STUDY TITLE: A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of MLD10 in the Prevention of Migraine Headache in Adults

PROTOCOL NO: **MLD10-002**

SPONSOR: **Pharmalyte Solutions LLC**
580 Commerce Street
Suite 100
Southlake, TX 76092

A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of MLD10 in the Prevention of Migraine Headache in Adults

INVESTIGATOR SIGNATURE PAGE

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices and all applicable laws and regulations.
- Maintain all information supplied by Clinvest in confidence and, when this information is submitted to an Institutional Review Board (IRB), it will be submitted with a designation that the materials are confidential.

I have read and agree to follow this protocol.

_____	_____	_____
Investigator Printed Name	Signature	Date

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A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF MLD10 IN THE PREVENTION OF MIGRAINE HEADACHE IN ADULTS

INDICATION

For the prophylaxis of migraine headaches in adults

STUDY PURPOSE

- To evaluate the daily use of MLD10 and placebo for the treatment of migraine, as measured by the change from baseline in the number of migraine headache days of subjects treated for 3 months.
- To compare daily use of MLD10 and placebo as measured by:
  - change in the quantitative and qualitative aspects of migraine headaches from baseline, during treatment, and at the conclusion of a 3-month treatment period.
  - safety and tolerability measures in migraine headache subjects through the monitoring of adverse events (AEs) and clinical chemistry values.

SUMMARY OF STUDY DESIGN

This is a double-blind, placebo-controlled, randomized, multi-center study. Subjects agreeing to participate in the study and meet the entry criteria assessed at the screening visit, will begin a 28 day baseline period to confirm their diagnosis, as well as establish baseline migraine characteristics. During this baseline period, subjects will continue treating their migraines as usual, simply recording the information in a daily headache diary. Subjects who, after completing the baseline, continue to meet entrance criteria will be eligible to enter into the treatment phase and be randomized according to the Clinvest generated randomization schedule. Approximately 142 subjects (71 subjects per arm) will be randomized and enter the treatment phase receiving MLD10 or placebo in a 1:1 design at a maximum of 8 US sites. Diary assessments will collect study medication adherence, pain severity, headache symptoms, acute medication usage, and unusual symptoms. Serum samples will be collected and analyzed for ionized Mg, electrolytes, and creatinine.

The study consists of 5 visits:

Baseline Period:	Visit 1 (Screening/Baseline Period)
Treatment Period:	Visit 2 (Randomization/Treatment Period Month 1)
	Visit 3 (Treatment Period Month 2)
	Visit 4 (Treatment Period Month 3)
	Visit 5 (Final Visit)

POPULATION SAMPLE

Subjects in the study are those:

- who have at least a 3 month history of 3-14 migraines, with or without aura, as defined by International Classification of Headache Disorders (ICHD) -3 beta (Appendix 1) or treat with a ergot or triptan and received relief.
- who received a diagnosis of migraine before age 50.
- who have used acute headache medication 14 or fewer days per month in the previous 3 months.

STUDY MEDICATION

Subjects will receive Investigational Drug Product MLD10 as follows: 2 MLD10 caplets, oral, twice daily or placebo caplets as follows: 2 placebo caplets, oral, twice daily.

BACKGROUND & STUDY RATIONALE

Magnesium is frequently used in the treatment and prevention of migraine, though there are relatively few clinical trials supporting its efficacy. While there is a sound scientific rationale for magnesium as a migraine preventative, different forms of magnesium differ significantly in their solubility and bioavailability. In addition, there are challenges in measuring bioactive magnesium levels in the body. Consequently, a discussion of the efficacy of magnesium needs to be specific to the formulation of magnesium being studied, its ability to be adequately absorbed, and physiologically active.

Magnesium is recognized to block the N-methyl-D-aspartate ion-dependent channel. Low levels of magnesium increase the sensitivity of the NMDA receptor to glutamate. Glutamate is an excitatory neurotransmitter and is considered central to the development of cortical spreading depression. In addition, glutamate is considered to play an excitatory role in the hyper-vigilant migraine nervous system. Thus, magnesium properly utilized physiologically has significant potential to protect the nervous system from migraine.

PRIMARY OBJECTIVE

To compare the change from baseline to treatment period months 1, 2, and 3 in the number of migraine headache days of subjects treated with MLD10 versus placebo.

SECONDARY OBJECTIVES

To compare change from baseline of subjects treated with MLD10 versus placebo on the following parameters during a 3 month treatment period:

- the number of headache days
- the average headache duration
- pain severity at headache onset
- the use of acute medications
- Migraine Disability Assessment Scale (MIDAS) scores
- Subject Global Impression of Change (SGIC)
- Physician Global Impression of Change (PGIC)

EXPLORATORY OBJECTIVES

To compare the change from baseline of subjects treating with MLD10 versus placebo on the following parameters during a 3 month treatment period.

- migraine with aura days
- serum ionized magnesium

SAFETY OBJECTIVES

Safety assessments will include monitoring the parameters during the length of the study.

- adverse events
- physical examination
- urine pregnancy tests for all females of childbearing potential

- vital signs including blood pressure, pulse rate, and weight
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- concomitant medications
- clinical chemistry measurements

SUBJECT SELECTION

Approximately 142 subjects will be randomized from the clinic and general population with a history of mild to severe migraine, with or without aura, that meets the International Classification of Headache Disorders (ICHD-3 beta) definition for episodic migraine with a frequency of 3-14 days of migraine (or headache treated with migraine specific medication) per month. Subjects will have a stable history of headaches meeting the above parameters for at least 3 months prior to enrollment. Subjects on migraine preventative medications will be required to be on a stable regimen for 30 days prior to and throughout the study period.

