

**STUDY TITLE: A Randomized Pilot Study of Nuedexta® for the Prevention
and Modification of Disease Progression in Episodic Migraine**

PROTOCOL NO: 14-001AV

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A Randomized Pilot Study of Nuedexta® for the Prevention and Modification of Disease Progression in Episodic Migraine

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 Randomized Pilot Study of Nuedexta® for the Prevention and Modification of Disease Progression in Episodic Migraine

SUMMARY OF RATIONALE

The purpose of this study is to evaluate the efficacy and effectiveness of daily dextromethorphan/quinidine (Nuedexta®) in reducing the frequency and progression of episodic migraine.

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. A total of 45 subjects will be randomized and enter the treatment phase receiving Nuedexta® or placebo in a 1:1 design. Diary assessments will collect pain severity, symptoms, acute medication usage, and unusual symptoms.

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 6-14 migraines, with or without aura, as defined by International Classification of Headache Disorders (ICHD) - 3beta (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

The oral capsule formulation of dextromethorphan/quinidine will be used. Subjects will be instructed to take one capsule daily for 7 days, then increase to twice daily.

BACKGROUND

Migraine is best conceptualized as a genetic vulnerability with the potential to become a chronic disease. The frequency of migraine attacks in the population ranges from one or two per year to daily. For many individuals migraine begins and remains throughout their lifetime as an episodic disorder. However, for a significant population of migraineurs, over time, migraine becomes increasingly more frequent and eventually evolves from its episodic form into its highly disabling chronic form or chronic migraine. Chronic migraine creates significant disability, which can be measured both during and between attacks of migraine. The personal and socioeconomic impact of migraine increases dramatically as migraine becomes more frequent and chronic.

Treatment of migraine has historically been divided into acute and preventive. Acute treatment is directed at terminating a migraine attack after it has begun while preventive therapies are used to decrease the nervous system's susceptibility to migraine being initiated or triggered. Demarcation of this distinction has recently been blurred as some acute medications such as triptans have been successfully used to prevent migraine and some preventive medications such as valproic acid have been used in acute treatment.

The pathophysiology of migraine is not completely understood but numerous central and peripheral factors and neurotransmitters are known to be involved. Recently there has been increasing interest in the excitatory amino acid glutamate. Glutamate as a free amino acid is released from activated neurons, and is involved peripheral and central sensitization as well as cortical spreading depression. Furthermore, higher levels of glutamate have been found in the brains of patients with migraine (Gonzalez 2013). Upon release from neurons glutamate binds to NMDA and AMPA receptors, activating a variety of inflammatory pathways implicated in migraine. The less studied Sigma-1 receptor is involved in calcium signaling and is also implicated in pain processing. Selective antagonists to the sigma-1 receptor have been effective at reducing nociception and orofacial pain behaviors in animal models (Kwon 2009, Roh 2013). Nuedexta® is a potent NMDA and Sigma-1 receptor antagonist with high CNS availability with a long half-life. Nuedexta® is indicated for pseudobulbar affect which is sudden episodes of inappropriate crying or laughter associated with several neurological diseases.

This study proposes to evaluate the effectiveness of daily dextromethorphan/quinidine (Nuedexta®) in reducing the frequency and progression of frequent episodic migraine.

PRIMARY OBJECTIVE

To evaluate the daily use of Nuedexta® and placebo for the treatment of migraine, as measured by the average number of headache days per month.

SECONDARY OBJECTIVES

To compare daily use of Nuedexta® and placebo as measured by:

1. change in the number of headache days reported from baseline to the end of treatment.
2. change in the number of migraine days per month at each interim visit.
3. change in headache severity per month at each study visit.
4. change in headache duration reported during baseline to each study visit.
5. the number of subjects with at least a 50% reduction in number of headache days from baseline to each month.

6. change in total number of doses of acute medication taken per month.
7. compare the total number of adverse events.
8. comparing MIDAS scores at Visit 2 vs. Visit 5.
9. changes in the Headache Health Score from baseline to each study visit.

SUBJECT SELECTION

Approximately 45 adult subjects 18 years and older who meet criteria for episodic migraine with or without aura, as defined by International Classification of Headache Disorders, 3rd edition (ICHD-3beta), and with 6-14 migraines per month will be enrolled in the study. All subjects will be monitored through the use of electronic diaries for one month prior to treatment to ensure they meet inclusion and exclusion criteria, as well as meet at least an 80% participation in diary procedures.

