Allodynic THERAPEUTICS

CLINICAL STUDY PROTOCOL

A Migraine Prevention Study (ANODYNE-3)

A Single Center, Phase 2B, Randomized, Double Blind, Study to Assess the Efficacy, Safety, and Tolerability of Oral Twice Daily ALLOD-2 vs. Placebo in the Prevention of Episodic Migraine in Adults

Brief Title:

Efficacy, Safety, and Tolerability of Twice Daily Oral ALLOD-2 vs. Placebo in Episodic Migraine Prevention (ANODYNE-3)

The Study's Treatment Groups:

Experimental: Naltrexone [redacted] *mg/acetaminophen* [redacted] *mg (ALLOD-2),*

Placebo comparator: Placebo.

Study Phase: 2B

Investigational New Drug (IND) number: [redacted]

Study and Protocol Name: ANODYNE-3

Version 1.0, Submitted to DNP on May 5, 2017

Version 1.1, Approved by IRB on July 28, 2017

ALLOD-2 is being investigated for treatment of chronic low back pain [redacted]

ClinicalTrials.gov Identifier: NCT03194555

Sponsor/Investigator: Annette C. Toledano, M.D.

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Study Pharmacist: Ayman Mohamed, [redacted]

Contact Dr. Mohamed in the event of need to unmask a study participant

Study IRB: Schulman Associates IRB, Inc., 888-557-2472, 8 a.m.-6 p.m., M-F

Study Protocol Signature Page

The Allodynic Therapeutics representative listed below has approved this protocol

Annette C. Toledano, MD	Allodynic Therapeutics, LLC
Role:	Protocol Author, Sponsor
Signature:	Date:

Protocol Title: A Single Center, Phase 2B, Randomized, Double Blind, Study to Assess the Efficacy, Safety, and Tolerability of Oral Twice Daily ALLOD-2 vs. Placebo in the Prevention of Episodic Migraine in Adults.

Investigator Agreement:

I have read and understood this Allodynic Therapeutics protocol, including all appendices, attachments, and the Investigator's Brochure.

I fully understand the objective(s) of this study. I clearly and unequivocally understand that all information contained in this protocol is confidential and shall not be disclosed without prior written authorization of the sponsor. Disclosure to a patient of this study may only be permissible for purposes of obtaining a patient's consent to participate in this Study.

I agree to conduct all aspects of this Study in adherence with this protocol and the in accordance of the terms outlined in the Clinical Study Site Agreement. I agree to conduct this study in accordance with Good Clinical Practices, including ethical and safety considerations. I will ensure that all individuals assisting with the study are adequately trained.

I acknowledge, agree, and understand that premature termination or suspension of this study may occur at any time for whatever reason, with or without cause, by the sponsor. Notice of such termination or suspension shall be communicated to me in writing. However, in the event of my withdrawal from this study or execution thereof, I shall immediately communicate my decision or intent in writing to the sponsor without undue delay.

I agree to keep records on all patient information (case report forms, shipment and drug return forms, and all other information collected during the study) in accordance with the current GCP and local regulations.

Should any discrepancy arise between this study protocol and the Clinical Study Site Agreement, the terms of study protocol shall prevail regarding the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Site Agreement shall prevail.

Annette C. Toledano, MD	Investigator
Signature:	Date:

Protocol Synopsis

The Product	The Investigational Product, code-named, ALLOD-2 is a solid oral fixed dose combination of naltrexone hydrochloride [redacted] mg with acetaminophen [redacted] mg.
Study Name	ANODYNE-3
Protocol Nº	ANODYNE-3, Version 1.1
Study Phase	2B
Brief Title	Efficacy, Safety, and Tolerability of Twice Daily Oral ALLOD-2 in Episodic Migraine Prevention (ANODYNE-3)
Study Title	A Single Center, Phase 2B, Randomized, Double Blind, Study to Assess the Efficacy, Safety, and Tolerability of Oral Twice Daily ALLOD-2 vs. Placebo in the Prevention of Episodic Migraine in Adults
Indication	Prevention of episodic migraine with or without aura in adults.
Brief Description of the Investigational Product	ALLOD-2 is an investigational combination of a Toll-Like Receptor-4 (TLR4) antagonist, naltrexone hydrochloride, with a highly selective Cyclooxygenase-2 (COX-2) inhibitor, acetaminophen, intended for use in this study for prevention of episodic migraine associated with moderate to severe nausea. Naltrexone is an opioid antagonist[1], which has been marketed in the United States for treatment of opioid and alcohol dependence since 1984. However, the whole time, its analgesic properties have not been wildly acknowledged. Recent basic science research found naltrexone to act also as a TLR4 antagonist, which is the purported mechanism of action of its analgesic action. Acetaminophen was first approved in the United States in 1955, by 1972; acetaminophen was already established for OTC use for temporary relief of minor aches and pains associated with the common cold, headache pain, toothache, muscular aches, and backache.[2] Naltrexone and Acetaminophen inhibit two distinct neuro-inflammation producing targets in the TLR4 signaling cascade pathway. Naltrexone inhibits TLR4-induced release of pro-inflammatory cytokines, and acetaminophen, inhibits TLR4-induced COX-2 expression. Both components are present in the Investigational Product in an immediate-release formulation.
Mechanism of Action	TLR4 detects and reacts to endogenous ligands that occur after tissue injury or cellular stress, known as damage-associated molecular patterns

[1] ReVia® (naltrexone hydrochloride; NDA 18-932)
[2] 1953 NDA 08-717 (acetaminophen tablet)

	(DAMPs).[3] Activation of the TLR4 signaling pathway in the glia induces release of pro-inflammatory cytokines [nitric oxide (NO), tumor necrosis factor-α (TNF-α), and reactive oxygen species (ROS)][4] causing neuro-inflammation. In addition, activation of the TLR4 signaling pathway induces expression of COX-2 (the TLR4-COX-2-prostaglandin E2 axis[5]), also causing neuro-inflammation. TLR4 induced neuro-inflammation nearby spinal nerve roots or the trigeminal nerve system leads, in predisposed individuals, to neuropathic pain, manifested clinically as radicular back pain or migraine (and other clinical presentations). There is a strong biological rationale for the use of naltrexone and acetaminophen in combination since each inhibits a distinct target in the same molecular pathway[6] (the TLR4 signaling cascade). TLR4 activation in response to endogenous DAMPs is another example of exuberant innate immunity response that is detrimental to the host. Naltrexone and acetaminophen calm the immune over-activation and neuro-inflammation nearby spinal nerve roots and the trigeminal nerve system eliminating back pain and migraine. In patients suffering from chronic back pain, an injury nearby a spinal nerve root (e.g., disk herniation) can activate TLR4 and cause neuropathic pain along its anatomical distribution.
Clinicaltrials.gov summery (Identifier: NCT03194555)	While many individuals are able to limit therapy to treatment of migraine attacks, others need medication to reduce the frequency and/or severity of attacks. Patients with prolonged or severe attacks leading to substantial disability, or patients who are refractory to abortive treatments can benefit from migraine prevention. The investigational product is a combination of two re-purposed marketed drugs used for migraine prevention through the discovery of biologically and clinically relevant affinity for new targets. Both drugs are being re-purposed at a significantly lower dosage compared to the approved marketed indications dosage. The combination is a First-in-Class drug due its new and unique mechanism of action. The investigators propose that in predisposed individuals, migraine attacks occur due to exuberant innate immune system activation nearby

[3] Liu T, Gao YJ, Ji RR. Emerging role of Toll-like receptors in the control of pain and itch. Neurosci Bull. 2012;28:131-44.
[4] Wang X, Zhang Y, Peng Y, et al. Pharmacological characterization of the opioid inactive isomers (+)-naltrexone and (+)-naloxone as antagonists of toll-like receptor 4. Br J Pharmacol. 2016;173(5):856-69.
[5] Hernandez Y, Sotolongo J, Fukata M. Toll-like receptor 4 signaling integrates intestinal inflammation with tumorigenesis: lessons from the murine model of colitis-associated cancer. Cancers (Basel). 2011;3(3):3104-13.
[6] Draft guidance for Industry for Co-development of Two or More New Investigational Drugs for Use in Combination
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/gui%20dances/ucm236669.pdf

	the trigeminal nerve and other cranial nerves. The innate immunity activation leads to release of pro-inflammatory cytokines [nitric oxide (NO), tumor necrosis factor-α (TNF-α), and reactive oxygen species (ROS)], and to COX-2 activation, which produces neuro-inflammation, causing pain and various migraine-associated symptoms. ALLOD-2 reverses the neuro-inflammation through dual action, inhibition of the release of the pro-inflammatory cytokines and inhibition of the COX-2 activation. Efficacy of this product for migraine headache pain and for migraine-associated symptoms, especially nausea (which is refractory to other known migraine treatments), may suggest the product addresses the root cause of migraine.
Definitions	Migraine with or without aura is defined according to the International Classification of Headache Disorders (ICHD)-3rd edition (beta version). Probable migraine is defined according to the ICHD – 3 (beta version) criteria, as attacks fulfilling all but one of criteria A-D for migraine with or without aura, where criteria B is headache attacks lasting 4-72 hours (untreated or unsuccessfully treated). A migraine/probable migraine headaches must be moderate or severe and lasting ≥30 minutes. When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening.
Study Objectives	The primary objective is to compare the reduction in the mean migraine/probable migraine headache days from baseline to the last 28 days of the 12-week Treatment Period. A secondary objective is to compare the reduction in the mean headache days from baseline to the last 28 days of the 12-week Treatment Period. Another secondary objective is to compare the reduction in the mean proportion of patients responding to treatment (as measured by a 50% or more reduction in 28-day migraine frequency) from baseline to the last 28 days of the 12-week Treatment Period. Another secondary objective is to compare the reduction in the mean migraine headache severity, headache duration, nausea severity, light sensitivity, noise sensitivity, and number of days of rescue medications intake from baseline to the last 28 days of the 12-week Treatment Period. Another secondary objective is to compare the reduction in the mean migraine disability assessment scale (MIDAS) and headache impact test (HIT-6) from baseline to End-of-Treatment Visit. An exploratory objective is to compare the reduction of mean Pittsburgh Insomnia Rating Scale-20 (PIRS-20) from baseline to End-of-Treatment Visit.

Concomitant Emotional Pain and/or Chronic Low Back Pain (CLBP)	Pilot study data demonstrated emotional pain relief by the investigational product. The investigator postulates that the investigational product relief of emotional pain is greater than that of acetaminophen alone. Additionally, pilot study data demonstrated efficacy of the investigational product for CLBP. Patients found at the screening visit to have concomitant emotional pain co-existing with episodic migraine would be asked to complete an emotional daily diary as well as the migraine prevention daily diary. The stressors causing emotional pain, as explained to patients include adjustment to new life for immigrants, adjustment to separation from children who recently left home, or adjustment to loss of a pet. These complaints are currently treated with psychotherapy. The ICD-10-CM diagnosis code is F43.20 “adjustment disorder, unspecified”. Additionally, patients with concomitant emotional pain will complete the Beck's Depression Inventory instrument on every site visit. If a patient is found at the screening visit to have concomitant CLBP co-existing with episodic migraine they will be asked to complete a CLBP daily diary as well as the migraine prevention daily diary. (See the attached daily diary forms). Additionally, patient with concomitant CLBP will complete the Oswestry Disability Index instrument on every site visit.
The Study Treatment Groups	Patients will be randomized to one of two treatment groups: 1. Naltrexone [redacted] mg/acetaminophen [redacted] mg (ALLOD-2), 2. Placebo. Comparing the naltrexone/acetaminophen group to the placebo group will provide data to support efficacy of the product for episodic migraine prevention. The study plans to enroll 48 patients randomized to one of two treatment groups in a ratio of 1:1 for 24 patients in each group. Investigators, site personnel, and patients will be masked to the treatment assignment.
Pre-Enrollment Migraine-Assessment	The investigator will obtain medical records confirming a diagnosis of migraine (physician’s note, pharmacy records for migraine specific medications, etc.). Additionally, the investigator will review the completed migraine intake form. The investigator will forward anonymized medical records and the completed migraine intake form to the sponsor prior to enrolling a patient.
Study Population	The study population will include non-pregnant, non-lactating females and males. Both must be 18 years of age or older. Patients have an average of at least 4 moderate-to-severe migraine episodes but 15 or less headache days per month in the previous 3 months and during the baseline period. Patients have history of migraine with or without aura according to the International Classification of Headache Disorders (ICHD)-3rd edition (beta version) for at least one-year with onset of migraine prior to age 50