POWER ANALYSIS

A power analysis, using GPower Version 3.1.7, indicated a total sample size of 128 subjects would be needed to detect medium effects (d = .25) with 80% power using an analysis of covariance (ANCOVA) test to include fixed effects, main effects, and interactions with alpha being .05. Given an estimated 10% early termination rate, a total estimated sample size of 142 subjects is needed.

INCLUSION CRITERIA

Subjects must meet the following inclusion criteria:

1. male or female, in otherwise good health, 18 to 65 years of age.
2. history of frequent episodic migraine (3-14 migraine days per month) (with or without aura) according to the ICHD-3 beta for at least 3 months.
3. onset of migraine before age 50.
4. stable history of migraine at least 3 months prior to screening.
5. not currently taking a migraine preventive or has been taking preventive for at least 30 days prior to screening and agrees to not start, stop, or change medication and/or dosage during the study period.
6. if female of childbearing potential, has a negative urine pregnancy test at Visits 1-5 and uses, or agrees to use, for the duration of the study, a medically acceptable form of contraception as listed:
    - complete abstinence from intercourse from 2 weeks prior to administration of study drug, throughout the study, and for 7 days after completion or premature discontinuation from the study; surgically sterile (hysterectomy or tubal ligation or otherwise incapable of pregnancy); sterilization of male partner when in a monogamous relationship; intrauterine device with published data showing lowest expected failure rate is less than 1% per year; double barrier method (i.e., 2 physical barriers OR 1 physical barrier plus spermicide) for a least 1 month prior to Visit 1 and throughout study; or hormonal contraceptives for at least 3 months prior to Visit 1 and throughout study.
7. completion of online diary must be ≥ 80% compliance, unless otherwise approved by the Sponsor and/or Clinvest.

EXCLUSION CRITERIA

Subjects must **NOT** meet any of the following exclusion criteria:

1. unable to understand the study requirements, the informed consent, or complete headache records as required per protocol.
2. pregnant, actively trying to become pregnant, or breast-feeding.
3. diagnosed with ICHD-3 beta criteria for Chronic Migraine within 3 months prior to screening, at the time of screening, and/or during the baseline period.
4. experienced the following migraine variants: basilar migraine, aura without headache, familial hemiplegic migraine, complicated migraine, ophthalmoplegic migraine and retinal migraine within the last year.
5. history of medication overuse headache (MOH) (Appendix II) in the 3 months prior to study enrollment or during the baseline phase.
6. history of medication overuse (MO) of ergotamines, triptans, opioids, analgesics, NSAIDS and combination therapies, as defined by ICHD-3 beta criteria and/or MO during baseline period.
7. history of substance abuse and/or dependence, in the opinion of the Investigator.
8. history of impaired renal function that, in the investigator's opinion, contraindicates participation in this study.
9. unstable neurological condition or a significantly abnormal neurological examination with focal signs or signs of increased intracranial pressure.
10. suffers from a serious illness, or an unstable medical condition, one that could require hospitalization, or could increase the risk of adverse events.
11. has significant risk of suicide, defined as a "yes" answer to any of the following questions on the Columbia-Suicide Severity Rating Scale (C-SSRS), either at the screening visit (when assessing the prior 12 months) or at visit 2 (when assessing time since the screening visit):
    a. Questions 4 or 5 on the suicidal ideation section
    b. Any question on any item in the suicidal behavior section
12. any psychiatric disorder with psychotic features, and/or any other psychiatric disorder not stable or well controlled, that would interfere in their ability to complete study activities.
13. hypersensitivity, intolerance, or contraindication to the use of magnesium L-lactate dehydrate or any of its components.
14. received any investigational agents within 30 days prior to Visit 1.
15. plans to participate in another clinical study at any time during this study.

STUDY DESIGN

This is a multi-center, double-blind, randomized, placebo-controlled, parallel study of MLD10 for the prevention of migraine headache. The study population will consist of approximately 142 male and female subjects between 18 and 65 years of age with frequent episodic migraine as defined by ICHD-3 beta criteria. Two MLD10 (243 mg of elemental magnesium) or placebo caplets will be taken twice daily for a total daily dose of 486 mg.

INFORMED CONSENT

The investigator must obtain documented consent from each potential subject, or legally authorized representative, prior to any study related procedures being performed. Consent must

be documented by the subject's dated signature on an Informed Consent Form (ICF) along with the dated signature of the persons conducting the consenting process. A copy of the signed and dated consent form should be given to the subject before participating in the study.

If the subject is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the subject should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the person conducting the consent process.

VISIT 1 - SCREENING

The following will be completed at Visit 1:

1. Obtain written Informed Consent. The informed consent will be obtained in accordance with Good Clinical Practices (GCP) and all applicable regulatory requirements from each subject prior to participation in the study.
2. Verify Inclusion/Exclusion Criteria. Subjects will meet all the inclusion and none of the exclusion criteria.
3. Obtain demographics (race, ethnicity, sex, date of birth)
4. Obtain medical, medication, and headache history. Data collected will include medical history and diagnoses, age at onset of migraine and other pertinent migraine/headache history, history of acute and prophylactic headache medications within the past 30 days, and history of other recent/concomitant medications.
5. Obtain date of last menstrual cycle and perform urine pregnancy test, if appropriate. Results of the pregnancy test must be negative to continue in study.
6. Perform physical and neurological examinations.
7. Measure vital signs (height, weight, resting heart rate, and blood pressure).
8. Review Baseline Headache Diary. Subjects will be instructed to complete a daily online headache diary. Assessments to be captured are start/stop time, severity, associated symptoms, use of rescue medications, and unusual symptoms.
9. Administer Columbia-Suicide Severity Rating Scale (C-SSRS).
10. Schedule Visit 2.

