs, clinical laboratories, ECGs, physical examinations and vital signs) will be kept in the database, separated by date and included in the final study report.

20. APPENDIX 5. Liver Safety: Suggested Actions and Follow-Up Assessments

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology^a	Haptoglobin^a
Hemoglobin	
Hematocrit	Hepatic Coagulation^a
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	Hepatic Serologies^{a,b}
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry^a	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	Anti-nuclear antibody^a
AST	
GGT	Alkaline Phosphatase Isoenzymes^a
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)^a

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalised ratio; RBC = red blood cells; WBC = white blood cells.

^a Assayed by Lilly-designated laboratory.

^b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

21. APPENDIX 6. Protocol Amendment History

Protocol H8H-CD-LAHL/COL MIG-305 [An Open-label, Long-term, Safety Study of Lasmiditan (200 mg and 100 mg) in the Acute Treatment of Migraine] has been amended. The new protocol is indicated by amendment (D)/V4 and will be used to conduct the study in place of any preceding version of the protocol.

The rationale for the amendment include the following:

- As part of the lasmiditan clinical development process, Lilly reviewed the totality of the lasmiditan data, including the recently concluded Study LAIF that assessed duration of driving impairment at a maximum lasmiditan dose of 200 mg. In light of the lack of driving study data on potential impairment at doses above 200 mg, Lilly has determined that the maximum permitted dose in 24 hours will be 200 mg across the lasmiditan clinical development program. Therefore, patients in this study will be instructed to no longer take a second dose of lasmiditan 200 mg in a 24-hour period.
- While a second dose of lasmiditan 100 mg will continue to be permitted, pooled results of prior studies do not provide clear evidence of clinical benefit when a second dose is taken for rescue. However, there is some evidence that a second dose of 100 mg could be effective for headache recurrence (the pain goes away completely and later returns). Therefore the study is limiting second dose with lasmiditan 100 mg to use for recurrence only.
- The re-dispensing of unused study drug is no longer allowed, and therefore language pertaining to re-dispensing has been deleted.
- As lasmiditan was associated with driving impairment in a study of healthy volunteers on a computer-based driving simulator, language was updated to indicate patients should restrict their driving, operation of heavy machinery, or other similar activities after taking study drug as described in the ICF.
- As the standard Lilly hepatic monitoring language and tests were omitted from the study when the protocol was previously updated, these have been included in order to effectively assess abnormalities pertaining to hepatic laboratory analytes.
- Clarification to the schedule of activities footnote was made to indicate that repeat and/or additional laboratory testing may be necessary if clinically significant laboratory results are obtained.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol H8H-CD-LAHL(D)/COL MIG-305 V4

Section # and Name	Description of Change	Brief Rationale
3 List of Abbreviations	Added abbreviations for hepatic laboratory analytes.	Section on hepatic safety monitoring added.
1 Synopsis; 4.3 Minimization of Risk; 5.4 Overall Study Design and Plan: Description ; 5.5.2 Treatment; 7.3.1 Rescue Medication; 7.3.2 Recurrence Medication; 7.5 Treatment Compliance; 8.1 Study Drug; 8.5 Administration; 9.1.7 Dosing Instructions 9.1.8 Subject Diary; 9.1.8.1 Recording Use of Rescue Medication and Migraine Symptoms; 9.1.8.2 Recording Recurrence and Migraine Symptoms	Updated wording to reflect that a second dose of study drug is only permitted for lasmiditan 100 mg and no longer for lasmiditan 200 mg, and that the second dose of lasmiditan is only to be taken for recurrence and not for rescue.	The maximum permitted dose of lasmiditan has been determined to be 200 mg in a 24-hour period. There is no clear evidence for the benefit of a second dose of lasmiditan 100 mg for rescue.
Schedule of Assessments	Added wording to footnote number 4 to state that repeat and/or additional laboratory testing may be necessary if clinically significant laboratory results are obtained.	Updated for clarification.
4.3 Minimization of Risk	Updated wording to indicate that patients are to restrict their driving/operation of heavy machinery.	Wording was updated to reflect the fact that lasmiditan was associated with driving impairment in a study of healthy volunteers on a driving simulator and to refer to the ICF for further instruction.
8.5 Administration	Deleted wording regarding the re-dispensing of study drug.	Re-dispensing of study drug is no longer allowed.
9.1.5.3 Hepatic Safety Monitoring	Section added.	To outline required hepatic monitoring.
20 Appendix 5 Liver Safety: Suggested Actions and Follow-Up Assessments	Section added.	To outline suggestions for action in case of clinically significant hepatic abnormalities.