<table>
<tr><td></td><td>years of age.
Patients with coexisting types of headache pains (e.g., tension-type headache) can be included if they can distinguish migraine headache from the other headaches.
Patients must have high-frequency moderate to severe migraine-associated nausea (i.e., associated nausea ≥ half the migraine attacks) to be admitted into the study. Patients who experience vomiting can be admitted, however, they will be advised that vomiting within 30 min after taking the study drug can purge the study drug. Patients will be asked to take the study drug when they can assume that they will not vomit within 30 mins.
Patients who in the opinion of the investigator may have medication-overuse headaches (as defined by ICHD – 3 (beta version) criteria for medication-overuse headache. The definition of medication overuse for this study is usage of ≥15 days/month of acetaminophen, NSAIDs, or usage of ergotamine, and triptans <10 days/month or usage of opioids and barbiturates >2 days/month during the 3 months preceding screening or during the baseline period.
Patients who in the opinion of the investigator, have chronic migraine (as defined by ICHD – 3 (beta version) criteria for chronic migraine) (headache, tension-type-like and/or migraine-like on ≥15 days per month) during the 3 months preceding screening or during the baseline period will be excluded.
In addition, patients using any disallowed concomitant medications or patients who used an investigational medication within 4 weeks before the Screening Visit will not qualify.
Care should be taken to exclude other potentially serious neurologic conditions before enrolling patients not previously diagnosed with migraine headache or who experience headache that is atypical for them.</td></tr>
<tr><td>Study Duration</td><td>The study includes seven site visits and five telephone contacts occurring over a 5-month period.
<u>Study visits schedule:</u>
<table>
<tr><td></td><td>Visit-1, Screening Visit</td><td>Visit-2, randomization Visit</td><td>Visit-3, Treatment Period Visit</td><td>Visit-4, Treatment Period Visit</td><td>Visit-5, Treatment Period Visit</td><td>Visit-6, End of Treatment Period Visit</td><td>Visit-7, Post-Treatment Period Visit</td></tr>
<tr><td>Study Day</td><td>-28</td><td>0</td><td>7</td><td>28</td><td>56</td><td>84</td><td>112</td></tr>
<tr><td colspan="8">All visits may have ±5-day visit window except visit-6, which must take place no sooner than 84 (+5 days) from the beginning of the double-blind Treatment Period. Day 84 of the Treatment Period is considered the last day of treatment for data analysis purposes.</td></tr>
</table>
<u>Telephone contacts Schedule:</u>
<table>
<tr><td>Telephone contacts</td><td>Phone-1, Baseline Period</td><td>Phone-2, Treatment Period</td><td>Phone-3, Treatment Period</td><td>Phone-4, Treatment Period</td><td>Phone-5, Post Treatment Period</td></tr>
<tr><td>Study Day</td><td>-21</td><td>14</td><td>42</td><td>70</td><td>98</td></tr>
<tr><td colspan="6">All Phone Visits may have ±2-day visit window.</td></tr>
</table></td></tr>
</table>

Study Design	This is a 20-week, single-center, double blind, randomized, placebo-controlled, parallel-arm study for patients requiring migraine prevention. Patients will be treated for 12-weeks with oral BID combination of naltrexone [redacted] mg/APAP [redacted] mg or placebo. The study consists of three study periods: a 28-day baseline period, a 12-week double blind Treatment Period, and 28-day Post-Treatment Follow-up Period. The 28-day duration of the baseline period is designed to assess the baseline frequency and severity of migraine. The 12-week duration of the Treatment Period is designed to meet the requirement for a migraine prevention studies. A 28-day Post-Treatment Follow-up Period is designed to assess any safety issues with the study drug. Additionally, it will assess whether there is a carry-over effect of the study drug on migraine prevention. Given the risk for both naltrexone and acetaminophen to cause hepatotoxicity, laboratory assessments (hematology, hepatic and renal function).will be obtained pre-dose (Visit 1) and monthly thereafter (i.e., Visit 4, Visit 5, and Visit 6). On Day 0 of the Treatment Period, (the day of Visit 2), patients will take the first dose of the study drug at home at 8:00 p.m. Patients will complete the Migraine Diary assessments approximately at 10:00 p.m. or at bedtime every day (whichever is earlier) every day of the study. During each visit of the study, except Visit 3, patients will complete the Headache Impact Test (HIT-6). Patients will complete the Pittsburgh Insomnia Rating Scale-20 (PIRS-20) every site visit. Patients will complete the Migraine Disability Assessment Scale (MIDAS) On Visit 1, 2 and 6. Patients will and receive study drug on visit 2, 3, 4 and 5. **Study Visit 1 - Screening Visit:** during this visit, patients who met inclusion/ exclusion criteria will give an informed consent after the nature of the study is explained and before any study-specific procedures are performed. During the screening visit, the investigator will obtain medical history, migraine headache history, history of substance abuse and/or dependency, and medication history. In addition, the investigator will perform a complete physical examination, vital signs measurements, a 12-lead ECG, a urine drug screen, and a urine pregnancy test (for childbearing age females). Additionally, the investigator will draw blood sample for laboratory assessments, (hematology, hepatic and renal function). The 5-panel urine drug screen (cocaine, marijuana, opiates, methamphetamines, and Oxycodone) and the pregnancy test must be negative to continue with the screening visit procedures. At the screening visit, the MIDAS score must be higher than 11, (moderate or severe disability), and the HIT-6 score, must be higher than 56 (substantial or very severe impact).

	During the Screening Visit, the investigator will go over the following items: • How to rate the intensity of headache pain, nausea and satisfaction with migraine prevention on a 4-point (0-3) scale. • How to rate light sensitivity, noise sensitivity, neck/shoulder pain, and vomiting as absent or present. • How to distinguish migraine headache from non-migraine headache. • How to take rescue medications, wait ½ hour after a migraine started before taking their own usual migraine medications. • How and when to complete the Migraine Diary assessments. • How to record rescue medications. • About the "placebo effect." The investigator will enroll only patients into the baseline period if they demonstrate ability to complete the Migraine Diary. At the conclusion of the Screening Visit, patients will receive a paper migraine diary to be completed daily for a 28-day baseline period. Patients will have a phone contact on day 8 and day 15 of the baseline period. After completion of the 28-day baseline period patients will return for the Randomization Visit. **Study Visit 2 - Randomization Visit:** In this visit, the investigator will review the baseline period Migraine Diary. Patients who had at least 4 moderate-to-severe migraine episodes, but 15 or less headache days during the 28-day baseline period and continued to meet all other inclusion and exclusion criteria will be eligible for randomization. Patient must complete the assessments for all the 28 days of the baseline period to qualify for randomization. In addition, at the Randomization Visit, the MIDAS score must be higher than 11, (moderate or severe disability), and the HIT-6 score must be higher than 56 (substantial or very severe impact). During the Randomization Visit, the investigator will go over the following items: • How to take the study drug. • How to take rescue medications, (wait ½ hour after a migraine started before taking own usual migraine medications). • How to record rescue medications. Patients will be randomized in a 1:1 ratio to naltrexone [redacted] mg/acetaminophen [redacted] mg (ALLOD-2) or placebo and enter into the 12-week Treatment Period. Randomized patients will receive a paper Migraine Diary form and a blinded study drug to use in the outpatient settings. **Study Visit 3 – 1 week after the Treatment Period started:** during this visit, the investigator will confirm the patient understands of how to take

	the study drug and how to complete the Migraine Diary. During this visit, assessment of adverse events and adjustment to the study drug dosage will be made. **Study Visits 4 and 5:** these visits will occur on days 28, and 56 (±5 - day visit window) of the Treatment Period. Additionally, there will be telephone contacts two weeks after these visits (±2 - day visit window). **Study Visit 6 - End-of-Treatment Period Visit:** This visit will take place no sooner than day 84 (+5 days) from the beginning of the Treatment Period. During this visit, patients final count and reconciliation of the study drug. **Study Visit 7 - End-of-Study Visit:** This visit will take place on day 28 (+5 - day visit window) of the Follow-up Period. During the Follow-up Period, patients will continue to complete the daily diary, but they will not consume the study drug.
The Migraine Diary assessments and other study assessments	**The Migraine Daily Diary assessments:** • Study drug morning dose consumption • Study drug evening dose consumption • Presence of a headache, (yes/no). • Start time and the end time of the headache. • Intake of additional migraine medications. • Severity of the headache pain, (0=none; 1=mild; 2=moderate; 3=severe). • Severity of the nausea/vomiting, (0=none; 1=mild; 2=moderate; 3=severe). • Presence One-sided headache, (yes/no). • Pulsating quality, (yes/no). • Worsening with activity (yes/no). • Light sensitivity, (yes/no). • Noise sensitivity, (yes/no). • Neck pain, (yes/no). **Other assessments:** • Migraine Disability Assessment Scale (MIDAS), (3-month assessment) Visits 1, 2 and 6. • Headache Impact Test (HIT-6), (4 week assessment) every visit except Visit 3. • Pittsburgh Insomnia Rating Scale-20 (PIRS-20), (7-day assessment) every visit. • Patient Global Impression of Change (PGIC) • Patient satisfaction with migraine prevention, Visits 3 - Visit 7, (0=not at all satisfied, 1=partly satisfied, 2=satisfied, 3=very satisfied).
Concomitant Medications Restrictions	Patients receiving chronic opioids cannot take the study drug since naltrexone may precipitate opioid withdrawal symptoms. Patients must have a negative urine drug screen during the Screening Visit, and during the Randomization Visit. Patients cannot take any opioid medications

<table>
<tr><td></td><td>from the 7 days before the Screening Visit to 7 days after taking the last dose of the study drug.
Patients will be eligible if they have been taking a stable dose of a medication with migraine prevention potential for at least 3 month prior to the screening visit and agree to not start, stop, or change dosage of any medication with migraine prevention potential during the study period. (E.g., beta-blockers, calcium channel blockers, tricyclic antidepressants, anticonvulsants, selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine re-uptake inhibitors (SNRIs), magnesium or riboflavin supplements at high doses, herbal preparations (e.g. feverfew or St. john’s wort)), Botulinum toxin must be discontinued one year prior to Visit 1.</td></tr>
<tr><td>Use of Rescue Medications</td><td>Patients can use their own usual migraine medication during the study for untreated or partially treated migraine, including during the baseline period and the Post-Treatment Follow-up Period. Patients will wait ½ hour after a migraine started to take a rescue medications. Patients will record every rescue medication in the migraine diary.
Permitted rescue medications include aspirin, acetaminophen, NSAIDs, ergot derivatives, and triptans.
Opioids are not permitted.
The acetaminophen dose contained in the study drug is 650 mg per day. The maximal dose of acetaminophen from the study drug and any other acetaminophen-containing product must not exceed 4000 mg per day.</td></tr>
<tr><td>Instructions for taking the Study Drug and for completing the Migraine Diary</td><td>The study drug is provided in two vials. During the Treatment Period, patients will take <u>one capsule from each vial twice a day</u> (approximately 8:00 a.m. and 8:00 p.m.). Patients will take the study drug with sufficient amount of water. They may take the study drug with food to decrease stomach upset. The study drug may cause drowsiness; patients should avoid driving until they know how the study drug affects them. If deemed necessary due to intolerance, the investigator will decrease the dosage to one dose a day - the 8:00 p.m. dose, for the duration of the Treatment Period.
On Day 0 of the Treatment Period, (the day of Visit 2), patients will take the first dose of the study drug at home at 8:00 p.m.
Patients will complete the Migraine Diary assessments approximately at 10:00 p.m. or at bedtime every day (whichever is earlier).
Figure 1: Medication vials for the Migraine Prevention Study
  </td></tr>
<tr><td>Inclusion Criteria</td><td>All patients must meet the following inclusion criteria:<table><tr><th colspan="2">Inclusion Criteria</th></tr><tr><td>1.</td><td>The patient is a male or a female 18 years of age or older.</td></tr><tr><td>2.</td><td>History of migraine with or without aura according to the</td></tr></table></td></tr>
</table>

		International Classification of Headache Disorders (ICHD)-3rd edition (beta version) for at least one-year with onset of migraine prior to 50 years of age. Migraine attacks meet the following criteria: • Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated). • Migraine attacks are separated by at least 24 hours of absence of headache pain. • Headache has at least two of the following three characteristics: Unilateral location, Pulsating quality, Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs). • During the headache both of the following: nausea and/or vomiting, photophobia or phonophobia.
	3.	Migraine-associated nausea with ≥half of migraine attacks.
	4.	5-14 migraine/probable migraine headache days on average per month in the three months prior to Visit 1 and during the Baseline Period.
	5.	The patient agrees to refrain from taking opiate medications from Visit 1 to 7 days after the last dose of the study drug.
	6.	The patient is able to complete study questionnaires, comply with the study requirements and restrictions, and willing to provide written informed consent and authorize HIPAA.
	7.	The patient has been taking a stable dose of a medication with migraine prevention potential for at least 3 month prior to the screening visit and agrees to not start, stop, or change dosage of any medication with migraine prevention potential during the study period. (E.g., beta-blockers, calcium channel blockers, tricyclic antidepressants, anticonvulsants, selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine re-uptake inhibitors (SNRIs), magnesium or riboflavin supplements at high doses, herbal preparations (e.g. feverfew or St. john's wort)), Botulinum toxin must be discontinued one year prior to Visit 1.
	8.	The patient agrees to forgo any elective surgery for the duration of the study.
	9.	The female patient who is premenopausal or postmenopausal less than 1 year, or have not had surgical sterilization (i.e., tubal ligation, partial or complete hysterectomy) must have a negative urine pregnancy test, be non-lactating, and commit to using 2 methods of adequate and reliable contraception throughout the study and for 28 days after taking the last dose of the study drug (e.g., barrier with additional spermicidal, intra-uterine device, hormonal contraception). Male patients must be surgically sterile or commit to the use of 2 different methods of birth control

	during the study and for 28 days after the study.
Exclusion Criteria	Patients will be excluded if they have met any of the exclusion criteria:

Exclusion Criteria	
1.	Usage of acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) ≥15 days/month, or ergotamine and triptans >10 days/month, or opioids and barbiturates >2 days/month in the 3 months prior to Visit 1 or during the Baseline Period.
2.	Tension-type-like, and/or migraine-like headache on ≥15 days per month in the 3 months prior to Visit 1 or during the Baseline Period. Diagnosis of chronic migraine, cluster headache or neurologically complicated migraine (hemiplegic, basilar, retinal, ophthalmoplegic migraine).
3.	Regular use of the following medications for any reason: acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), antipsychotic drugs, monoamine oxidase inhibitors, benzodiazepines, sleep medications, muscle relaxants, anti-emetic medications, blood thinning medications (e.g., warfarin or heparin), cannabinoids, or botulinum toxin to head and neck regions. Low-dose aspirin for cardiovascular disease prophylaxis is permitted.
4.	Confounding painful conditions, (e.g. fibromyalgia, chronic low back pain, complex regional pain syndrome, etc.)
5.	Diagnosis of any concurrent medical or psychiatric condition; this includes, chronic unstable debilitating diseases such as Parkinson's disease, multiple sclerosis, cancer, significant renal impairment, significant hepatic impairment, etc.
6.	The patient has a history or diagnosis of moderate-to-severe hepatic or renal impairment (>2 × the upper limit of normal [ULN] for alanine transaminase or aspartate transaminase. ≥1.5 × ULN for alkaline Phosphatase, bilirubin, BUN, or creatinine). (Patients with elevated bilirubin level due to Gilbert's syndrome are allowed).
7.	The patient has a history within the previous 5 years of abuse of any drug, prescription, illicit, or alcohol.
8.	The Female patient is pregnant, actively trying to become pregnant, or breast-feeding. The Male patient is not practicing 2 different methods of birth control with their partner during the study, and for 28 days after the investigational drug last dose or will not remain abstinent during the study, and for 28 days after the last dose.
9.	The patient has known-allergy to any of the components of the investigational drug.
10.	Participation in another study with an investigational drug within 30 days before Visit 1 or during the study.
11.	Use of emergency care treatment more than 3 times in the previous 6

	months. 12. The patient is in the opinion of the investigator, is unsuitable to participate in this study for any other reason.
Study Drug Dispensation	The study drug will be sequentially numbered according to a randomization list. The study drug will be administered sequentially. Randomization was balanced by using block randomization. Patients and investigators will be blinded to study drug assignment.
Sample Size Determination	This study is a proof of concept study for ALLOD-2 for migraine prevention. The investigator hypothesis a reduction in migraine headache days in the ALLOD-2 group versus the placebo group, for which 24 patients in each group can provide statistical significance.
Innovation	This product is a first-in-class TLR4 signaling cascade inhibitor for the treatment of migraine. Due to potential superiority over existing therapies, it represents a significant innovation. The high efficacy shown in the pilot study may indicate that its mechanism of action addresses the fundamental pathogenesis of migraine.
Statistics	All statistical analysis will summarize the number and percent of patients. Descriptive statistics by treatment group (mean, standard deviation, median, minimum, maximum, and confidence intervals) will be provided. A headache day is defined as a calendar day during which a patient had a migraine headache lasting ≥30 minutes, a migraine headache is defined as moderate to severe headache with at least one migraine-associated symptom, i.e., light sensitivity, noise sensitivity, nausea. Statistical analysis will be performed on patient reported data from the migraine diary, patient reported data from site visits, and data collected during site visits. Analysis will be performed for the comparison of the reduction in the mean migraine headache days, headache days, 50% or more reduction in monthly migraine frequency, severity, duration, nausea severity, light sensitivity, noise sensitivity, and days of rescue medication intake from baseline to the last 28 days of the 12-week Treatment Period. Analysis will be performed for the comparison of the reduction in MIDAS, HIT-6, and PIRS-20 from baseline to End-of-treatment Visit.
Statistical Analyses of the Study's Endpoints	Primary Endpoint 1) Change from baseline in the mean number of migraine/probable migraine headache days. Description: Migraine with or without aura is defined according to the International Classification of Headache Disorders (ICHD)-3rd edition (beta version). Probable migraine is defined according to the ICHD – 3 (beta version) criteria, as attacks fulfilling all but one of criteria A-D

		for migraine with or without aura, where criteria B is headache attacks lasting 4-72 hours (untreated or unsuccessfully treated). Migraine/probable migraine headaches must be moderate or severe and lasting ≥30 minutes. When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening. Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
	Secondary Endpoints	
	1)	Change from baseline in the mean number of headache days. Description: Headache days are defined as none-migraine headache days plus migraine headache days. Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
	2)	Proportion of patients with 50% or more reduction in migraine/probable migraine headache days. Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
	3)	Change from baseline in the mean migraine severity. Description: Measured on a 4-point (0-3) rating scale, (0=none, 1=mild, 2=moderate, 3=severe). Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
	4)	Change from baseline in the mean migraine duration. Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
	5)	Change from baseline in the mean nausea severity. Description: Measured on a 4-point (0-3) rating scale, (0=none, 1=mild, 2=moderate, 3=severe). Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
	6)	Change from baseline in the mean number of acute migraine medications intake days. Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
	7)	Proportion of patients "satisfied" or "extremely satisfied" with migraine prevention. Time Frame: week 12.
	8)	Change from baseline in the mean migraine disability assessment scale (MIDAS). Time Frame: From baseline to week 12 of the Treatment Period.
	9)	Change from baseline in the mean headache impact test (HIT-6). Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
	10)	Change from baseline in the mean Pittsburgh Insomnia Rating Scale-20 (PIRS-20).

		Time Frame: From baseline to week 12 of the Treatment Period.
	Safety Endpoints	
	1)	Comparison of the proportion of patients who experienced adverse events, defined as any untoward medical occurrences, regardless of their suspected cause. Time Frame: A 12-week Treatment Period.
	2)	Comparison of the proportion of patients who experienced treatment emergent adverse events. Time Frame: A 12-week Treatment Period.
	3)	Comparison of the change from screening in the mean blood counts, hepatic, and renal function. Time Frame: A 12-week Treatment Period.
	4)	Comparison of the change from screening in the mean systolic blood pressure, diastolic blood pressure, and pulse. Time Frame: A 12-week Treatment Period.

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Acronyms and Abbreviations

ACRONYMS AND ABBREVIATIONS	
AE	Adverse event
ALP	Alkaline phosphatase (serum)
ALT	Alanine aminotransferase
APAP	Acetaminophen
AST	Aspartate aminotransferase
ALLOD-2	Investigational drug containing naltrexone/acetaminophen
ATNC05	Naltrexone/clonidine combination, investigated in the phase 2 IND trial
AUC	Area under the curve
bpm	Beats per min
Cmax	Maximum (or peak) serum concentration
CFR	Code of federal regulations
CRF	Case report form
CLBP	Chronic low back pain
COX-2	Cyclooxygenase type 2
DAMP	Damage associated molecular patterns
DCF	Data correction form
DILI	Drug-induced liver injury
ECG	Electrocardiogram
FDA	Food and drug administration
GCP	Good clinical practice
HIPAA	Health insurance portability and accountability act
IC	Informed consent
ICH	International conference on harmonization
IND	Investigational new drug
IRB	Institutional review board
ITT	Intent to treat
MACE	Major adverse cardiovascular events
MedDRA®	Medical dictionary for regulatory activities
NRS	Numeric rating scale
NSAID	Non-steroidal anti-inflammatory drugs
PAMP	Pathogen-associated molecular patterns
SAE	Severe adverse events
SNRI	Serotonin-norepinephrine re-uptake inhibitor
SSRI	Selective serotonin re-uptake inhibitor
TBL	Total bilirubin (serum)

TLR4	Toll-like receptors 4
ULN	Upper limit of normal

1 BACKGROUND

1.1 Brief Description of the Investigational Product

ALLOD-2 is an investigational combination of a Toll-Like Receptor-4 (TLR4) antagonist, naltrexone hydrochloride, with a highly selective Cyclooxygenase-2 (COX-2) inhibitor, acetaminophen, intended for use in this study for the acute treatment of moderate to severe migraine associated with nausea.

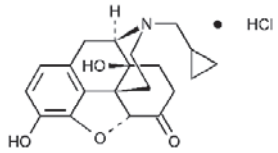
Naltrexone is an opioid antagonist, which has been marketed in the United States for treatment of opioid and alcohol dependence since 1984. However, the whole time, its analgesic properties have not been wildly acknowledged. Recent basic science research found naltrexone to act also as a TLR4 antagonist, which is the purported mechanism of action of its analgesic action. Acetaminophen was first approved in the United States in 1955, by 1972; acetaminophen was already established for OTC use for temporary relief of minor aches and pains associated with the common cold, headache pain, toothache, muscular aches, and backache.

Naltrexone and Acetaminophen inhibit two distinct neuro-inflammation producing targets in the TLR4 signaling cascade pathway. Naltrexone inhibits TLR4-induced release of pro-inflammatory cytokines, and acetaminophen, inhibits TLR4-induced COX-2 expression. The combination is expected to show the most synergistic effect shortly after treatment (in the first two hours), since continues TLR4 blockade would prevent eventual downstream activation of COX-2.

Both components are present in the Investigational Product in an immediate-release formulation.

1.2 Description of the Chemical Formulae of Naltrexone and Acetaminophen

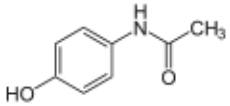
Naltrexone hydrochloride is chemically designated as (5α)-17-(cyclopropylmethyl)-3,14-dihydroxy-4,5-epoxymorphinan-6-one hydrochloride and has the following structure:



Its chemical formula is C20H24ClNO4; representing a molecular weight of 377.862 Da. It is a white to off-white powder with a bitter taste, readily soluble in water and saline. [7]

[7] REVIA® (naltrexone hydrochloride tablets USP) 50 mg Opioid Antagonist packaging insert, Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/018932s017lbl.

Acetaminophen is a medication used to treat pain and fever. Its chemical name is Nacetyl-p-aminophenol and its chemical formula is C8H9NO2. Acetaminophen's molecular weight is 151.163 Da. It is a white crystalline powder with bitter taste. Acetaminophen has the following structure: [8]



1.3 Absorption/Pharmacokinetics of Naltrexone and Acetaminophen

Naltrexone: "Following oral administration, naltrexone undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the gastrointestinal tract." "Peak plasma levels of both naltrexone and 6-ß-naltrexol (a major active metabolite of naltrexone) occur within one hour of dosing. The mean elimination half-life (T-1/2) values for naltrexone and 6-ß-naltrexol are 4 hours and 13 hours, respectively."

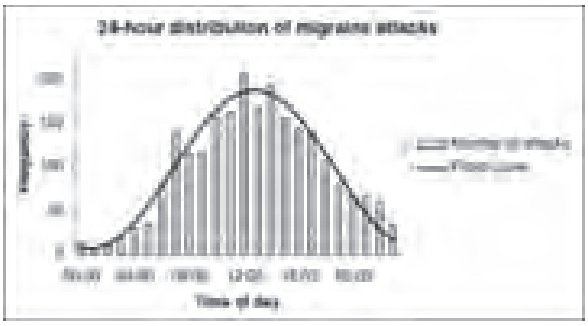
Acetaminophen: "In fasting healthy patients, absorption of paracetamol in solution is very rapid with peak plasma concentrations often occurring within 15-30 min of ingestion. Absorption from tablets is usually slower. Absorption is slowed if gastric emptying is delayed by food, posture, disease, or drugs such as propantheline and narcotic analgesics, but the total amount absorbed is not decreased. "[9] Paracetamol is extensively metabolized and the plasma half-life is 1.5-2.5 hours."

1.1 24-Hour Distribution of Migraine Attacks

Migraine attacks tend to recur in a harmonic 24-hour cyclic manner with a peak around the middle of the day and that there is no difference between migraine with aura and migraine without aura regarding this. [10]

Figure 2: 24-hour distribution of migraine attacks

[8] https://upload.wikimedia.org/wikipedia/commons/thumb/a/a9/N-Acetyl-p-aminophenol.svg/120px-N-Acetyl-p-aminophenol.svg.png
[9] Prescott LF. Kinetics and metabolism of paracetamol and phenacetin. Br J Clin Pharmacol. 1980;10 Suppl 2:291S-298S.
[10] Alstadhaug et al., 2007. 24-hour distribution of migraine attacks. Headache 48:95-100.



1.4 Relation to Fed Conditions

"Migraineurs may have delayed gastric emptying even when not experiencing migraine,[11] and gastric stasis occurs during migraine attacks. Thus, even for migraine with nocturnal onset, fasting conditions might not be met. Recent evidence suggests that peak incidence of migraine might actually occur in the middle of the day, potentially within a few hours of eating. In the U.S. phase 3 study, about 1/3rd of patients reported eating within 1 hour before taking study medication, and a large majority of migraines had onset during the day, potentially within a few hours of eating (Figure 2). It seems reasonable to conclude that PK parameters in clinical use would often fall between fed and fasted state."[12]

1.5 The Investigational Drug Components, naltrexone and Acetaminophen

Naltrexone is a commonly used opioid antagonist, which is a competitive antagonist that binds to the opioid receptors with higher affinity than the agonists bind but does not activate the receptor.

Naltrexone was marketed as ReVia ® for treatment of opioid dependence in 1984 and for treatment of alcohol dependence in 1995. It is now available in several generic formulations.

Acetaminophen is one of the most commonly used medications in the United States; it was first approved in the United States in 1955. By 1972, acetaminophen was already established for OTC use for temporary relief of minor aches and pains associated with the common cold, headache pain, toothache, muscular aches, and backache. Acetaminophen has been marketed in the United States under the trade name Tylenol. Acetaminophen is used by 23% of adults in the United States in any given week.[13] Prescribing information for acetaminophen is available for OFIRMEV[14] intravenous acetaminophen.