VISIT 2 - RANDOMIZATION

1. Verify Inclusion/Exclusion Criteria. Subjects must continue to meet all inclusion (including $\geq$ 3 days of migraine during baseline) and none of the exclusion criteria.
2. Perform urine pregnancy test, if appropriate. Results of the pregnancy test must be negative to continue in study.
3. Measure vital signs (weight, resting heart rate, and blood pressure).
4. Record any changes to concomitant medications.
5. Record any Serious Adverse Events (SAE) since signing the Informed Consent.
6. Review Baseline Headache Diary for completeness and continuing eligibility.
7. Randomize subject
8. Review Month 1 Headache Diary instructions (same instructions as those discussed for Baseline Headache Diary).
9. Dispense Month 1 study medication. Subjects will be instructed how to take study medication, prohibited medications, dosage limitations of study medication, and storage requirements. Subjects will be instructed to return all used/partially

used/unused study medication at next office visit and medications reconciliation will be performed to ensure a compliance of at least 80%. Subjects not complying at an 80% level will be withdrawn, unless otherwise approved by the Sponsor and/or Clinvest. (Estimated to be < 10%)

10. Administer C-SSRS.
11. Administer MIDAS.
12. Collect serum samples for electrolytes, creatinine, and ionized Mg.
13. Schedule Visit 3.

VISIT 3 - END OF TREATMENT PERIOD MONTH 1

1. Record any changes to concomitant medications.
2. Record any Non-Serious Adverse Events (NSAE) and/or SAEs.
3. Perform urine pregnancy test, if appropriate. Results of the pregnancy test must be negative to continue in study.
4. Measure vital signs (weight, resting heart rate, and blood pressure).
5. Review Month 1 Headache Diary for completeness.
6. Review instructions for Month 2 Headache Diary (same instructions as those discussed for Month 1 Headache Diary).
7. Collect Month 1 unused study medication and used packaging. Confirm 85% compliance of medication usage per study protocol.
8. Dispense Month 2 study medication and review the dosage limitations of study medication, storage requirements, and to return all used/partially used/unused study medication at next office visit.
9. Perform drug accountability.
10. Administer C-SSRS.
11. Collect serum samples for electrolytes, creatinine, and ionized Mg.
12. Schedule Visit 4.

VISIT 4 - END OF TREATMENT PERIOD MONTH 2

1. Record any changes to concomitant medications.
2. Record any NSAEs/SAEs.
3. Perform urine pregnancy test, if appropriate. Results of the pregnancy test must be negative to continue in study.
4. Measure vital signs (weight, resting heart rate, and blood pressure).
5. Review Month 2 Headache Diary for completeness.
6. Review instructions for Month 3 Headache Diary (same instructions as those discussed for Month 2 Headache Diary).
7. Collect Month 2 unused study medication and used packaging. Confirm 85% compliance for medication usage per study protocol.
8. Dispense Month 3 study medication and review the dosage limitations of study medication, storage requirements, and to return all used/partially used/unused study medication at next office visit.
9. Perform drug accountability.
10. Administer C-SSRS.
11. Collect serum samples for electrolytes, creatinine, and ionized Mg.
12. Schedule Visit 5.

VISIT 5 - END OF TREATMENT PERIOD MONTH 3

1. Record any changes to concomitant medications.
2. Record any NSAEs/SAEs.
3. Perform urine pregnancy test, if appropriate.
4. Measure vital signs (weight, resting heart rate, and blood pressure)
5. Perform physical/neurological examinations.
6. Collect Month 4 unused study medication and used packaging.
7. Perform drug accountability.
8. Administer SGIC & complete PGIC.
9. Administer MIDAS.
10. Administer C-SSRS.
11. Collect serum samples for electrolytes, creatinine, and ionized Mg.
12. Exit subject.

Table 1. Study Procedures

	Screening	Randomization	Treatment		
	Visit 1 Day 0	**Visit 2 Day 29 (+/- 3)**	**Visit 3 Day 58 (+/- 3)**	**Visit 4 Day 87 (+/- 3)**	**Visit 5 Day 116 (+/- 3)**
Informed Consent	X				
Physical/Neurological Exam	X				X
Vital Signs	X	X	X	X	X
Verify Inclusion/Exclusion	X	X			
Subject Randomization		X			
Medical History	X				
Migraine History	X				
Medication History	X				
Update Medications		X	X	X	X
Urine Pregnancy Test	X	X	X	X	X
SGIC					X
PGIC					X
Dispense Study Medication		X	X	X	
Drug Accountability			X	X	X
Headache Diary	X	X	X	X	
Review Diary		X	X	X	X
Collect Adverse Events		X	X	X	X
Administer C-SSRS	X	X	X	X	X
Administer MIDAS		X			X
Serum Electrolytes & Creatinine		X	X	X	X
Serum Ionized Mg		X	X	X	X

STUDY MEDICATION RANDOMIZATION

Eligible subjects will be randomized 1:1 to receive magnesium L-lactate dehydrate (243 mg of elemental mg++ BID for a total of 486mg daily) or placebo at Visit 2. If at any time during the

study the subject withdrawals from the study, they will be instructed to return all used packaging and unused medication.

Group A

Subjects randomized to MLD10 (Group A) will be dispensed a 28 day supply of magnesium L-lactate dehydrate 10 mEq (121.5 mg of elemental mg++ caplets) for daily treatment. A total of 120 caplets will be given each time at Visit 2, 3, and 4. Additional overage will be given to account for the 3 day window. Subjects will be instructed to take two caplets of study medication BID at about the same time each day (i.e. 8AM & 8PM for a total of 486mg's of elemental mg++ per day). Subjects will be instructed regarding storage requirements and will be asked to return all used/partially used/unused medication containers at the next office visit.