Revised Protocol Sections

Note: Deletions have been identified by ~~strikethroughs~~.
Additions have been identified by the use of underscores.

1 Synopsis:

Study Design:

...

Subjects will be asked to treat all migraine attacks with study drug on an outpatient basis for up to 12 months. Each patient's study participation will consist of a screening visit (Visit 1) and a treatment period of up to 12 months during which the subject will treat all migraine attacks with either lasmiditan 200 mg or lasmiditan 100 mg (with a second dose of study drug permitted between 2 and 24 hours (h) for ~~rescue or~~ recurrence of migraine only for subjects randomized to lasmiditan 100 mg).

...

Subjects will be randomly assigned in a 1:1 ratio, to receive lasmiditan 100 mg (L100 mg) or lasmiditan 200 mg (L200 mg). Subjects randomized to lasmiditan 100 mg will be allowed to take a second dose of ~~their assigned treatment~~ study drug if needed for ~~rescue or~~ recurrence of migraine.

Treatment Period: Subjects will be asked to use lasmiditan as the first treatment for each new migraine attack within 4 hours of onset providing that the headache severity is at least moderate at that time and not improving. Subjects should not exceed a total dose of 200 mg of lasmiditan in a 24-hour period. 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 (headache pain) 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~~ only for subjects randomized to lasmiditan 100 mg. 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 of study drug is used (for subjects randomized to lasmiditan 100 mg). Subjects using an alternate medication other than a second dose of study drug for the treatment of migraine rescue or recurrence will report the use of medication and continue to record their responses in the electronic diary up to the 48 hour timepoint.

Schedule of Assessments - Footnotes:

...

4. Clinical laboratory tests include hematology, biochemistry, lipid profile and urinalysis. In the event of clinically significant laboratory findings, including but not limited to hepatic laboratory abnormalities, repeat or additional laboratory testing may be required outside a scheduled clinic visit.

3 List of Abbreviations and Definitions

...

APALP Alkaline phosphatase

CPK Creatine phosphokinase

...

<u>GGT</u>	<u>Gamma glutamyl transferase</u>
...	
<u>Ig</u>	<u>Immunoglobulin</u>
...	
<u>INR</u>	<u>International Normalised Ratio</u>
...	
<u>RBC</u>	<u>Red blood cell</u>
...	
<u>TBL</u>	<u>Total bilirubin</u>
...	
<u>ULN</u>	<u>Upper limit of normal</u>

4.3 Minimization of Risk

...

All doses of lasmiditan were associated with driving impairment in a study of healthy volunteers on a computer-based driving simulator. Patients should restrict their driving, operation of heavy machinery, or other similar activities after taking study drug, as described in the informed consent form (ICF). Since somnolence, dizziness and fatigue have been reported with study drug administration, patients participating in this study will be advised not to drive or operate machinery after taking treatment until they know how they will react to lasmiditan.

Rescue medication (other than study drug) 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.

For subjects randomized to lasmiditan 100 mg, 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.

5.4 Overall Study Design and Plan: Description

...

Subjects will be asked to treat all migraine attacks with study drug on an outpatient basis for up to 12 months. Each patient's study participation will consist of a screening visit (Visit 1) and a treatment period of up to 12 months during which the subject will treat all migraine attacks with either lasmiditan 200 mg or lasmiditan 100 mg (with a second dose of study drug permitted between 2 and 24 hours (h) for rescue or recurrence of migraine only for subjects randomized to lasmiditan 100 mg).

...

Subjects will be randomly assigned in a 1:1 ratio, to receive lasmiditan 100 mg (L100 mg) or lasmiditan 200 mg (L200 mg). Subjects randomized to lasmiditan 100 mg will be allowed to take a second dose of their assigned treatment study drug if needed for rescue or recurrence of migraine.

Treatment Period: Subjects will be asked to use lasmiditan as the first treatment for each new 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 (headache pain) 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. For subjects randomized to lasmiditan 100 mg, 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 should not exceed a total dose of 200 mg of lasmiditan in a 24-hour period. 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 of study drug lasmiditan 100 mg is used. Subjects using an alternate medication other than a second dose of study drug lasmiditan 100 mg for the treatment of migraine rescue or recurrence will report the use of medication and continue to record their responses in the electronic diary up to the 48 hour timepoint.~~

5.5.2 Treatment

Subjects will be allowed to treat all acute migraine attacks with study drug. Study migraines should be of moderate or severe intensity that is not improving. The attack is to be treated within 4 hours of onset. Subjects should not exceed a total dose of 200 mg of lasmiditan in a 24-hour period.

...

- 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 if a second dose of study drug is taken for ~~rescue or recurrence of migraine~~ (for subjects randomized to lasmiditan 100 mg) (See Section 9.1.8).