1.6 TLR4 - A Pattern Recognition Receptor - Detects Infection/Tissue Injury and Promotes Inflammation

"Toll-like receptors (TLRs) are germline-encoded pattern-recognition receptors that initiate

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[11] Aurora, S et al., 2007. Gastric stasis occurs in spontaneous, visually induced, and interictal migraine. Headache 47:1443-1446.
[12] Ronald Farkas, MD, PhD Clinical Review for Cambia, http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022165s000MedR.pdf
[13] Kaufman DW, Kelly JP, Rosenberg L, et al. Recent patterns of medication use in the ambulatory adult population of the United States: The Slone survey. JAMA. 2002; 287: 337-344
[14] Full prescribing information for OFIRMEV Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022450lbl.

innate immune responses by recognizing molecular structures shared by a wide range of pathogens, known as pathogen-associated molecular patterns (PAMPs). After tissue injury or cellular stress, TLRs also detect endogenous ligands known as damage-associated molecular patterns (DAMPs). TLRs are expressed in both non-neuronal and neuronal cell types in the central nervous system (CNS) and contribute to both infectious and non-infectious disorders in the CNS. Following tissue insult and nerve injury, TLRs (such as TLR2, TLR3, and TLR4) induce the activation of microglia and astrocytes and the production of the proinflammatory cytokines in the spinal cord, leading to the development and maintenance of inflammatory pain and neuropathic pain." "Activation of TLRs is known to produce various inflammatory mediators including cytokines (e.g., TNF-α), chemokines (e.g. MCP-1), and enzymes (e.g. COX-2 and MMP-9), as well as other inflammatory mediators (e.g., prostaglandins)" [15]

1.7 Proposed Mechanism of Action of Naltrexone/Acetaminophen

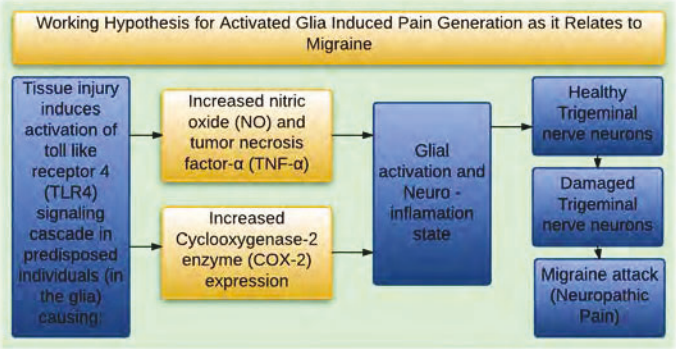
TLR4 detects and reacts to endogenous ligands that occur after tissue injury or cellular stress, known as damage-associated molecular patterns (DAMPs). Activation of the TLR4 signaling pathway in the glia induces release of pro-inflammatory cytokines [nitric oxide (NO), tumor necrosis factor-α (TNF-α), and reactive oxygen species (ROS)] causing neuro-inflammation. In addition, activation of the TLR4 signaling pathway induces expression of COX-2 (the TLR4-COX-2-prostaglandin E2 axis), also causing neuro-inflammation. TLR4 induced neuro-inflammation nearby spinal nerve roots or the trigeminal nerve system leads, in predisposed individuals, to neuropathic pain, manifested clinically as radicular back pain or migraine (and other clinical presentations).

There is a strong biological rationale for the use of naltrexone and acetaminophen in combination since each inhibits a distinct target in the same molecular pathway (the TLR4 signaling cascade).

TLR4 activation in response to endogenous DAMPs is another example of exuberant innate immunity response that is detrimental to the host. Naltrexone and acetaminophen calm the immune over-activation and neuro-inflammation nearby spinal nerve roots and the trigeminal nerve system eliminating back pain and migraine. In patients suffering from chronic back pain, an injury nearby a spinal nerve root (e.g., disk herniation) can activate TLR4 and cause neuropathic pain along its anatomical distribution.

Figure 3: Working hypothesis for activated glia induced pain generation as it relates to migraine

[15] Liu T, Gao YJ, Ji RR. Emerging role of Toll-like receptors in the control of pain and itch. Neurosci Bull. 2012;28(2):131-44.



1.8 Clinicaltrials.gov summery (Identifier: NCT03194555)

While many individuals are able to limit therapy to treatment of migraine attacks, others need medication to reduce the frequency and/or severity of attacks. Patients with prolonged or severe attacks leading to substantial disability, or patients who are refractory to abortive treatments can benefit from migraine prevention.

The investigational product is a combination of two re-purposed marketed drugs used for migraine prevention through the discovery of biologically and clinically relevant affinity for new targets. Both drugs are being re-purposed at a significantly lower dosage compared to the approved marketed indications dosage.

The combination is a First-in-Class drug due its new and unique mechanism of action.

The investigators propose that in predisposed individuals, migraine attacks occur due to exuberant innate immune system activation nearby the trigeminal nerve and other cranial nerves. The innate immunity activation leads to release of pro-inflammatory cytokines [nitric oxide (NO), tumor necrosis factor-α (TNF-α), and reactive oxygen species (ROS)], and to COX-2 activation, which produces neuro-inflammation, causing pain and various migraine-associated symptoms.

ALLOD-2 reverses the neuro-inflammation through dual action, inhibition of the release of the pro-inflammatory cytokines and inhibition of the COX-2 activation. Efficacy of this product for migraine headache pain and for migraine-associated symptoms, especially nausea (which is refractory to other known migraine treatments), may suggest the product addresses the root cause of migraine.

1.9 Dose Selection Rationale

Marketed naltrexone 50 mg tablet (e.g., Revia®), and Tylenol [redacted] mg are the reference-listed products for Allodynic's planned 505(b)(2) submission.

The dose of acetaminophen, [redacted] mg is the highest allowed in prescription combination drug

products containing acetaminophen (since January 2014).[16]

Naltrexone is marketed as a 50 mg tablet to be taken once a day. Naltrexone [redacted] mg a day, in [redacted] mg BID (to reduce likelihood of side effects from the entire dose taken at once) was used in Allodynic's IND phase 2 clinical trial on patients with chronic back pain. The [redacted] mg dose was based on Doctor Bihari's studies with low dose naltrexone ([redacted] mg/day), for the treatment of autoimmune disorders [17] and on studies for treatment of fibromyalgia that used 4.5 mg of naltrexone by Younger et al.

1.10 Migraine-associated nausea is an Important Target for Treatment

The publication "Frequency and Burden of Headache-Related Nausea: Results from the American Migraine Prevalence and Prevention (AMPP) Study" 18 states:

"Among the 6488 respondents with episodic migraine, approximately half (49.5%) reported high-frequency nausea (i.e., ≥half the time) with headache. High-frequency nausea was more common in females. Persons with high-frequency nausea, compared with the no/rare or less than half the time nausea groups, reported significantly more headache symptoms and more headache-related impact.

High-frequency migraine-associated nausea is common and is a marker for severe, debilitating migraine. Nausea makes an independent contribution to migraine-associated disability and impact. Management strategies that take nausea into account could reduce the burden of migraine. Nausea is an important target for monitoring and treatment."

1.11 Nausea Associated with Acute Migraine Represents a Significant Unmet Treatment Need

FDA Guidance for Industry Migraine: Developing Drugs for Acute Treatment states: "Because migraine is a complex disorder characterized by, in addition to headache, several associated symptoms (i.e., nausea, photophobia, and phonophobia); a drug effect on headache pain alone is not considered sufficient to grant a claim for the acute treatment of migraine. In the past 2 decades, approval of drugs for the acute treatment of migraine involved the demonstration of an effect on 4 co-primary endpoints: pain, nausea, photophobia, and phonophobia. More recently, approval based on an effect on headache pain and nausea as co-primary endpoints has been considered."

The goal of this study is to establish the investigational product addresses not only headache pain but also other migraine associated symptoms, specifically, nausea. Migraine-associated nausea

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[16] FDA recommends health care professionals discontinue prescribing and dispensing prescription combination drug products with more than [redacted] mg of acetaminophen to protect consumers, January 14, 2014. http://www.fda.gov/Drugs/DrugSafety/ucm381644

[17] Bihari B. Bernard Bihari, MD: low-dose naltrexone for normalizing immune system function. Altern Ther Health Med. 2013;19(2):56–65. [PubMed]

[18] Lipton RB, Buse DC, Saiers J, Fanning KM, Serrano D, Reed ML. Frequency and burden of headache-related nausea: results from the American Migraine Prevalence and Prevention (AMPP) study. Headache. 2013;53(1):93-103.

purportedly represents a significant unmet treatment need. Efficacy for migraine associated symptoms, especially nausea it will indicate the product's mechanism of action addresses the fundamental pathogenesis of migraine.

Clinical trials with medications that represent the current standard of care for migraine, sumatriptan, NSAIDS, and a combination of the two (sumatriptan/naproxen) showed no difference from placebo for absence of nausea at 2 hours after dosing. This supports the argument that nausea in episodic migraine represents a high degree of unmet treatment need. A summary of findings of the study "Sumatriptan-Naproxen for Acute Treatment of Migraine Clinical Trial"[19] is presented in the table below.

Figure 4: Nausea frequency in an acute migraine study

Absence of nausea at 2 hours						
	Sumatriptan /Naproxen Sodium, No. (%)	Sumatriptan, No. (%)	Naproxen Sodium, No. (%)	Placebo, No. (%)	*P* Value Sumatriptan/ Naproxen Sodium vs Placebo	*P* Value Sumatriptan/ Naproxen Sodium vs Sumatriptan
Study 2	237 (65)	233 (64)	249 (68)	244 (64)	.71	.56
Brandes JL, Kudrow D, Stark SR, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial.						

1.12 Claimed Innovation

This product is a first-in-class TLR4 signaling cascade inhibitor to be used for treatment of migraine. Due to potential superiority over existing therapies, it represents a significant innovation. The high efficacy shown in the pilot study may indicate that its mechanism of action addresses the fundamental pathogenesis of migraine.

1.13 Approved Migraine Prevention Oral Treatments

While many individuals are able to limit therapy to acute treatment of migraine attacks, others need medication to reduce the frequency and/or severity of attacks. Patients with prolonged or severe attacks leading to substantial disability, or patients who are refractory to abortive treatments can benefit from migraine prophylaxis.

The following treatments have been approved in the U.S. for episodic migraine prevention:

- Topiramate[20]
- Sodium valproate and Extended-release divalproex sodium[21]
- Propranolol[22]

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[19] Brandes JL, Kudrow D, Stark SR, et al. Sumatriptan-naproxen for acute treatment of migraine: a randomized trial. JAMA. 2007;297(13):1443-54

[20] Brandes JL, Saper JR, Diamond M, et al. Topiramate for migraine prevention: a randomized controlled trial. JAMA. 2004;291(8):965-73.

[21] Freitag FG, Collins SD, Carlson HA, et al. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Neurology. 2002;58(11):1652-9.

[22] Diener HC, Tfelt-hansen P, Dahlöf C, et al. Topiramate in migraine prophylaxis--results from a placebo-controlled trial with propranolol as an active control. J Neurol. 2004;251(8):943-50.

- Timolol, brand Blocadren[23]
- onabotulinum Toxin Type A, brand Botox (approved for chronic Migraine only, Migraine occurring 15 or more days a month)[24]

A 50% reduction in the frequency of migraines is generally deemed successful. Compliance is a major issue because patients experience medication side effects before any benefit from prophylactic drugs.

An agent that has the potential for the high benefit and low risk to the patient is needed.

1.14 Migraine Pathogenesis

"Migraine represents a central neural hypersensitivity. During an attack, migraine sufferers can be hypersensitive to normal levels of sound, light, smell and movement. If the central neuronal hypersensitivity associated with migraine represents glial cell activation, drugs that block glial cell activation and the subsequent release of neuro-excitatory substances could have therapeutic potential in both acute migraine treatment and migraine prophylaxis." [25]

The glia, when activated produces and releases a variety of neuro-excitatory substances including reactive oxygen species, nitric oxide and inflammatory cytokines. Glial activation and the subsequent release of proinflammatory mediators has been implicated in the initiation and maintenance of a number of pain states.

Endogenous TLR4 agonists (ligands) may include components of damaged tissue, termed Damage Associated Molecular Patterns (DAMPs). DAMPs may consist of extracellular matrix degradation products or dead cell components such as DNA, RNA, or plasma proteins. [26]

1.15 The Prevalence, Impact, and Economic Burdens of Migraine in the United States

Population-wide studies have found that approximately 9% of the US population – approximately 28 million Americans - have migraine headache.[27] Overall, migraine affects 18.2% of women and 6.5% of men aged 12 years and older.

"The burden of headache pain was highest in females 18-44, where the 3-month prevalence of migraine or severe headache pain was 26.1% and head pain was the third leading cause of ED visits. Triptans accounted for almost 80% of antimigraine analgesics prescribed at office visits in 2009, nearly half of which were for Sumatriptan. Migraine is associated with increased risk for

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[23] Blocadren package insert, https://www.drugs.com/pro/blocadren.html
[24] Aurora SK, Winner P, Freeman MC, et al. OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Headache. 2011;51(9):1358-73.
[25] Bartley J. Could glial activation be a factor in migraine? Med Hypotheses. 2009 Mar;72(3):255-7. doi: 10.1016/j.mehy.2008.09.048. Epub 2008 Nov 25.
[26] Kato J, Svensson CI., Role of Extracellular Damage-Associated Molecular Pattern Molecules (DAMPs) as Mediators of Persistent Pain, Prog Mol Biol Transl Sci. 2015;131:251-79. doi: 10.1016/bs.pmbts.2014.11.014. Epub 2015 Jan 30
[27] Impact of migraine headache in the united states – Jennifer H. Lofland Adv Stud Pharm. 2007;4 (1): 8-10) Available at: http://utasip.com/files/articlefiles/pdf/ASIP_4_1p8_10.

other physical and psychiatric comorbidities, and this risk increases with headache pain frequency." [28]

According to the World Health Organization's recent Global Burden of Disease report, which included 291 diseases, migraine was globally the seventh most disabling.