Group B

Subjects randomized to placebo (Group B) will be dispensed a 28 day supply of matching placebo for daily treatment. A total of 120 caplets will be given each time at Visit 2, 3, and 4. Additional overage will be given to account for the 3 day window. Subjects will be instructed to take two caplets of study medication BID at about the same time each day (i.e. 8AM & 8PM). Subjects will be instructed regarding storage requirements and will be asked to return all used/partially used/unused medication containers at the next office visit.

RESCUE MEDICATION

Subjects will be instructed they may take their investigator approved rescue medications for headaches, if needed. Rescue medication usage and dosage will be recorded on the headache diary.

CONCOMITANT MEDICATIONS

Therapy considered necessary for the subject's welfare may be given at the discretion of the investigator. Concomitant medication usage and dosage will be recorded on the concomitant medication form.

Routine medications, including migraine preventative medications, should be maintained on a stable dose and regimen for the duration of the study period. Additionally, any concomitant chronic therapies should be maintained at a stable dose and dose regimen during the study.

Allowed Medications

1. All acute migraine medications currently taken by subject at Visit 1 will be allowed during the study.
2. All migraine preventative medications, excluding magnesium, that are currently taken by subject at Visit 1 will be allowed if on a stable dose for at least 30 days prior to Visit 1 and subject agrees to continue at that dose throughout the study.

Prohibited Medications

Any medication containing magnesium 30 days prior to screening.

HEADACHE DIARY

The primary and much of the secondary endpoints will be derived from the electronic daily headache diary. Site personnel will be responsible for instructing subjects on the requirement for timely and daily completion of the electronic diary. Each day, the subject will be asked to record diary data for the previous day (24 hour period). If a subject does not experience a headache in the previous 24 hour period, the diary must still be completed and recorded as no headache. Subject's diaries may vary day to day based on their responses. Subjects will be asked to document all headaches experienced regardless of severity for one month. All subjects should have at least 80% compliance with diary completion throughout the length of the study. Subjects will record headache severity, symptoms, use of acute medications, as well as additional questions as required. Headache severity will be subjectively rated by the subject as follows: no pain, mild pain, moderate pain, or severe pain. These ratings will be collected at pre-defined time points.

UNSCHEDULED VISITS

If a subject has an unscheduled visit, the unscheduled visit form must be completed. If the visit occurs for safety reasons, all relevant safety data should be captured and reported on the appropriate forms. If the unscheduled visit results in an early termination, all applicable final study visit procedures will be performed and the early termination form will need to be completed as well.

BLINDING/UNBLINDING

At randomization (Visit 2), neither the subject nor the investigator will be aware to which treatment group the subject has been assigned. If needed, for safety and proper treatment of the subject, the investigator can unblind the subject's treatment assignment to determine which treatment has been assigned and institute appropriate follow-up care. When possible, Clinvest should be notified prior to unblinding study medication.

Individual unblinding envelopes are shipped with study medication. Each study medication kit has a corresponding unblinding envelope. Unblinding will include matching the kit and unblinding envelope with the subject drug number.

To unblind a subject without breaking the blind for remaining subjects' treatment the following instructions described below will be followed:

- Obtain the security envelope containing the unblinding envelopes.
- Remove the unblinding envelope with the study drug number corresponding with the study medication kit dispensed to the subject.
- Break the seal of the unblinding envelope and remove the subjects' treatment label.
- Return the subjects' treatment label to the unblinding envelope.
- Return the unblinding envelope to the security envelope.
- Document on the unblinding form located in the eAdmin Binder.
- Email copy of unblinding form to study@clinvest.com within 24 hours of unblinding.
- Complete and email or fax the Sterling IRB, unanticipated problem report form, to Sterling IRB within 10 business days of unblinding.

DISCONTINUATION/WITHDRAWAL FROM STUDY

All subjects who withdraw from the study, for any reason, must return all study medication and supplies to the investigator or his/her delegate at the first available opportunity.
Subjects may withdraw at any time or be dropped from the study at the discretion of the investigator or Clinvest if he/she violates the study plan or for administrative and/or safety reasons. When a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the final study visit should be performed at the time of discontinuation, as well as the completion of the early termination form and unscheduled visit form (if appropriate). Any adverse experiences which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in the adverse event reporting section of this protocol.

REPORTING PREGNANCY

Although not considered an adverse event, if a female of childbearing potential becomes pregnant during the study, the investigator will notify Clinvest and Pharmalyte Solutions LLC by phone immediately after the pregnancy is confirmed. The subject will not receive any further treatment and will be withdrawn from the study. The subject should be followed for 12 weeks after the last study treatment and at least 6-8 weeks following the report of pregnancy, before being exited from the study. The investigator will (1) notify the subject's physician that the subject was being treated with an investigational drug MLD10 and (2) follow the progress of the pregnancy until delivery. The investigator should document the outcome of the pregnancy and provide a copy of the documentation to Clinvest.

REPORTING ADVERSE EVENTS

The investigator will be responsible for the detection, collection, and evaluation of all events meeting the definition of an adverse event (AE). An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with the study product. An adverse event can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of the study product, whether or not related to the study product.

An adverse event observed after the initial dose of the study product will be considered a "treatment-emergent adverse event". Treatment-emergent adverse events will be analyzed and discussed in the clinical study report for this study. Adverse event terms should include a diagnosis, as available, in preference to the listing of individual signs and symptoms. If a diagnosis is not possible, each sign and symptom should be recorded as an individual adverse event.