INCLUSION CRITERIA

Subject is/has:

1. male or female, in otherwise good health, 18 to 65 years of age.
2. history of frequent episodic migraine for at least 3 months as defined by 6-14 migraine days per month with or without aura according to the ICHD-3beta or a migraine treated with an ergot or triptan which resulted in relief.
3. onset of migraine before age 50.
4. stable history of headache at least 3 months prior to screening.
5. if using daily migraine preventive medications for migraine or for other medical conditions (e.g. propranolol being used for hypertension) and has been on a stable dose and regimen for at least 2 months prior to beginning the baseline period.
6. female, of childbearing potential, and agrees to maintain true abstinence or use (or have their partner use) one of the listed methods of birth control for the duration of the study: hormonal contraceptive, intrauterine device (IUD), condoms, diaphragm, and/or vasectomy. The use of barrier contraceptive (condom or diaphragm) should always be supplemented with the use of a spermicide.

Note: To be considered not of childbearing potential, subject must be 6 weeks post-surgical bilateral oophorectomy, hysterectomy, or bilateral tubal ligation, or postmenopausal for at least one year.

EXCLUSION CRITERIA

Subjects will be excluded from the study if any of the following criteria apply.

Subject is/has:

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. female of childbearing potential not using adequate contraceptive measures.
4. experienced the following migraine variants: basilar migraine, aura without headache, familial hemiplegic migraine, complicated migraine, ophthalmoplegic migraine and retinal migraine.
5. history of Medication Overuse Headache (Appendix II) in the 3 months prior to study enrollment or during the baseline phase.
6. history of acute migraine treatment greater than 14 days per month in 3 months prior to screening.

7. history of 3 or more failed preventative medications due to lack of efficacy for prophylactic treatment of migraine after an adequate therapeutic trial.
8. received onabotulinumtoxinA injections within 3 months prior to screening and/or will receive onabotulinumtoxinA injections during the study.
9. abused, in the opinion of the Investigator, any of the following drugs, currently or within the past 1 year: opioids, alcohol, barbiturates, benzodiazepine, cocaine.
10. taken, or plans to take: a monoamine oxidase inhibitor (MAOI) including herbal preparations containing St. John's wort (*Hypericum perforatum*) within 14 days of Visit 1, concomitant medications and/or foods containing dextromethorphan, quinidine, quinine, mefloquine, paxil, dicyclomine, digitalis, thioridazine or pimozide (medications that prolong QT interval) anytime within the 2 weeks prior to screening through 2 weeks post final study treatment.
11. history of hypersensitivity to medications containing dextromethorphan.
12. history of hypersensitivity to medications or foods containing quinidine.
13. at an increased risk of developing serotonin syndrome, in the opinion of the investigator.
14. history of impaired hepatic or renal function that, in the investigator's opinion, contraindicates participation in this study.
15. unstable neurological condition or a significantly abnormal neurological examination with focal signs or signs of increased intracranial pressure.
16. cardiovascular disease (ischemic heart disease, including angina pectoris, myocardial infarction, documented silent ischemia, or with Prinzmetal's angina); has symptoms of ischemic heart disease, ischemic abdominal syndromes, peripheral vascular disease or Raynaud's Syndrome.
17. ECG results outside normal limits (> 470 msec), prolonged QT interval, congenital long QT syndrome, torsades de pointes, or complete AV block.
18. has uncontrolled hypertension ($\geq 140/90$ mmHg in either the systolic or diastolic measurements in 2 out of 3 BP readings at screening).
19. serious illness, or an unstable medical condition, one that could require hospitalization, or could increase the risk of adverse events, in the opinion of the investigator.
20. any psychiatric disorder with psychotic features and any other psychiatric disorder not stable or well controlled, that would interfere in their ability to complete study activities.
21. received any investigational agents within 30 days prior to Visit 1.
22. plans to participate in another clinical study at any time during this study.

STUDY DESIGN

This is a double-blind, placebo-controlled, randomized, multi-center study to be conducted at headache clinics and clinical research centers in the United States. Approximately 45 subjects, 18 to 65 years of age, with frequent episodic migraine (6-14 days per month), with (1.2) or without aura (1.1) as defined by ICHD-3beta, will enter a 1-month baseline period to confirm the migraine diagnosis, as well as establish baseline characteristics. At Visit 1, subjects must not have a history of utilization of acute treatment greater than 14 days per month in the preceding 3 month period. Subjects must have a current history of ICHD-3beta migraine with 6-14 migraine days per month in the 3 months prior to the study enrollment. Eligible subjects will be randomly assigned to one of two groups in a 1:1 ratio. Randomization will occur using a computer-

generated allocation schedule. Subjects meeting entrance criteria as determined both at screening and through the review of the baseline headache diary will be given the lowest available allocation number for that site. Migraine preventative use is permitted if the subject has been on a stable dose for at least 2 months prior to screening and has not failed more than 3 migraine preventatives due to lack of efficacy. The study will consist of 5 office visits per subject: Visit 1 - screening, Visit 2 - randomization, and Visits 3 to 5 - three-month treatment period. During the baseline period, the subject will treat migraines with their current preferred acute treatment of choice.