Tension-type headache pain (TTH) (estimated global prevalence 20.1%) and migraine (14.7%) ranked respectively as second and third most common diseases in the world (behind dental caries) in both males and females. For migraine, the estimated proportion of time spent in the ictal state (during attacks) was 5.3%, and the disability assigned to migraine attacks was 43.3% disability. Migraine was, by a wide margin, the leading cause of disability among neurological disorders.[29]

Headache pain disorders impose a recognizable burden on sufferers including sometimes-substantial personal suffering, impaired quality of life and financial cost. Repeated headache pain attacks, and often the constant fear of the next one, damage family life, social life and employment. The long-term effort of coping with a chronic headache pain disorder may also predispose the individual to other illnesses. For example, anxiety and depression are significantly more common in people with migraine than in healthy individuals.[30]

1.16 Unmet Treatment Needs for Migraine and Limitations of Existing Treatments

NSAIDs and triptans are the mainstays of acute migraine therapy, and antiemetic drugs can be added as necessary. Opioids and combination analgesics containing opioids should not be used routinely. [31] Most current treatments are not viewed as being completely effective.

As each of the most prescribed products for acute treatment of migraine, NSAIDS, Triptans and opioid carry significant risks, there is a real unmet need for a safe, non-narcotic alternative medication for this condition. In a significant number of patients, triptans carry a cardiovascular risk, NSAID and opiates are ineffective, for these patients, naltrexone/APAP, can offer an effective and safe alternative.

1.17 Emotional Pain Relief Properties of Acetaminophen

DeWall et al. (2010) [32] found that acetaminophen 1000 mg/day reduces self-reported feelings of hurt reported in a diary study ($p < .005$). In a second study, after taking the study drug with

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[28] Smitherman TA1, Burch R, Sheikh H, Loder E. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. Headache. 2013 Mar;53(3):427-36.
[29] Steiner TJ, Stovner LJ, Birbeck GL. Migraine: the seventh disabler. J Headache Pain. 2013;14(1):1.
[30] Murray CJ, Atkinson C, Bhalla K, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA. 2013;310(6):591-608.
[31] Becker WJ. Acute Migraine Treatment. Continuum (Minneap Minn). 2015 Aug;21(4 Headache):953-72. https://www.ncbi.nlm.nih.gov/pubmed/26252584
[32] DeWall C. N., et al., Acetaminophen reduces social pain: Behavioral and neural evidence. Psychological Science, 21, 931-937 (2010).

acetaminophen 2000 mg/day for 3 weeks, fMRI (functional MRI) [33] neural activity in the dACC (Dorsal anterior cingulate cortex) and amygdala was greater for participants who took placebo than for those who took acetaminophen. The dACC and amygdala are brain regions that have been linked to aggression. He postulates, "Physical pain and social pain-may rely on some of the same behavioral and neural mechanisms that register pain-related affect". He explains "Overlapping social and physical pain systems probably conferred an advantage among our evolutionary ancestors" and "The social attachment system in humans may have evolved by piggybacking directly onto the physical pain system to promote survival". His work demonstrated substantial overlap between social and physical pain. Baldwin M. Way is currently investigating Acetaminophen and Social Processes in borderline personality disorder (BPD). [34]

1.18 Concomitant Emotional Pain and/or Chronic Low Back Pain (CLBP)

Pilot study data demonstrated emotional pain relief by the investigational product. The investigator postulates that the investigational product relief of emotional pain is greater than that of acetaminophen alone.

Additionally, pilot study data demonstrated efficacy of the investigational product for CLBP.

Patients found at the screening visit to have concomitant emotional pain co-existing with episodic migraine they will be asked to complete an emotional daily diary as well as the migraine prevention daily diary. The stressors causing emotional pain, as explained to patients include adjustment to new life for immigrants, adjustment to separation from children who recently left home, or adjustment to loss of a pet. These complaints are currently treated with psychotherapy. The ICD-10-CM diagnosis code is F43.20 "adjustment disorder, unspecified". Additionally, patients with concomitant emotional pain will complete the Beck's Depression Inventory instrument on every site visit.

If a patient is found at the screening visit to have concomitant CLBP co-existing with episodic migraine they will be asked to complete a CLBP daily diary as well as the migraine prevention daily diary. (See the attached daily diary forms). Additionally, patient with concomitant CLBP will complete the Oswestry Disability Index instrument on every site visit.

1.19 Potential Advantages of a Low-Dose Naltrexone/Acetaminophen Product

People who are normally resistant to consuming prescription medications or people who have experienced negative side effects from medications, may accept low-dose naltrexone /acetaminophen because of the "low-dose" of the two medications, and the wide acceptance of acetaminophen.

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[33] Functional MRI (fMRI) is a functional neuroimaging procedure using MRI technology that measures brain activity by detecting changes associated with blood flow.
[34] Acetaminophen and Social Processes, https://clinicaltrials.gov/ct2/show/NCT02108990

2 STUDY DESIGN OUTLINE

2.1 Study Objectives

The primary objective is to compare the reduction in the mean migraine/probable migraine headache days from baseline to the last 28 days of the 12-week Treatment Period.

A secondary objective is to compare the reduction in the mean headache days from baseline to the last 28 days of the 12-week Treatment Period.

Another secondary objective is to compare the reduction in the mean proportion of patients responding to treatment (as measured by a 50% or more reduction in 28-day migraine frequency) from baseline to the last 28 days of the 12-week Treatment Period.

Another secondary objective is to compare the reduction in the mean migraine headache severity, headache duration, nausea severity, light sensitivity, noise sensitivity, and number of days of rescue medications intake from baseline to the last 28 days of the 12-week Treatment Period.

Another secondary objective is to compare the reduction in the mean migraine disability assessment scale (MIDAS) and headache impact test (HIT-6) from baseline to End-of-Treatment Visit.

An exploratory objective is to compare the reduction of mean Pittsburgh Insomnia Rating Scale-20 (PIRS-20) from baseline to End-of-Treatment Visit

2.2 Inclusion Criteria

All patients must meet the following inclusion criteria:

	Inclusion Criteria (Mark each met criteria)
1.	The patient is a male or a female 18 years of age or older.
2.	History of migraine with or without aura according to the International Classification of Headache Disorders (ICHD)-3rd edition (beta version) for at least one-year with first migraine prior to age 50. Migraine attacks meet the following criteria: • Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated). • Migraine attacks are separated by at least 24 hours of absence of headache pain. • Headache has at least two of the following three characteristics: Unilateral location, Pulsating quality Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs). • During the headache both of the following: nausea and/or vomiting, photophobia or phonophobia.
3.	Migraine-associated nausea with ≥half of migraine attacks.
4.	5-14 migraine headache days on average per month in the three months prior to Visit 1 and during the Baseline Period.
5.	The patient agrees to refrain from taking opiate medications from Visit 1 to 7 days after the last dose of the study drug.
6.	The patient is able to complete study questionnaires, comply with the study requirements and restrictions, and willing to provide written informed consent and authorize HIPAA.

7.	The patients is eligible if he/she has been taking a stable dose of a medication with migraine prevention potential for at least 3 month prior to the screening visit and agrees to not start, stop, or change dosage of any medication with migraine prevention potential during the study period. (E.g., beta-blockers, calcium channel blockers, tricyclic antidepressants, anticonvulsants, selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine re-uptake inhibitors (SNRIs), magnesium or riboflavin supplements at high doses, herbal preparations (e.g. feverfew or St. john's wort)), Botulinum toxin must be discontinued one year prior to Visit 1.
8.	The patient agrees to forgo any elective surgery for the duration of the study.
9.	The female patient who is premenopausal or postmenopausal less than 1 year, or have not had surgical sterilization (i.e., tubal ligation, partial or complete hysterectomy) must have a negative urine pregnancy test, be non-lactating, and commit to using 2 methods of adequate and reliable contraception throughout the study and for 28 days after taking the last dose of the study drug (e.g., barrier with additional spermicidal, intra-uterine device, hormonal contraception). Male patients must be surgically sterile or commit to the use of 2 different methods of birth control during the study and for 28 days after the study.

2.3 Exclusion Criteria

Patients will be excluded from the study, if they have met any of the exclusion criteria:

Exclusion Criteria	
1.	Usage of acetaminophen and NSAIDs ≥15 days/month, ergotamine and triptans >10 days/month, opioids and barbiturates >2 days/month in the 3 months prior to Visit 1 or during the Baseline Period.
2.	Tension-type-like, and/or migraine-like headache on ≥15 days per month in the 3 months prior to Visit 1 or during the Baseline Period. Diagnosis of chronic migraine, cluster headache or neurologically complicated migraine (hemiplegic, basilar, retinal, ophthalmoplegic migraine).
3.	Regular use the following medications for any reason: acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), antipsychotic drugs, monoamine oxidase inhibitors, benzodiazepines, sleep medications, muscle relaxants, anti-emetic medications, blood thinning medications (e.g., warfarin or heparin), cannabinoids, or botulinum toxin to head and neck regions. Low-dose aspirin for cardiovascular disease prophylaxis is permitted.
4.	Confounding painful conditions, (e.g. fibromyalgia, chronic low back pain, complex regional pain syndrome, etc.)
5.	Diagnosis of any concurrent medical or psychiatric condition; this includes, chronic unstable debilitating diseases such as Parkinson's disease, multiple sclerosis, cancer, significant renal impairment, significant hepatic impairment, etc.
6.	The patient has a history or diagnosis of moderate-to-severe hepatic or renal impairment (>2 × the upper limit of normal [ULN] for alanine transaminase or aspartate transaminase. ≥1.5 × ULN for alkaline Phosphatase, bilirubin, BUN, or creatinine). (Patients with elevated bilirubin level due to Gilbert's syndrome are allowed).

7.	The patient has a history within the previous 5 years of abuse of any drug, prescription, illicit, or alcohol.
8.	The Female patient is pregnant or breast-feeding. The Male patient is not practicing 2 different methods of birth control with their partner during the study, and for 28 days after the investigational drug last dose or will not remain abstinent during the study, and for 28 days after the last dose.
9.	The patient has known-allergy to any of the components of the investigational drug.
10.	Participation in another study with an investigational drug within 30 days before Visit 1 or during the study.
11.	Use of emergency care treatment more than 3 times in the previous 6 months.
12.	The patient is in the opinion of the investigator, unsuitable to participate in this study for any other reason.

2.4 Study Design

This is a 20-week, single-center, double blind, randomized, placebo-controlled, parallel-arm study for patients requiring migraine prevention. Patients will be treated for 12-weeks with oral BID combination of naltrexone [redacted] mg/APAP [redacted] mg or placebo. The study consists of three study periods: a 28-day baseline period, a 12-week double blind Treatment Period, and 28-day Post-Treatment Follow-up Period.

The 28-day duration of the baseline period is designed to assess the baseline frequency and severity of migraine. The 12-week duration of the Treatment Period is designed to meet the requirement for a migraine prevention studies. A 28-day Post-Treatment Follow-up Period is designed to assess any safety issues with the study drug. Additionally, it will assess whether there is a carry-over effect of the study drug on migraine prevention.

Given the risk for both naltrexone and acetaminophen to cause hepatotoxicity, laboratory assessments (hematology, hepatic and renal function).will be obtained pre-dose (Visit 1) and monthly thereafter (i.e., Visit 4, Visit 5, and Visit 6).

On Day 0 of the Treatment Period, (the day of Visit 2), patients will take the first dose of the study drug at home at 8:00 p.m.

Patients will complete the Migraine Diary assessments approximately at 10:00 p.m. or at bedtime every day (whichever is earlier) every day of the study.

During each visit of the study, except Visit 3, patients will complete the Headache Impact Test (HIT-6). Patients will complete the Pittsburgh Insomnia Rating Scale-20 (PIRS-20) every site visit. Patients will complete the Migraine Disability Assessment Scale (MIDAS) On Visit 1, 2 and 6.

Patients will and receive study drug on visit 2, 3, 4 and 5.

Study Visit 1 - Screening Visit; during this visit, patients who met inclusion/ exclusion criteria will give an informed consent after the nature of the study is explained and before any study-specific procedures are performed.

During the screening visit, the investigator will obtain medical history, migraine headache

history, history of substance abuse and/or dependency, and medication history. In addition, the investigator will perform a complete physical examination, vital signs measurements, a 12-lead ECG, a urine drug screen, and a urine pregnancy test (for childbearing age females). Additionally, the investigator will draw blood sample for laboratory assessments, (hematology, hepatic and renal function).

The 5-panel urine drug screen (cocaine, marijuana, opiates, methamphetamines, and Oxycodone) and the pregnancy test must be negative to continue with the screening visit procedures.

At the screening visit, the MIDAS score must be higher than 11, (moderate or severe disability), and the HIT-6 score, must be higher than 56 (substantial or very severe impact).

During the Screening Visit, the investigator will go over the following items:

- How to rate the intensity of headache pain, nausea and satisfaction with migraine prevention on a 4-point (0-3) scale.
- How to rate light sensitivity, noise sensitivity, neck/shoulder pain, and vomiting as absent or present.
- How to distinguish migraine headache from non-migraine headache.
- How to take rescue medications, wait ½ hour after a migraine started before taking their own usual migraine medications.
- How and when to complete the Migraine Diary assessments.
- How to record rescue medications.
- About the "placebo effect."

The investigator will enroll only patients into the baseline period if they demonstrate ability to complete the Migraine Diary.

At the conclusion of the Screening Visit, patients will receive a paper migraine diary to be completed daily for a 28-day baseline period.

Patients will have a phone contact on day 8 and day 15 of the baseline period. After completion of the 28-day baseline period patients will return for the Randomization Visit.