All adverse events, whether or not related to the study drug, must be completely documented on the appropriate adverse event eCRF (electronic case report form) page. If a subject is withdrawn from the study due to an adverse event, this must also be recorded on the appropriate eCRF pages.

The site staff must record all directly observed AEs and all spontaneously reported AEs. At each visit, the site staff will ask the subject a non-specific question (e.g., "Have you noticed any

change in your health since your last visit?") to assess AE occurrence since the last report or visit.

Non-Serious Adverse Event (NSAE)
NSAE's will be collected beginning after the first dose of study medication or within 14 days following cessation of treatment and will include any change from the subject's condition at Visit 2. These include physical findings, clinical signs and symptoms, or sequelae. Any worsening (i.e. any clinically significant adverse change in the frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the provided product, is also considered to be an adverse event. Events such as medical/surgical procedures or anticipated day-to-day fluctuations of pre-existing conditions present at screening that do not worsen are not considered NSAE's.

All NSAE's noted will be captured on the non-serious adverse events eCRF. Information captured will include start date/time, end date/time, severity, relationship of causality to study drug, course of action taken, and outcome.

Serious Adverse Event (SAE)
An SAE is defined as any untoward medical occurring after signing of the informed consent and until cessation of the study which:

1. results in death.
2. is life threatening (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.).
3. requires subject hospitalization or prolongation of existing hospitalization.
4. results in persistent or significant disability/incapacity; or a congenital anomaly/birth defect.

Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. These should also be considered serious. SAE's will be reported in compliance with all applicable safety reporting requirements as set forth in the Code of Federal Regulations. SAE's assessed as life threatening or death "possibly related to the study medication" will be reported to Clinvest, Pharmalyte Solutions LLC, and Sterling IRB within 24 hours of knowledge of the event by study staff. All other SAE's (such as hospitalization, disability, congenital anomaly, and an important medical event) will be reported to Clinvest, Pharmalyte Solutions, and Sterling IRB within 48 hours of knowledge of the event by study staff. A MedWatch Form FDA 3500A will also be completed and forwarded to Pharmalyte Solutions LLC and Clinvest.

Included in the SAE Report Form will be an assessment of the causal relationship between the Pharmalyte Solutions LLC Materials and the SAE. SAE's will be followed

by study staff until the event(s) have returned to normal, stabilized, or have been otherwise explained, for at least 2 weeks following the last dose of study drug.
If the investigator learns of any SAEs after a subject has been discharged from the study and he/she considers the event reasonably related to the investigational product, the investigator will notify Clinvest and Pharmalyte Solutions LLC.

CLINICAL SUPPLIES
Clinical supplies will be packaged for subjects in accordance to an allocation schedule generated by Clinvest.

LABORATORY ANALYSIS
Laboratory specimens for the serum ionized magnesium test will be shipped to the Center for Biomedical and Life Sciences for analysis. Laboratory specimens for the serum electrolytes and creatinine will be sent to the sites local laboratories for analysis. The collection, storage, shipping, and processing of the specimens will be documented.

STORAGE REQUIREMENTS
The study medication and clinical supplies 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. Clinical supplies and medications are to be dispensed only as defined in the protocol. It is the investigator's responsibility to keep accurate records of the supplies received, the amount dispensed to and returned by subjects, and the remaining amount at the end of the study. Study staff should not open individual study medication containers prior to dispensing to the subject.

Study medication received from the Sponsor will be inventoried and accounted for throughout the study. Drug Accountability will be maintained for subjects randomized in the study. Study staff will record the amount of study medication dispensed and amount returned at each appropriate office visit. Any missing caplets or discrepancies will be addressed and reconciled as needed.

Study medication should be kept in a secure location and stored according to the package insert.

The study medication storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified on study medication temperature log. Documentation of temperature monitoring should be maintained.

CONFIDENTIALITY
By signing this protocol, the investigator affirms to Clinvest information furnished to the investigator by Clinvest will be maintained in confidence. Likewise, data generated by this study will be considered confidential by the investigator, with the exception of information included in a publication.

The investigator also agrees that Clinvest, Institutional Review Board (IRB), or Regulatory Agency representatives may consult and/or copy study documents in order to verify data. By signing the consent form, the subject agrees to this process. If study documents will be

photocopied during the process of verifying information, the subject will be identified by a unique subject number only. Full names will be masked prior to transmission to Clinvest. Signing of this protocol also means the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance will all applicable privacy laws, rules and regulations, including applicable provisions of Health Insurance Portability and Accountability Act (HIPPA).

COMPLIANCE WITH LAW, AUDIT, AND DEBARMENT

By signing the protocol, the investigator agrees to conduct the study in a diligent manner and in conformance with the protocol, standards of the Declaration of Helsinki under its most recent amendment and including Good Clinical Practice (GCP) according to the International Conference on Harmonisation (ICH) guidelines, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

Prior to trial initiation, the investigator at each site will provide Clinvest a fully executed and signed Food and Drug Administration (FDA) Form 1572 and curriculum vitae (CV).

The investigator also agrees to allow monitoring, audits, IRB review, and regulatory agency inspection of trial-related documents and procedures. Centralized monitoring will be performed to verify accuracy of data entered into the electronic data capture system (EDC).

Additionally, the investigator agrees not to seek reimbursement from subjects, their insurance providers, or from government programs for procedures included as part of the study that are reimbursed by Clinvest.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on Clinvest studies. The investigator will immediately disclose in writing to Clinvest if any person who is involved in study conduct is debarred, or if any proceeding for debarment is pending or threatened.