INFORMED CONSENT

The investigator must obtain documented consent from each potential subject, 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, along with copies of how to take the study medication.

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

At Visit 1 following informed consent, a physical and neurological exam, vital signs, urine pregnancy test, if appropriate, and an ECG will be completed. Medical, migraine and medication history will be collected. Prohibited medications will be reviewed. Subjects will be given instruction on how to access the online diary and complete a test diary. All eligible subjects will participate in a 28 day baseline period and complete a daily headache diary to report migraine symptoms, migraine pain severity, and quantity of medications being used. Subjects will be required to obtain an 80% diary completion rate in order to continue in the study.

Note: Subject diaries are to be completed by the subject only. At each visit, the subject diary will be thoroughly reviewed by a delegate to ensure diary compliance standards are met.

VISIT 2-RANDOMIZATION/TREATMENT PERIOD

At Visit 2, day 28 \pm 3, subjects will return for randomization. Any change in medical or medication history since the previous visit will be recorded and a urine pregnancy test will be performed, if appropriate. Vital signs will also be collected. The subject's baseline diary will be reviewed. Medications and unusual symptoms reported on the subject's diary will be added to the medication and or adverse event pages if necessary. Subjects must have six or more migraine days during the baseline period to be eligible for randomization at Visit 2. Subjects continuing to meet eligibility criteria will be instructed to complete the online treatment period headache diary daily. Subjects will be administered the MIDAS. Those meeting eligibility criteria will be randomized to take either Nuedexta® (Group A) or placebo (Group B) on a daily basis for 84 days. Subjects will be instructed on how to take medication, dosage, storage

requirements, and to return all used/partially used/unused medication containers at the next office visit. Prohibited medications will be reviewed and study medication will be dispensed.

VISITS 3 AND 4-TREATMENT PERIOD

At Visit 3 (day 57 \pm 3) & Visit 4 (day 85 \pm 3), any change in medication or medical history will be collected. A urine pregnancy test will be performed, if appropriate. The subject's diary will be reviewed for an 80% compliance rate. Medications and unusual symptoms reported on the subject's diary will be added to the medication and or adverse event pages if necessary. Drug accountability will be performed and study medication will be dispensed for the next 28 day period. Adverse events will be collected.

VISIT 5-FINAL VISIT

At Visit 5 (day 113 \pm 3), any change in medication and/or medical history will be collected. A urine pregnancy test will be performed, if appropriate. The subject's diary will be and any medications and unusual symptoms will be added to the appropriate form if necessary. Drug accountability will be performed and adverse events will be collected. The MIDAS will be administered.

Table 1. Study Procedures

	Visit 1 (Day 0)	Visit 2 (Day 28)	Visit 3 (Day 57)	Visit 4 (Day 85)	Visit 5 (Day 113)
Informed Consent	X				
Physical/Neurological Exam	X				
12-lead ECG	X				
Vital Signs	X	X	X	X	X
Inclusion/Exclusion Criteria	X	X			
Subject Randomization		X			
Medical History	X				
Migraine History	X				
Medication History	X				
Update Medical, Migraine and Medication History		X	X	X	X
Pregnancy Test	X	X	X	X	X
Dispense Study Medication		X	X	X	
Perform Drug Accountability			X	X	X
Dispense Diary	X				
Review Diary		X	X	X	X
Collect Adverse Events		X	X	X	X
Administer MIDAS		X			X

STUDY MEDICATION

At Visit 2, subjects will be randomized 1:1 to either Nuedexta[®] (Group A) or placebo (Group B). Both groups will receive a one month (28 day) supply of study medication. Both groups will take the study medication in the morning for first 7 days following randomization. Beginning on day 8 all subjects will take study medication every 12 hours for the duration of the study. Subjects will return at the end of each month. A one-month supply of medication will be provided at Visits 3 and 4. Subjects will be instructed on how to take medication, dosage, storage requirements, and to return all used/partially used/unused medication containers at each office visit. Subjects will be instructed to contact the study site if they discontinue/fail to take study medication for more than two days and investigator will assess clinical significance.

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.

Table 2. Prohibited Medications

Timeframe for Exclusion	Medication
<ul style="list-style-type: none"> • 14 days prior to beginning the study • Throughout the study • 14 days post study medication dose 	MAOI, St. John's Wort, drugs and or foods containing: dextromethorphan, quinidine, quinine, mefloquine, paxil, dicyclomine, digitalis, thioridazine, and pimozide

CONCOMITANT MEDICATIONS

Therapy considered necessary for the subject's welfare may be given at the discretion of the investigator.