Study Visit 2 - Randomization Visit: In this visit, the investigator will review the baseline period Migraine Diary. Patients who had at least 4 moderate-to-severe migraine episodes, but 15 or less headache days during the 28-day baseline period and continued to meet all other inclusion and exclusion criteria will be eligible for randomization. Patient must complete the assessments for all the 28 days of the baseline period to qualify for randomization.

In addition, at the Randomization Visit, the MIDAS score must be higher than 11, (moderate or severe disability), and the HIT-6 score must be higher than 56 (substantial or very severe impact).

During the Randomization Visit, the investigator will go over the following items:

How to take the study drug.

How to take rescue medications, (wait ½ hour after a migraine started before taking own usual migraine medications).

How to record rescue medications.

Patients will be randomized in a 1:1 ratio to naltrexone [redacted] mg/acetaminophen [redacted] mg (ALLOD-2) or placebo and enter into the 12-week Treatment Period.

Randomized patients will receive a paper Migraine Diary form and a blinded study drug to use in the outpatient settings.

Study Visit 3 – 1 week after the Treatment Period started: during this visit, the investigator will confirm the patient understanding of how to take the study drug and how to complete the daily Migraine diary. During this visit, assessment of adverse events and adjustment to the study drug dose can be made.

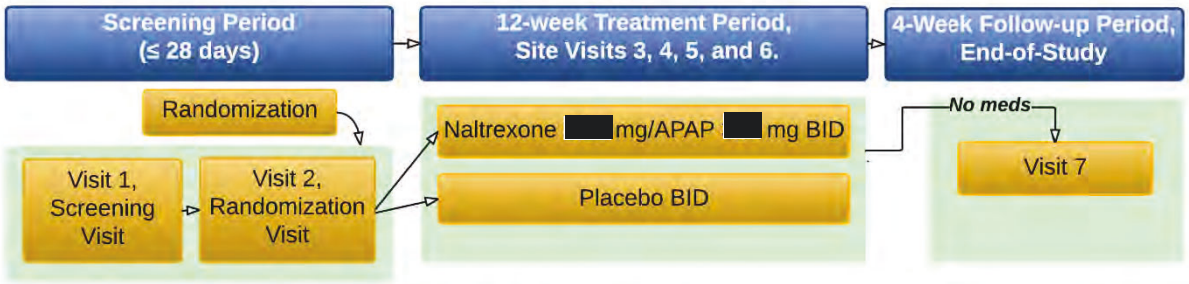
Study Visits 4 and 5: these visits will occur on days 28, and 56 (±5 - day visit window) of the Treatment Period. Additionally, there will be telephone contacts two weeks after these visits (±2 - day visit window).

Study Visit 6 - End-of-Treatment Period Visit: This visit will take place no sooner than day 84 (+5 days) from the beginning of the Treatment Period. During this visit, patients final count and reconciliation of the study drug.

Study Visit 7 - End-of-Study Visit: This visit will take place on day 28 (+5 - day visit window) of the Follow-up Period. During the Follow-up Period, patients will continue to complete the daily diary, but they will not consume the study drug.

Figure 5: Study Design Illustration

A Single Center, Phase 2B, Randomized, Double Blind, Study to Assess the Efficacy, Safety, and Tolerability of Oral Twice Daily ALLOD-2 vs. Placebo in the Prevention of Episodic Migraine in Adults



- BID=Two times daily. Patients will take the study drug at 8:00 a.m. and at 8:00 p.m. with sufficient amount of water. Patients may take the study medication with food to decrease stomach upset. Patients will be advised that the study drug may cause drowsiness. Patient should avoid driving or operating machinery until they know how the study drug will affect them.
- Permitted rescue medications for migraine/headaches include aspirin, acetaminophen, NSAIDs, ergot derivatives, and triptans.
- Patients cannot use more than 675 mg of acetaminophen for the first 6 hours after taking the study drug and cannot take more than 4350 mg per day. The dose of acetaminophen cannot exceed 4000 mg per day.
- 7 site visits on days: -28, 0, 7, 28, 56, 84, 112.
- 5 Phone contacts on days: -21, 14, 42, 70, 98.
- APAP=Acetaminophen.
- ALLOD-2=Naltrexone 2.25 mg/Acetaminophen 325 mg.

2.5 Migraine Diary and Other Study Assessments

- Study drug morning dose consumption
- Study drug evening dose consumption
- Presence of a headache, (yes/no).
- Start time and the end time of the headache.
- Intake of additional migraine medications.
- Severity of the headache pain, (0=none; 1=mild; 2=moderate; 3=severe).
- Severity of the nausea/vomiting, (0=none; 1=mild; 2=moderate; 3=severe).
- Presence One-sided headache, (yes/no).
- Pulsating quality, (yes/no).
- Worsening with activity (yes/no).
- Light sensitivity, (yes/no).
- Noise sensitivity, (yes/no).
- Neck pain, (yes/no).

Other assessments:

- Migraine Disability Assessment Scale (MIDAS), (3-month assessment) Visits 1, 2 and 6.
- Headache Impact Test (HIT-6), (4 week assessment) every visit except Visit 3.
- Pittsburgh Insomnia Rating Scale-20 (PIRS-20), (7-day assessment) every visit.
- Patient Global Impression of Change (PGIC)

2.6 Patient satisfaction with migraine prevention, Visits 3 - Visit 7, (0=not at all satisfied, 1=partly satisfied, 2=satisfied, 3=very satisfied).Study Duration

The study consists of seven visits and five telephone contacts occurring over a 5-month period.

Study visits schedule:

	Visit-1, Screening Visit	Visit-2, randomization Visit	Visit-3, Treatment Period Visit	Visit-4, Treatment Period Visit	Visit-5, Treatment Period Visit	Visit-6, End of Treatment Period Visit	Visit-7, Post-Treatment Period Visit
Study Day	-28	0	7	28	56	84	112
All visits may have ±5-day visit window except visit-6, which must take place no sooner than 84 (+5 days) from the beginning of the double-blind Treatment Period. Day 84 of the Treatment Period is considered the last day of treatment for data analysis purposes.							

Phone contacts Schedule:

Phone contact	Phone-1, Baseline Period	Phone-2, Treatment Period	Phone-3, Treatment Period	Phone-4, Treatment Period	Phone-5, Post Treatment Period
Study Day	-21	14	42	70	98
All Phone Visits may have ±2-day visit window.					

2.7 Study Population

The study population will include non-pregnant, non-lactating females and males. Both must be 18 years of age or older.

Patients have an average of at least 4 moderate-to-severe migraine episodes but 15 or less headache days per month in the previous 3 months and during the baseline period.

Patients have history of migraine with or without aura according to the International

Classification of Headache Disorders (ICHD)-3rd edition (beta version) for at least one-year with onset of migraine prior to age 50 years of age.

Patients with coexisting types of headache pains (e.g., tension-type headache) can be included if they can distinguish migraine headache from the other headaches.

Patients must have high-frequency moderate to severe migraine-associated nausea (i.e., associated nausea ≥ half the migraine attacks) to be admitted into the study. Patients who experience vomiting can be admitted, however, they will be advised that vomiting within 30 min after taking the study drug can purge the study drug. Patients will be asked to take the study drug when they can assume that they will not vomit within 30 mins.

Patients who in the opinion of the investigator may have medication-overuse headaches (as defined by ICHD – 3 (beta version) criteria for medication-overuse headache. The definition of medication overuse for this study is usage of ≥15 days/month of acetaminophen, NSAIDs, or usage of ergotamine, and triptans <10 days/month or usage of opioids and barbiturates >2 days/month during the 3 months preceding screening or during the baseline period.

Patients who in the opinion of the investigator, have chronic migraine (as defined by ICHD – 3 (beta version) criteria for chronic migraine) (headache, tension-type-like and/or migraine-like on ≥15 days per month) during the 3 months preceding screening or during the baseline period will be excluded.

In addition, patients using any disallowed concomitant medications or patients who used an investigational medication within 4 weeks before the Screening Visit will not qualify.

Care should be taken to exclude other potentially serious neurologic conditions before enrolling patients not previously diagnosed with migraine headache or who experience headache that is atypical for them.

2.8 Exclusions Due to Coexisting Conditions

Patients who tested positive for a cocaine, marijuana, opiates, methamphetamines or oxycodone in the five-panel urine drug test at Screening Visit will not qualify due to possible precipitation of drug withdrawal symptoms when combined with naltrexone.

Patient taking warfarin will not qualify. An interaction between warfarin and acetaminophen may result in significant elevations of international normalized ratio (INR), putting patients at increased risk for hemorrhagic complications.[35]

Patients diagnosed with Parkinson's disease or dementia for which treatment with specific medications is required will be excluded from the study.

Patients who have any clinically significant abnormality in the 12 lead ECG; have uncontrolled heart failure; myocardial infraction or a stroke within the last 6 months; or symptomatic with angina, palpitations; dyspnea, arrhythmia, will be excluded due to risk to their health. Patients

[35] Gregory J. Hughes, et al., Effect of Acetaminophen on International Normalized Ratio in Patients Receiving Warfarin Therapy; Pharmacology and Drug Therapy, Volume 31, Issue 6, pages 591–597, June 2011

who have significant uncontrolled neurological, psychiatric; hepatic, renal; endocrine, cardio-vascular; gastrointestinal, pulmonary; hematologic or metabolic disease are not candidates for experimental clinical studies due to the risk to their health.

Patients who have been diagnosed with severe psychotic or bipolar disorders will not qualify due to inability to personally provide an Informed Consent, and the likely hindrance to the patient's ability to adhere to the study protocol.

2.9 Substance Abuse and Alcohol Use Restrictions

Due to the naltrexone component of the investigational drug, an opioid antagonist, patients with substance abuse may be vulnerable to opioid overdose and/or a naltrexone-precipitated opioid withdrawal. Patients with a past or present history of substance abuse and/or a history of admission to a drug rehabilitation facility will be excluded from the study.

Patients must agree to refrain from excessive alcohol consumption during the study. The allowable limit is four drinks per week. Patients with a history of significant alcohol consumption require six months of sobriety and adherence to less than four drinks per week. A standard drink is equal to 14.0 grams (0.6 ounces) of pure alcohol. Generally, this amount of pure alcohol is found in: 12-ounces of beer (5% alcohol content), 8-ounces of malt liquor (7% alcohol content), 5-ounces of wine (12% alcohol content) and 1.5-ounces or a "shot" of 80-proof (30% alcohol content) distilled spirits or liquor (e.g., gin, rum, vodka, whiskey).

2.10 Concomitant Medications Restrictions

Patients receiving chronic opioids cannot take the study drug since naltrexone may precipitate opioid withdrawal symptoms. Patients must have a negative urine drug screen during the Screening Visit, and during the Randomization Visit. Patients cannot take any opioid medications from the 7 days before the Screening Visit to 7 days after taking the last dose of the study drug.

Patients will be eligible if they have been taking a stable dose of a medication with migraine prevention potential for at least 3 month prior to the screening visit and agree to not start, stop, or change dosage of any medication with migraine prevention potential during the study period. (E.g., beta-blockers, calcium channel blockers, tricyclic antidepressants, anticonvulsants, selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine re-uptake inhibitors (SNRIs), magnesium or riboflavin supplements at high doses, herbal preparations (e.g. feverfew or St. john's wort)), Botulinum toxin must be discontinued one year prior to Visit 1.

Figure 6: Concomitant Medications Restrictions

Medication class, Most Commonly Used Examples	Restriction
Opiates (including tramadol)	Not permitted from 7 days before screening visit to 7 days after taking the study drug.
Opiate Antagonist	Not permitted.
Acetaminophen	The acetaminophen dose contained in the study drug is 650 mg per day. The maximal dose of acetaminophen from the study drug and any other acetaminophen-containing product must not exceed 4000 mg per day.

Triptans, ergotamine preparations.	Less than 10 days/month.
Non-steroidal anti-inflammatory drugs (NSAID), cyclooxygenase type 2 (COX-2) Inhibitors,	Equal or less than 15 days/month.
Barbiturate preparations, opiates	Less than 2 days/month.
Angiotensin inhibitors	Permitted
Anticonvulsants, tricyclic antidepressants, calcium channel blockers, Beta-blockers, Selective serotonin re-uptake inhibitors (SSRIs), selective serotonin-norepinephrine re-uptake inhibitors (SNRIs).	Dose must be stable for 3 months prior to Visit 1 and remain the same during the study.
Aspirin 81 mg/day	Permitted for CVD prophylaxis
Benzodiazepines, muscle relaxants, sleeping pills, anti-emetics	Not permitted
Antipsychotics, mood stabilizers, MAO-B inhibitors	Not permitted
Cannabinoids	Not permitted
Dopamine agonists	Not permitted
blood thinning medication (e.g., warfarin or heparin)	Not permitted
Botox (Onabotulinumtoxin A Injection)	None in 1 year prior to screening

2.11 Rescue Medications

Patients can use their own usual migraine medication during the study for untreated or partially treated migraine, including during the baseline period and the Post-Treatment Follow-up Period. Patients will wait ½ hour after a migraine started to take a rescue medications. Patients will record every rescue medication in the migraine diary.

Permitted rescue medications include aspirin, acetaminophen, NSAIDs, ergot derivatives, and triptans.

Opioids are not permitted. The acetaminophen dose contained in the study drug is 650 mg per day. The maximal dose of acetaminophen from the study drug and any other acetaminophen-containing product must not exceed 4000 mg per day.