QUALITY CONTROL/ASSURANCE

It is Clinvest's responsibility for implementing and maintaining quality control and assurance with written SOPs to ensure the trial is conducted in compliance with GCP standards and all applicable federal, state, and local laws, rules, and regulations. Appropriate tools will be provided to the site to facilitate quality management of the subject and continuity through the trial.

Quality control should be applied by all parties and to each stage of subject management, investigational product management and data handling to ensure all data are reliable and have been processed correctly. All clinical data are to be generated and processed by personnel with relevant clinical and GCP knowledge. Subject generated data should be preceded with appropriate subject training and technical support for questions that arise during the trial.

Agreements, made by the sponsor, or their designee, with the investigator, institution and/or with any other parties involved with clinical trial should be in writing in a separate agreement.

Pharmalyte Solutions LLC has transferred trial-related duties and functions to Clinvest, but ultimate responsibility for the quality and integrity of the trial data resides with Pharmalyte Solutions LLC. The investigator agrees to be responsible for the integrity of all study conduct at their site.

During the trial Clinvest will conduct remote monitoring and safety oversight periodically. The clinical monitors may review eCRFs, central laboratory findings, etc. at intervals throughout the study to verify appropriate inclusion of subjects, adherence to the protocol, and completeness, correctness, and accuracy of eCRF entries. Any source upload should be reviewed for privacy elements and removed. Source uploads should only include the subject enrollment number as identifying information.

The study will be registered on www.clinicaltrials.gov by Clinvest.

STUDY DOCUMENTATION

Data for this trial will be primarily collected in a web-based electronic data capture (EDC) REDCap platform. The EDC access will be supplied by Clinvest with relevant training support to sites. Sites will be responsible for training study subjects in the EDC system. All data specified should be captured by the site personnel or subjects in the EDC system. All eCRFs are to be completely filled out by personnel administering the study procedures at the time of the visit. The eCRF will be considered the source document for all data collected other than laboratory and procedure findings, which will be uploaded into the eCRF as source. All data must be reviewed and signed by the investigator or sub-investigator at the conclusion of the study for each subject. The eCRFs should not be made available in any form to third parties, without written permission from the sponsor.

It is the investigator's responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the eCRF and confirmation the data is accurate, authentic, attributable, complete, and consistent. The investigator or sub-investigator must sign the eCRFs within the EDC system to attest the information contained with the eCRF is true and causality of any safety information has been assessed.

RECORD RETENTION

Study documentation includes all workbooks, worksheets, forms, lab reports, logs, signature pages, appointment schedules, investigator correspondence, electronic data (i.e. data stored on cds, flash drives, etc.), and regulatory documents. The original recording of an observation should be retained as the source document.

1. Investigator will maintain essential documents for the conduct of a clinical study and any other documentation as specified by applicable regulatory requirements.
2. Investigator will maintain a binder containing written informed consent records.
3. Conduct of study visits will be maintained on appropriate Source Documentation/Case Report Forms. Patient anonymity will be maintained on these forms by identification codes (i.e., subject initials and number). The Investigator's electronic signature will verify that all data entries in the CRF's are complete and accurate.

4. Investigator will maintain a Subject Identification Log. Information such as full name of subject, address, contact information, and additional subject identifiers will be recorded. This log will be kept confidential and not copied.
5. Investigator will maintain a Subject Screening/Enrollment Record. This record will record chronologically subjects who were seen for Visit 1, randomized at Visit 2, additional visits conducted during study, and completion/discontinuation information.
6. Clinvest will maintain a Drug Assignment Log. This log will record chronologically study medication received from Pharmalyte Solutions LLC, as well as medication returned or destroyed at the completion of the study.
7. Investigator will maintain a Site Drug Accountability Record. This record will record chronologically study medication received from the Sponsor, as well as medication returned or destroyed at the completion of the study.

Government agency regulation and directives require all study documentation pertaining to the conduct of a clinical trial must be retained by the investigator for at least 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The investigator will maintain all study documentation on file in a secure and safe location. Clinvest will notify the investigator in writing when retention is no longer necessary. No study records will be destroyed without prior agreement between Pharmalyte Solutions LLC and Clinvest.

INSTITUTIONAL REVIEW BOARD

Clinvest is responsible for obtaining IRB approval of the protocol, informed consent document, written information provided to the subject, recruiting material, and all other appropriate documents. The trial will not be initiated until IRB approval of all trial documents. The investigator will provide Pharmalyte Solutions LLC with documentation that the IRB has approved the protocol, informed consent, and any study-related materials to be provided to the subject before the study begins. In the event an amendment is needed to any document, Clinvest will also be responsible for the approval of all subsequent major changes. The investigator is responsible for obtaining initial and continuing review (annually if necessary) of the study by an IRB. Written approval must be forwarded to Clinvest before clinical supplies will be shipped. For continuing studies, written approval from the IRB must be sent to Clinvest at intervals not to exceed 1 year. All other appropriate reports on the progress of the study will be made to the IRB and the Sponsor by Clinvest in accordance with applicable governmental regulations and in agreement with the policy established by the Sponsor and the IRB.

TRAINING

Each approved study site will participate in a protocol training program prior to enrollment of any subjects in the study. The program must be attended by the principal investigator at the site, and at least one research coordinator, including the coordinator who will have the lead responsibility for coordination of the study at the site.

Comprehensive training will be provided by Clinvest to site personnel. Training topics will include protocol, study design, study documents, electronic data capture system, reporting of AEs and pregnancy, and any other study related tasks.

SAFETY MEASURES

Adverse Events

Adverse events (AEs) will be monitored throughout the study. All reported AEs will be documented on the appropriate eCRF.