Subjects may take acute headache medications as prescribed; however, this should be recorded on the daily headache diary and concomitant headache medications log.

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

HEADACHE DIARY

The primary and much of the secondary endpoints will be derived from the electronic daily 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 record headache severity, symptoms, use of acute medications, as well as additional questions as required. Headache severity will be subjectively rated by the subject at predefined time points as follows: no pain, mild pain, moderate pain, or severe pain.

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.

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 zip lock bag 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 envelope.
- Return the envelope to the zip lock bag.
- 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, supplies, and documents 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 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 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, before being withdrawn from the study. The investigator will (1) notify the subject's physician that the subject was being treated with an investigational drug Nuedexta[®] 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, Avanir, 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, Avanir, and Sterling IRB within 48 hours of knowledge of the event by study staff.

Included in the SAE Report Form will be an assessment of the causal relationship between the Avanir 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 Avanir.

DATA ANALYSIS

The statistical analysis of the data obtained from this study will be the responsibility of Clinvest. For the purpose of the final analysis, the database will not be unblended until medical/scientific review has been completed and data has been declared "clean".

PRIMARY ENDPOINT

Change in the average number of headache days at treatment period months 1, 2, and 3 (28 day period for each month) compared to baseline (28 day run-in period) in the Nuedexta[®] arm vs. the placebo arm.

SECONDARY ENDPOINTS

1. Change in the number of headache days reported in baseline compared to the end of treatment period, month 3 (28 day period), in the Nuedexta[®] arm vs. the placebo arm.
2. Change in the average number of migraine days at treatment period months 1, 2, and 3 (28 day period for each month) compared to baseline in the Nuedexta[®] arm vs. the placebo arm.
3. Change in average headache severity per month comparing baseline to each treatment period month: 1, 2, and 3 (28 day period for each month) in the Nuedexta[®] arm vs. the placebo.
4. Change in mean headache duration (time of onset to pain free) comparing baseline to each treatment period months 1, 2, and 3 (28 day period for each month) in the Nuedexta[®] arm vs. the placebo.
5. The number of subjects with at least a 50% reduction in number of headache days comparing baseline to each visit (treatment period months 1, 2, and 3: 28 day for each month) in the Nuedexta[®] arm vs. the placebo arm.
6. Change in the total number of doses of acute medication taken per month comparing baseline to treatment period months 1, 2, and 3 (28 day period for each month).
7. Compare the number of adverse events in the Nuedexta[®] arm vs. the placebo arm.
8. MIDAS scores at Visit 2 vs. Visit 5 (end of treatment period month 3).
9. Changes in the Headache Health Score at baseline, month 1, month 2, and month 3 (28 day period for each month) post treatment for the Nuedexta[®] arm vs. the placebo arm.

APPROACHES TO ANALYSIS

The primary analysis will use a full data set. This analysis will include all randomized subjects who have at least one assessment in the treatment period. In cases where the daily diary are not completed, it will be assumed no migraine headache pain was experienced by the subject that day.

An exploratory per-protocol analysis may be performed to establish the robustness of conclusions from the primary efficacy analysis by excluding subjects whose violations of the protocol would significantly impact the outcome of the study due to the violation and not in direct relation to the study medication.

All subjects treated will be included in the safety and demographic analysis.

STATISTICAL METHODS

Descriptive statistics will establish baseline characteristics and adverse event frequency. A mixed factorial repeated measures ANOVA will be performed to detect differences among each time point for the primary and secondary endpoints. Post hoc analyses will be conducted as appropriate. Chi-Square and two-tailed t-tests will also be used to measure the significance of the differences in response rate between group A and B for the primary and secondary endpoints. Subgroup analysis of the type and frequency of rescue medication on primary and secondary

endpoints will also be performed. All analyses will be considered statistically significant $p \leq .05$. All data assumptions will be verified and nonparametric methods may be employed if deemed appropriate.

CLINICAL SUPPLIES

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

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.

At the end of study, all supplies including partial and empty containers must be returned to Clinvest.

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 with 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 agree 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

By signing this protocol, Clinvest agrees to be responsible for implementing and maintain 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. The study will be registered on www.clinicaltrials.gov by Clinvest.

STUDY DOCUMENTATION AND 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.

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. Clinvest will notify the investigator in writing when retention is no longer necessary.

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. 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 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

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.

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. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

- A. At least 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 and are usually followed

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 \geq 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 ischaemic 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.