2.12 Instructions for Taking the Study Drug and for completing the Migraine Diary

The study drug is provided in two vials. During the Treatment Period, patients will take **one capsule from each vial twice a day** (approximately 8:00 a.m. and 8:00 p.m.). Patients will take the study drug with sufficient amount of water. They may take the study drug with food to decrease stomach upset. The study drug may cause drowsiness; patients should avoid driving until they know how the study drug affects them. If deemed necessary due to intolerance, the investigator will decrease the dosage to one dose a day - the 8:00 p.m. dose, for the duration of the Treatment Period.

On Day 0 of the Treatment Period, (the day of Visit 2), patients will take the first dose of the study drug at home at 8:00 p.m.

Patients will complete the Migraine Diary assessments approximately at 10:00 p.m. or at bedtime every day (whichever is earlier).

2.13 Randomization Scheme and Treatment Groups

Patients will be randomized to one of two treatment groups:

1. Naltrexone [redacted] mg/acetaminophen [redacted] mg (ALLOD-2),

2. Placebo.

The placebo group will provide data to support efficacy of the product.

The study plans to enroll 48 patients randomized into two treatment groups in a ratio of 1: 1 with 24 patients in each group. Investigators, site personnel, and patients will be masked to the treatment assignment.

3 STUDY CONDUCT

3.1 Identification and Recruitment of Study Patients

The Clinical Investigator will design a recruitment process that is likely to lead to identification of potential study candidates that meet the protocol criteria. He/she will ensure that the recruitment process includes safeguards for the protection of vulnerable populations.

The screening of interested volunteers can be conducted via phone and email, and include assessment of migraine history, general physical and mental health, drug and medication use. After initial screening, patients will be invited to participate in the procedures underlined in the study protocol.

3.2 Screened Patients' Log Record Keeping

The site will maintain a log of all the screened patients. Screened patients are patients who signed the Informed Consent, in compliance with ICH-GCP 8.3.20, all screened patients must be documented. The screened patients log will include the patients full name, sex, date of birth, gender, whether inclusion/exclusion criteria were met, and if not, a list of each failed Inclusion/Exclusion criterion, and date of Informed Consent. The screened patient list will be updated to include the identification (I.D.) for patients who were randomized.

Every prospective patient will complete a contact information form, which will include contact information and how patients learned about the study. The contact information will be authenticated with a photo I.D. A copy of driver's license or other valid form of photo I.D. will be obtained for each patient screened patients.

Screen failure is defined as a patient who has given Informed Consent and failed to meet at least one of the exclusion criteria and/or has not been randomized or administered the investigational drug as defined by the protocol.

3.3 HIPAA Compliance with regards to previous medical records

The Clinical Investigator will obtain the patient's migraine-qualifying documentation required by the study protocol after ensuring all authorizations for release of medical records were obtained.

The Clinical Investigator will anonymize the medical records, in accordance with HIPAA regulations (45 CFR Parts 160 and 164), prior to submission to the sponsor. The following personal identifiable information must be redacted prior to submission to the sponsor, full name (including name derived initials), home address, birth date (except birth year), email address, social security number, medical records numbers, health plan beneficiary numbers, account numbers, vehicular license number, credit card numbers, telephone number and any other unique

identifying number, characteristic or code. The records are permitted to include only the prospective patient's ID, year of birth and gender.

3.4 Protocol Deviation/Violations

A protocol deviation/violation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change.

A protocol minor deviation/violation occurs when, without significant consequences, the activities on a study diverge from the Institutional Review Board-approved protocol.

Examples of protocol violations include but are not limited to the following:

- Participant does not show up for scheduled research visit
- Failure of participant to return investigational drugs
- Missing original signed and dated consent form (only a photocopy is available)
- A failure to follow the approved study procedure that, in the opinion of the PI, does not affect patient safety or data integrity

A protocol major deviation/violation is defined as a deviation from the IRB-approved protocol that may affect the patient's rights, safety or well-being and/or the completeness, accuracy and reliability of the study data. Examples of protocol violations include but are not limited to the following:

- A research patient received the wrong treatment or incorrect dose
- Performance of a study procedure not approved by the IRB
- A research patient met withdrawal criteria during the study but was not withdrawn
- A research patient received an excluded, concomitant medication
- Breaches of confidentiality
- A research patient was enrolled, but does not meet the protocol's eligibility inclusion/exclusion criteria
- Failure to treat research patients per protocol procedures that specifically relate to primary efficacy outcomes
- Inadvertent loss of data
- Failure to obtain Informed Consent prior to initiation of study-related procedures
- Failure to report serious adverse events within required timeframe to the IRB and/or sponsor and FDA
- Falsifying research or medical records
- Performing tests or procedures beyond the individual's professional scope or privilege status (credentialing)

In the event of a significant deviation from the protocol, the Clinical Investigator will contact the sponsor at the earliest possible time by telephone. The Clinical Investigator and the sponsor's

study team will come to a joint decision regarding the patient's continuation in the study. The decision will be documented by the Clinical Investigator and the sponsor.

Any violation from study procedures should be noted in the source documents and added to the protocol deviations log. Major protocol deviations should be reported to the sponsor immediately. Protocol violations are divided into the following categories:

Protocol Violation Categories		
□ Consent Procedure	□ Study Procedures	□ Randomization Procedures
□ Inclusion/Exclusion Criteria	□ Investigational drug Dosing	□ Visit Schedule/Interval
□ Concomitant Medication/Therapy	□ SAE Reporting	□ Other
□ Laboratory Assessments		

3.5 Protocol Adherence and Compliance with Protocol Revisions

Prior to beginning the study, the Clinical Investigator must sign the Clinical Study Agreement and the Clinical Investigator's signature page documenting his/her agreement to conduct the study in accordance with the protocol. The Clinical Investigator must not deviate from this protocol, except to protect the life and physical well-being of a patient in an emergency.

The Per Protocol (PP) Sample will consist of all patients who did not present with any major protocol violations in accordance with the study specific inclusion/exclusion criteria.

The study must be conducted as described in this approved protocol. The sponsor is responsible for preparation of all revisions to the protocol. The Clinical Investigator should not implement any violation or change to the protocol without prior review and documented approval from the IRB of an amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

3.6 Informed Consent Procedure

The Clinical Investigator will obtain written Informed Consent from all study patients prior to performing any study-related procedures. The Informed Consent document will be approved by the IRB. The Clinical Investigator and the study site staff will be trained in the administration of the Informed Consent procedure.

Prior to initiating the Informed Consent documentation process, the Clinical Investigator will determine whether the prospective patient is legally capable to participate in the Informed Consent process. The Clinical Investigator will exclude legally incapacitated persons; legal guardians may not consent on behalf of incapacitated persons for this trial. The Clinical Investigator will communicate information regarding the nature of the study, potential risks, and potential benefits to the patient. Full and adequate oral and written information must be provided to each prospective trial patient. The information will be communicated in a manner that ensures trial patients have a meaningful understanding of the information. The Clinical Investigator will give the patients an opportunity to ask questions, provide information regarding whom to contact if patients have any more questions and ensure that the patient has the right to discontinue participation in the trial at any time. The Clinical Investigator will explain any payments to trial

patients and the requirements the patients must fulfill to receive the payments. It is the Clinical Investigator's duty to both assess the patients' capacity to consent and to answer patients' questions throughout the trial. The patients will receive a complete copy of the fully executed Informed Consent documentation.

The Clinical Investigator will explain to all patients that consumption of opiate medications during the trial may precipitate opiate withdrawal syndrome due to the naltrexone component of the investigational drug, which is an opioid receptor antagonist.

Prior to the initiation of any study specific procedures, the Clinical Investigator will verify that all Informed Consent documentation are properly signed and dated by the patient. A complete copy of all Informed Consent documentation includes both a complete set of all written information provided to the patient and the fully executed Informed Consent documentation. The original copy will be retained in the patient's study file.

3.7 Regulatory Compliance

Before the study can start, the IRB will review and approval all the study documents for ethical considerations according to local regulations. The IRB will identify all documents reviewed by name and version. The sponsor should submit for IRB approval patient information, Informed Consent form, the investigator brochure, any written instructions to be given to a patient, patient recruitment procedures (e.g. advertisements), information about payments and compensation to the patients, and documentation regarding the investigator required qualifications. Protocol amendment will be issued for changes in the conduct of the study.

The investigator must obtain approval from the IRB. The investigator will notify the IRB of deviations from the protocol or serious adverse events (SAEs) occurring at the clinic.

3.8 Concomitant Diagnosis and Medication Recording Requirements

Significant medical history, including events up to the Screening Visit will be recorded. Following consent, all events that occur will be recorded in the adverse event log.

During the Screening Visit, the Clinical Investigator will record all over-the-counter and prescription medications, therapies and procedures within 30 days prior to the beginning of the study. Concomitant medications consumed and therapies undergone by a patient during the course of the study (including those used in response to an AE/SAE) as well as new, concomitant diagnoses will be recorded. The patient will record concomitant rescue analgesics in the Migraine Diary.

3.9 Demographics, Baseline Measures, and Cardiovascular Risk Assessment

Baseline and demographic measures will be collected from each patient, including year of birth, age, gender, ethnicity, race, migraine duration, migraine severity, migraine associated symptoms, concomitant medications and treatments (by class) and self-reported cardiovascular risk factors.

3.10 Treatment Group Assignment Procedure

The Clinical Investigator is the only authorized individual allowed to randomize patients. After confirming that the patient has met all eligibility criteria, the Clinical Investigator can proceed to

the randomization procedure. The investigator will confirm that the patient intents to consume the investigational drug and dispense the medication vial using double-checking medication dispensation procedure.

3.11 Early Withdrawal and Early withdrawal Procedure

Since this study is a single dose study, early withdrawal refers to withdrawal after the patient was randomized and before the patient treated a migraine attack. Patients, investigators, or the sponsor may initiate early withdrawal. Patients are encouraged to communicate early withdrawal decisions as soon as possible. The Clinical Investigator or sponsor may terminate patient participation in the trial at any time out of safety concerns. The Clinical Investigator should discuss early withdrawal of a patient with the sponsor before carrying it out.

3.12 Patients Lost to Follow-up Prior to the End of the Trial

For patients who consumed the study drug but did not attend the end-of-treatment visit, attempts will be made to collect efficacy and safety data by telephone. The Clinical Investigator will make at least three documented attempts to contact the patient by telephone. If all telephone attempts fail, the Clinical Investigator will attempt contact by mailing a letter to the patient's last known address by certified mail and including a request for return receipt. This contact will ask the patient to return to the site for the final safety evaluation. Patients, who did not consume the study drug within two months from randomization, will be asked to return the study drug and the study forms.

4 STUDY TREATMENT SCHEDULE

4.1 Pre-enrollment Review

The investigator will obtain medical records confirming a diagnosis of migraine (physician's note, pharmacy records for migraine specific medications, etc.). Additionally, the investigator will review the completed migraine intake form. The investigator will forward anonymized medical records and the completed migraine intake form to the sponsor prior to enrolling a patient.

4.2 Rules for Rescreening

Rescreen will not be permitted.

4.3 Study Visit 1 - the Screening Visit

The first objective of this visit is to confirm that the prospective patient meets all the inclusion and exclusion criteria.

Prospective patients identified by the investigator will complete the "Patient Intake Form for the Migraine Prevention Study" (section-16.1). The sponsor must review the medical records, the ECG, the completed Patient Intake Form and approve the patient's participation before proceeding.

All prospective study participants will complete a contact information form and provide a photo ID; a copy of the photo I.D. will be obtained. Site personnel will verify contact information

matches the information on the photo ID.

The investigator will review with the patient the "Patient Handout for the Migraine Prevention Study" (section 16.2).

The investigator will go over with patients the following aspects:

- The 4-point rating scale,
- Self-assessment of pain intensity,
- Self-assessment of nausea,
- Self-assessment of satisfaction with migraine prevention,
- Completion of the Migraine Diary,
- The Placebo Effect and
- Prohibited medications.

The investigator will only enroll patients who demonstrated ability to perform the study task as outlined in the patient handout.

Prior to conducting any study-specific procedures, patients must sign the Informed Consent. The informed consent procedure must be executed as outlined in Section 4.6. The investigator must be available to answer any questions patients may have. The investigator will provide patients with a copy of the signed Informed Consent document for their records.

First, all patients will have an on-site urine drug screen (5-panel urine drug screen to test for cocaine, marijuana, opiates, methamphetamines, and oxycodone) and pre-menopausal women (or within one year of menopause) will have a urine pregnancy test. Screening urine tests must be negative to proceed.

The investigator will review the patients' medical history (section 6.5), migraine treatment history, and history of substance abuse. He/she will perform a physical examination. The patient will have an electrocardiogram (ECG) performed during the screening visit (section 6.6).

The height will be measured in inches, without shoes. The weight will be measured in pounds, with patients dressed in indoor clothing, shoes removed. During measurement of blood pressure and pulse, patients are required to sit in chairs with legs uncrossed for five minutes before measurements are collected (Section 15.10 and 15.11).

Procedures of the Screening Visit:

- Height, weight,
- Blood pressure, pulse (values must be in the range outlined in appendix 4).
- Electrocardiogram
- Draw blood samples for laboratory assessment (blood count, hepatic and renal function)

If it is determined during the Screening Visit that a patient cannot participate in the trial for any reason, or if the screening visit laboratory assessments are outside the acceptable range the patient will be considered as screening failure.

During the Screening Visit, the investigator will complete the following documents:

- Screening Visit progress note
- Inclusion/Exclusion Criteria,
- Demographics, Baseline Information, Medications, Diagnoses, Study Drug Number Assignment CRF, and
- Medical History/Physical Exam.

The investigator will complete the CRF form in two-part carbonless paper forms (provided by the sponsor) copies of the form are available in the protocol attachments section.