Physical Examination

At screening and study exit, the investigator will examine the patient for any detectable abnormalities of the following body systems: general appearance; neck (including thyroid); head, eyes, ears, nose, and throat; lungs; heart/cardiovascular; abdomen; neurologic; extremities; back; musculoskeletal; lymphatic; skin; and other. The neurologic examination should be conducted to detect the presence of any significant sensory/motor abnormalities. A digital rectal examination is not required. Gynecological examinations are not required.

Weight should be measured at screening, day 1, and each subsequent office visit using the same scale for all patients at a given investigator site when possible.

Pregnancy tests for all females of childbearing potential. Urine pregnancy testing will be conducted at screening, on day 1, and each subsequent office visit to confirm continued non-pregnant status prior to study drug administration or study completion.

Clinical Laboratory Tests

Blood samples will be collected for clinical laboratory testing at Visits 2-5 for all patients qualifying for randomization. Non-fasting blood samples (approximately 10 mL for Electrolytes, Creatinine, and Ionized Magnesium) should be collected using standard laboratory instructions and procedures provided by the laboratories.

Vital Signs

Vital signs will be measured at screening, day 1, and each subsequent office visit. Systolic and diastolic blood pressure and pulse rate over 30 seconds should be taken after patients have been at rest (seated) for at least 2 minutes. Blood pressure should be recorded in mmHg. Pulse rate should be measured in beats per minutes.

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS will be conducted at the screening visit and each subsequent office visit. The C-SSRS is a semi-structured interview designed to assess the severity and intensity of suicidal ideation, suicidal behavior, and non-suicidal self-injurious behavior over a specified time period (e.g., prior year, since last visit). The measurement of suicidal ideation is based on 5 “yes” or “no” questions (plus a description if answered “yes”) arranged in order of increasing severity. If the patient answers “yes” to either question 1 or 2, the intensity of ideation will then be assessed in 5 additional questions relating to the frequency, duration,

controllability, deterrents, and reasons for the most severe ideation. Suicidal behavior is then assessed by asking further questions to categorize the behaviors into actual, aborted, and interrupted attempts; preparatory behavior; and non-suicidal self-injurious behavior. The interview is used in full only if the initial questions are positive; this assessment is completed at all scheduled clinic visits at which other clinical assessments are to be carried out.

If any item(s) on the C-SSRS are answered with "yes", a clinician investigator must review patient's responses in order to:

a) at screening and baseline determine patient's study eligibility and potential need for referral to a mental health professional AND
b) during the study evaluate patient's need for appropriate medical management such as referral to a mental health professional.

A significant risk of suicide is defined as a "yes" in answer to:

a) questions 4 or 5 on the suicidal ideation section; OR
b) any questions on any item in the suicidal behavior section.

This must be reported as a serious adverse event and followed up accordingly. Additionally, if a patient responds "yes" to any of the suicidal ideation questions 1 to 3, a clinician investigator should apply clinical judgment to determine the need for reporting as an adverse event or serious adverse event and the need for any referral.

SUMMARY OF METHODS OF DATA COLLECTION

Data required for the evaluation of the primary and some secondary measures will be recorded by subjects using a daily e-diary. The following data will be collected daily with the e-diary (subject instructions and training for completion of the e-diary will be provided):

- Estimated total duration of headache that day (if no headache, subject will report 0 hours)
- Severity of headache at the time of onset (mild, moderate, or severe) only for subjects who report a headache duration > 0)
- Acute headache pain medication(s) usage
- Study medication usage
- Unusual symptoms

Should a subject skip a day of e-diary entry, the subject will be able to provide the missing information for up to 1 calendar day. The e-dairy should not be completed on the day of the office visit; the last e-dairy entry for the preceding period should be completed the day prior to the office visit.

Questionnaire data required to be directly collected from subject will be obtained at each appropriate visit using an electronic device as defined in the protocol. Questionnaires are to be completed by the subject and the answers to the questions on the questionnaires should come from the subject directly, not from family, friends, or the study support personnel.

Questionnaire data required to be collected directly from clinicians will be obtained at the appropriate visit and recorded in the eCRF per protocol.

STATISTI CAL ANALYSIS

Subjects will be randomized 1:1 into the treatment groups. Randomization will not include any type of stratification.

An alpha of .05 will be used for statistical significance. All statistical tests will be two-sided. All data will be analyzed using JMP (SAS Institute, Inc.).

Descriptive statistics will establish baseline characteristics and adverse event frequency. Data for the primary endpoint will be statistically analyzed via a repeated measures ANCOVA controlling for ionized serum Mg levels. Data for each of the secondary outcome measures will be statistically analyzed for both within and between group changes via a 2-tailed Repeated Measures ANOVA and/or independent or dependent t-tests as appropriate. All ANOVAs will be followed by univariate post-hoc tests as appropriate. Multiple comparison adjustments will be made if needed.

An interim analysis will be performed when approximately 60 subjects have completed the study. The results of the interim analysis may lead to stopping the study for safety or futility. The interim analysis will not lead to stopping the study for efficacy. Only the primary endpoint and first secondary endpoint of migraine and headache day reduction will be assessed at the time of the interim analysis, as well as adverse events for safety purposes.

Modified Intent-to-Treat Population (mITT)

The modified intent-to-treat (mITT) population will include all randomized subjects who received at least one dose of study drug and obtained at least one endpoint measurement (mean change from baseline in the number of hours with headaches) after treating. The mITT population will be used for efficacy analyses.

Safety Population

The safety population will include all randomized subjects who received at least one dose of study drug (active or placebo).