7.3.1 Rescue Medication

Rescue medication (other than study drug) 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.~~

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 (only for subjects randomized to lasmiditan 100 mg).

7.5 Treatment Compliance

Study drug will be taken by the subject on an outpatient basis throughout the study. Prior to discharge from **Screening/Visit 1** subjects will be given study drug to treat all migraine attacks for the first month. Information on the time and date of each dose (initial treatment along with the use of rescue medication or treatment of recurrence with a second dose of study drug for subjects randomized to lasmiditan 100 mg) will be recorded by the subject in the electronic diary.

8.1 Study Drug

Each dose of study drug will consist of one tablet for the treatment of a single migraine attack. For subjects randomized to lasmiditan 100 mg, a second dose may be used a second tablet for use as rescue medication or as for treatment of recurrence of migraine between 2 and 24 hours after the first dose. For subjects randomized to lasmiditan 200 mg, no additional study drug is to be taken within 24 hours of the dose, as the maximum dose of lasmiditan to be taken in a 24-hour period is 200 mg.

8.5 Administration

...

Subjects are to return all dosing cards (used and unused to each visit). ~~Remaining tablets can be re-dispensed along with the next assigned patient 8-tablet single card or carton as appropriate based on the individual subjects need.~~

...

Subjects will be instructed to take a second dose (one tablet) of study drug (only for those subjects randomized to lasmiditan 100 mg), if needed, with approximately 4 ounces of water for ~~rescue or for recurrence of migraine~~ at least 2 hours after the first dose. Subjects should not exceed a total dose of 200 mg of lasmiditan in a 24-hour period.

9.1.5.3 Hepatic Safety Monitoring

If a study subject experiences elevated ALT $\geq 3X$ ULN, AST $\geq 3X$ ULN, ALP $\geq 2X$ ULN, or elevated TBL $\geq 2X$ ULN, liver testing (Appendix 5; Section 20) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

Additional safety data should be collected if 1 or more of the following conditions occur:

- Elevation of serum ALT to $\geq 5X$ ULN on 2 or more consecutive blood tests
- Elevation of serum AST to $\geq 5X$ ULN on 2 or more consecutive blood tests
- Elevated serum TBL to $\geq 2X$ ULN (except for cases of known Gilbert's syndrome)
- Elevation of serum ALP to $\geq 2X$ ULN on 2 or more consecutive blood tests
- Subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- Hepatic event considered to be a SAE

9.1.7 Dosing Instructions

...

Subjects will be asked to treat each 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 should not exceed a total dose of 200 mg of lasmiditan in a 24-hour period. Subjects will be instructed not to use rescue medication (other than study drug) until at least 2 hours after taking study drug. If the subject does not become headache pain free within 2 hours, rescue medication (other than study drug) 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. For subjects randomized to lasmiditan 100 mg, 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

...

The need for an alternative treatment as rescue medication and second dosing of study drug or an alternative treatment will be assessed between 2 and 24 hours and at 48 hours. Recurrence of pain and second dosing of study drug (only for those randomized to lasmiditan 100 mg) will be assessed between 2 and 24 hours and at 48 hours.

9.1.8.1 Recording Use of Rescue Medication and Migraine Symptoms

Any use of a second dose of study drug for rescue medication (other than study drug) taken because headache pain freedom is not achieved at 2 hours will be recorded.

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. For subjects randomized to lasmiditan 100 mg, Ssubjects 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 time points specified above.

20. APPENDIX 5. Liver Safety: Suggested Actions and Follow-Up Assessments

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology^a

Hemoglobin

Hematocrit

RBC

WBC

Neutrophils, segmented

Lymphocytes

Monocytes

Eosinophils

Basophils

Platelets

Hepatic Chemistry^a

Total bilirubin

Direct bilirubin

Alkaline phosphatase

ALT

AST

GGT

CPK

Haptoglobina

Hepatic Coagulation^a

Prothrombin Time

Prothrombin Time, INR

Hepatic Serologies^{a,b}

Hepatitis A antibody, total

Hepatitis A antibody, IgM

Hepatitis B surface antigen

Hepatitis B surface antibody

Hepatitis B Core antibody

Hepatitis C antibody

Hepatitis E antibody, IgG

Hepatitis E antibody, IgM

Anti-nuclear antibody^a

Alkaline Phosphatase Isoenzymes^a

Anti-smooth muscle antibody (or anti-actin antibody)^a

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase;

GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalised ratio; RBC = red blood cells; WBC = white blood cells.

^a Assayed by Lilly-designated laboratory.

^b Reflex/confirmation dependent on regulatory requirements and/or testing availability.