A last observation carried forward (LOCF) method will be utilized to impute missing values for subjects continuing in the study, but missing values for this analysis. This type of imputation replaces the missing value with the last observation value obtained. Baseline observation carried forward (BOCF) method will be used if a subject discontinues the study. Thus, if a subject has a missing value at month 2 due to discontinuation, the baseline value will be utilized and the subject will be considered a non-responder.

PRIMARY ENDPOINT

To compare the mean change from baseline in the frequency of migraine headache days per 28-day period ending with the cessation of treatment period month 3 in subjects treated with MLD10 versus placebo.

A migraine headache day will be defined as a calendar day (00:00 to 23:59) with 4 or more hours of migraine headache, fulfilling ICHD-3 beta criteria, and/or any headache of any duration with the use of migraine-specific acute medications(s) (i.e. ergot alkaloids, ergot combinations, opioids, triptans, combination analgesics [simple analgesics combined with opioids or barbiturate with or without caffeine]).

SECONDARY ENDPOINTS

1. To compare change from baseline of subjects treated with MLD10 versus placebo on the following parameters during or after a 3 month treatment period:
    - the frequency of headache days
    - the average headache duration after 1, 2, and 3 months of treatment
    - reduction of pain severity at the time of headache onset
    - the use of acute medications after 1, 2, and 3 months of treatment
    - Migraine Disability Assessment Scale (MIDAS) scores at Visits 2 and 5
    - Subject Global Impression of Change (SGIC) at Visit 5
    - Physician Global Impression of Change (PGIC) at Visit 5
2. To assess the safety and tolerability of magnesium-L-lacate-dihydrate versus placebo in migraine headache subjects through the comparison of adverse events.

EXPLORATORY ENDPOINTS

To compare the change from baseline of subjects treating with MLD10 versus placebo on the following parameters during a 3 month treatment period.

- migraine with aura days
- serum ionized magnesium

SAFETY ENDPOINTS

Safety assessments will include:

- adverse events

COLLECTION AND DERIVATION OF ENDPOINTS

Data required for the evaluation of endpoints will be recorded for the duration of the study using electronic data capture and included subject and clinician reported outcomes.

Following visit 2, subsequent visits will occur every 28 days for 3 months. However, in practice, there may or may not be an exact 28-day duration between 2 consecutive visits. For data analysis purposes, the number of migraine headache days during the first 28 continuous days of the run-in period will serve at the "baseline" for calculating change from baseline for 28-day periods subsequent to each office visit. If the run-in period (starting with the screening visit and preceding the day before visit 2) exceeds 28 days, the run-in period will include the last 28-days. In order to be randomized, a subject must meet 80% diary completion compliance (22 days recorded unless otherwise approved by the Sponsor and/or Clinvest).

Primary Efficacy Variable

The primary efficacy variable is the mean change from baseline in the frequency of migraine headache days per 28-day period ending with the cessation of treatment period month 3 in subjects treated with MLD10 versus placebo. This variable is derived from

the e-dairy. It is based on the count of days with migraine headaches, fulfilling ICHD-3 beta criteria, and/or headaches of any duration with the use of migraine-specific acute headache medication(s). The primary time point is treatment month 3, encompassing the last 28-day period before study end.

Secondary Efficacy Variables

- Change from baseline in the frequency of headache days per 28-day period. This variable will be derived from daily e-diary reports. It will be based on the count of days with headaches.
- Change from baseline in the total cumulative hours of headache per 28-day period. This variable will be derived from daily e-diary reports. It will be based on the sum of total headache duration for days with any headache.
- Change from baseline in the average pain severity at time of onset compared to each 28-day period. This variable will be derived from the daily e-diary reports.
- Reduction from baseline in the total number of acute headache pain medications used. This variable will be derived from the daily e-diary reports.
- Change from baseline in the total MIDAS score. This variable will be derived from the subject questionnaire.
- SGIC score at the end of treatment. This variable will be derived from the subject questionnaire.
- PGIC score at the end of treatment. This variable will be derived from the clinician reports.

APPENDIX 1
Proposed Revised International Headache Society Criteria for Migraine Without and With Aura

Headache Classification Committee: J Olesen, et al. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013, 33:629-808.

1.1 Migraine without aura

Description:

Recurrent headache disorder manifesting in attacks lasting 4-72 hours.

Diagnostic criteria:

A. At least five attacks1 fulfilling criteria B–D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
C. Headache has at least two of the following four characteristics:
1. unilateral location
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D. During headache at least one of the following:
1. nausea and/or vomiting
2. photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis.

1.2 Migraine with aura

Description:

Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually.

Diagnostic criteria:

A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms:
1. visual
2. sensory
3. speech and/or language
4. motor
5. brainstem
6. retinal

C. At least two of the following four characteristics:
1. at least one aura symptom spreads gradually over _5 minutes, and/or two or more symptoms occur in succession
2. each individual aura symptom lasts 5-60 minutes
3. at least one aura symptom is unilateral
4. the aura is accompanied, or followed within 60 minutes, by headache

D. Not better accounted for by another ICHD-3 diagnosis, and transient ischemic attack has been excluded.

APPENDIX II
Proposed Revised International Headache Society Criteria for Medication-Overuse Headache

Headache Classification Committee: J Olesen, et al. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia*. 2013, 33:629-808.

Description:
Headache occurring on 15 or more days per month developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more, or 15 or more days per month, depending on the medication) for more than 3 months. It usually, but not invariably, resolves after the overuse is stopped.

General comment:
In the criteria set out below for the various subtypes, the specified numbers of days of medication use considered to constitute overuse are based on expert opinion rather than on formal evidence.

Diagnostic criteria:
A. Headache occurring on _15 days per month in a patient with a pre-existing headache disorder
B. Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache
C. Not better accounted for by another ICHD-3 diagnosis.