During the screening visit, patients will be asked to rate their satisfaction with migraine prevention (0=Not at all satisfied, 1=Partly satisfied, 2=Satisfied, 3=very satisfied) and to complete the following instruments:

- Migraine Disability Assessment Scale (MIDAS),
- Headache Impact Test (HIT-6), and
- Pittsburgh Insomnia Rating Scale-20 (PIRS-20).

Patients with concomitant emotional pain co-existing with episodic migraine would be asked to complete the emotional daily diary as well as the migraine prevention daily diary. Additionally, they will complete the Beck's depression inventory every visit.

Patient with concomitant CLBP would be asked to complete a CLBP daily diary as well as the migraine prevention daily diary. Additionally, they will complete the Oswestry Disability Index instrument on every site visit.

The site will contact the patient by phone on day 8 and day 15 (±2 days) of the baseline period.

4.4 Study Visit 2 - the Randomization Visit

After completing a 28-day baseline period, patients will return for the Randomization Visit.

Patients whom the baseline period Migraine Diary showed at least 4 moderate-to-severe migraine headache days but 15 or less headache days, Screening Visit blood work is in the acceptable range, and continued to meet all other inclusion/exclusion criteria, will be eligible to continue.

Patient must have in Visit 2, a negative urine drug screen, and urine pregnancy test (for childbearing age women). The blood pressure and pulse must be in the acceptable range.

Patients will be randomized in a 1:1 ratio to naltrexone [redacted] mg/acetaminophen [redacted] mg (ALLOD-2) or placebo and enter into the 12-week Treatment Period.

The investigator must be the person performing the randomization procedure. The investigator will label each of the four vials in the assigned study drug bag with the birth year. Double-checking procedure is required during the dispensing of the study drug.

Randomized patients will receive a paper Migraine Diary form and study drug (one vial containing 85 large capsules and one vial containing 85 small capsules) to use in the outpatient

settings.

During the Randomization Visit, patients will complete the following instruments:

- Migraine Disability Assessment Scale (MIDAS),
- Headache Impact Test (HIT-6), and
- Pittsburgh Insomnia Rating Scale-20 (PIRS-20).

The investigator will instruct the patient on how to use the study drug, what to do in the event of adverse effects and to return the medication vials in the next site visit. The investigator will set up all the upcoming follow up site visit appointments and phone contacts.

4.5 12-Week Outpatient Treatment Period

On Day 0 (the day of Visit 2) of the Treatment Period patients will take the first dose of the study drug at 8:00 p.m., and continue to take one capsule from each of the two vials twice a day (approximately 8:00 a.m. and 8:00 p.m.) during each day the 12-week Treatment Period. If deemed necessary due to intolerance, the investigator will decrease the patient's dose to one dose a day - the 8:00 p.m. dose, for the duration of the Treatment Period.

Patients will complete the Migraine Diary at 10 p.m. every day or at bedtime (whichever is earlier).

4.6 Study Visit 3 – 1 week after the Treatment Period started

During this visit, the investigator will confirm the patient understanding of how to take the study drug and how to complete the daily Migraine diary. During this visit, assessment of adverse events and adjustment to the study drug dose can be made. The patient will complete the PIRS-20 and receive study drug.

4.7 Study Visit 3 and Study Visit 4

The Treatment Period follow-up visits take place at the end of Week 4, and week 8 of the Treatment Period.

The investigator will ensure that the subject has not withdrawn the informed consent and continues to meets inclusion/exclusion criteria. The investigator will review the completed Migraine Diary form, reconcile the study drug, and interview subjects regarding adverse events by directly asking, "Have you had any health concerns since the last time you were seen?" The subject should be questioned regarding AEs in a general way, without asking about existence of specific symptoms. The investigator will question use of concomitant medications, or any prohibited medications since the last visit.

Weight, blood pressure and pulse will be measured.

In Visit 3, patients will receive the second vial containing 85 large capsules and the second vial containing small capsules. In Visit 4, patients' study drug vials will be counted, reconciled and returned to the patients.

Visit 3 and Visit 4 procedures:

1. Review the Migraine Diary form for completeness.

2. Review use of additional pain medications.
3. Interview patients regarding adverse effect.
4. Vital signs (B/P, pulse, weight).
5. Urine pregnancy for women of childbearing age.
6. Reconcile study drug.
7. Draw blood samples for laboratory assessments

The investigator will complete the following forms:

1. Update the patient contact information (if necessary)
2. Update the concomitant medications/concomitant diagnoses CRF
3. Complete progress note

Source/CRF forms are available in the protocol attachments section.

During the Visit 3, and Visit 4, patients will be asked to rate their satisfaction with migraine prevention (0=Not at all satisfied, 1=Partly satisfied, 2=Satisfied, 3=very satisfied) and to complete the following instruments:

- Migraine Disability Assessment Scale (MIDAS),
- Headache Impact Test (HIT-6), and
- Pittsburgh Insomnia Rating Scale-20 (PIRS-20).

The investigator will complete the following forms for the end-of-study visit:

4. Update the patient contact information (if necessary)
5. Update the concomitant medications/concomitant diagnoses CRF

Complete progress note

- Migraine Disability Assessment Scale (MIDAS),
- Headache Impact Test (HIT-6), and
- Pittsburgh Insomnia Rating Scale-20 (PIRS-20).

4.8 Study Visit 5 - End-of-Treatment Visit

The End-of-Treatment visit will take place on day 85 (+5 days).

During the end-of-treatment visit, patients will return the completed Migraine Diary form and the study drug vials.

The end-of-study visit procedures:

8. Review the Migraine Diary form for completeness.
9. Review use of additional pain medications.
10. Interview patients regarding adverse effect.
11. Brief physical examination.
12. Vital signs (B/P, pulse, weight,).

13. Draw blood samples, (complete blood count, hepatic function, and renal function)
14. Urine pregnancy for women of childbearing age.
15. Reconcile study drug.

During Visit 5, patients will be asked to rate their satisfaction with migraine prevention (0=Not at all satisfied, 1=Partly satisfied, 2=Satisfied, 3=very satisfied) and to complete the following instruments:

- Migraine Disability Assessment Scale (MIDAS),
- Headache Impact Test (HIT-6), and
- Pittsburgh Insomnia Rating Scale-20 (PIRS-20).

The investigator will complete the following forms for the end-of-study visit:

6. Update the patient contact information (if necessary)
7. Update the concomitant medications/concomitant diagnoses CRF
8. Complete progress note

Source/CRF forms are available in the protocol attachments section.

If a patient discontinues participation in the study after taking the study drug, every attempt should be made to collect efficacy and safety data. (Section 4.12).

4.9 Study Visit 6, End-of-Study Visit

This visit will take place on day 28 (+5 - day visit window) of the Follow-up Period. During the Follow-up Period, patients will continue to complete the daily diary, but they will not consume the study drug. Patients may resume opioid medications 7 days after taking the last dose of the study drug.

During Visit 6, patients will be asked to rate their satisfaction with migraine prevention (0=Not at all satisfied, 1=Partly satisfied, 2=Satisfied, 3=very satisfied) and to complete the following instruments:

- Migraine Disability Assessment Scale (MIDAS),
- Headache Impact Test (HIT-6), and
- Pittsburgh Insomnia Rating Scale-20 (PIRS-20).

The investigator will complete the following forms for the end-of-study visit:

1. Update the patient contact information (if necessary)
2. Update the concomitant medications/concomitant diagnoses CRF
3. Complete progress note

5 DEFINITION OF EVALUATIONS AND SPECIAL INSTRUCTIONS

This section explains the procedures found in Visit Encounter for the Migraine Prevention Study (Section-16.4).

5.1 Informed Consent Procedure

The Informed Consent process will occur during the Screening visit. The Clinical Investigator will discuss the trial protocol with the patient, what is expected of the patient, and the fact that the patient is free to withdraw from the trial at any time for any reason. The investigator must be present to answer questions, obtain written consent and to sign the Informed Consent (IC).

5.2 Inclusion/Exclusion Criteria

The Clinical Investigator will sign off on the inclusion/exclusion criteria.

5.3 Patient Education and the Four-Point Likert Scale Instrument

The investigator will educate patients as described in Section-3.2. A four-point unipolar Likert scale is used for headache pain and AE assessments (i.e., 0=none, 1=mild, 2=moderate, 3=severe) (TABLE 11), while a binary scale (present or absent) is used for migraine associated symptoms.

5.4 The Migraine Diary Instrument

The Migraine Diary is a carbonless paper duplicate form. The Migraine Diary is a patient reported daily assessments of headaches. It includes assessment of the severity and duration of headaches; associated migraine symptoms and satisfaction with migraine prevention. It includes usage of rescue medication.

Each daily assessment includes:

- Use of the study drug
- Use of Add. Pain Meds
- Headache Pain (0=None, 1=Mild, 2=Mod, 3=Severe),
- Light Sensitivity, Noise Sensitivity, Neck/Shoulder Pain (Absent=0 Present=1),
- Nausea (0=None, 1=Mild, 2=Moderate, 3=Severe).

5.5 Medical History, Physical Examination and Vital Signs Assessment

A Physical Examination will be conducted before patients are randomized and as needed during other site visits, the study physician or a nurse practitioner can conduct the physical examination. The physical examination should include evaluation of the general appearance, head, eyes, ears, nose, throat, neck, thyroid, chest, lungs, cardiovascular, abdomen, musculoskeletal, lymph nodes, extremities/skin and neurological examination.

The patient will have their vital signs taken. The height will be measured without shoes, in inches during the Screening Visit. The weight will be measured in pounds and rounded to the nearest half pound. With the patient dressed in indoor clothing, shoes removed. Patients should be weighed on the same scale every visit. For blood pressure and pulse measurements, patients are required to sit in chairs with legs uncrossed for five min before measurements are collected (refer to appendices 10 and 11 for more details on blood and pulse measurements).

For blood pressure and pulse measurements, patient should remove all clothing that covers the location of cuff placement. The Patient should refrain from talking during the procedure.

Weight, pulse, and blood pressure will be measured during every site visit.

5.6 Electrocardiogram

The Clinical Investigator will review the standard 12-lead ECG before randomization.

5.7 CBC, Hepatic and Renal Function Assessments

Patients will have non-fasting blood samples drawn at Visit 1, 3, 4, and 5. Analysis of the blood will include CBC, hepatic function (SGOT (AST), SGPT (ALT), Total Bilirubin, Alkaline Phosphatase), and renal function (BUN, and Creatinine). The purpose of evaluation is to screen out patients with hepatic or renal disease and to follow-up potential effect of the investigational drug on the hepatic and the renal function.

Patients who are known to have abnormal renal and/or hepatic function will be excluded from participation in the trial if their values are:

- Abnormal liver function tests with values ≥ 2 times the upper limit the normal range (ULN) for aspartate transaminase (AST/SGOT), alanine transaminase (ALT/SGPT), or alkaline Phosphatase, or total bilirubin level > 1.5 times the ULN, Patients with a total bilirubin level > 1.5 times the ULN due to Gilbert's syndrome will be allowed in the trial.
- Impaired kidney function with BUN or serum creatinine > 1.5 times the ULN.

The site phlebotomist will collect the blood samples into one tiger top tube and one lavender top tubes. Laboratory Corporation of America (Tampa, FL) will analyze the blood sample.

5.8 Five Panel Urine Drug Test and urine Pregnancy Test

At the Screening Visit, patients will be tested with a five-panel urine drug test, for the presence of cocaine, marijuana, opiates, methamphetamines, and Oxycodone.

Female patients of childbearing age will have a urine pregnancy test.

5.9 Concomitant Diagnosis and Treatments

Medical history, demographics information, and prior/concomitant medication information will be collected. Significant medical history including events up to the Screening Visit, diagnoses and procedures, approximate start date, stop date, disposition, and treatments will be recorded.

5.10 Concomitant Medications

The Clinical Investigator will review concomitant medications and treatments. Any prescription or over-the-counter medications patients are taking regularly will be recorded. The following information will be obtained: generic name, dose / unit, route of administration, frequency of administration per day, approximate start date, stop date, and disposition (ongoing or discontinued).

5.11 Adverse Events Assessment

Patients will be interviewed during the End-Of-Study Visit about any adverse events they may have experienced after taking the study drug.

5.12 Patient's Contact Information

The patient's contact information form will be completed before or during the Screening Visit. The personal contact information includes, name, address, phone number, email address, work contact information, the name and contact information of the treating physician, emergency contact, how did the patient learn about the study, and who referred them to the study.

The information should be reviewed with the patient and updated through the trial, the contact information form will be placed in patient's file as well as a copy of the patient's valid form of photo I.D.

5.13 Cardiovascular Risk Factor Assessment

Patients' cardiovascular risk assessment will be conducted during the Screening Visit. The following parameters will be assessed: Hypertension history of ≥ 140/90 or on treatment for it. Diabetes history (FBG ≥ 126 mg %) or on treatment for it. Obesity (BMI > 30). History of cholesterol ≥ 240. History of smoking ≥ 10 pack years. Parent had a stroke. Parent with Diabetes. Alternatively, no to all.

6 DRUG INTERACTIONS WITH THE IP AND POSSIBLE ADVERSE REACTIONS

6.1 Effects of Acetaminophen and Ethanol on Liver

Substances that induce or regulate hepatic cytochrome enzyme CYP2E1 may alter the metabolism of acetaminophen and increase its hepatotoxic potential. The clinical consequences of these effects have not been established. Effects of ethanol are complex, since excessive alcohol usage can induce hepatic cytochromes, but ethanol also acts as a competitive inhibitor of the metabolism of acetaminophen.[36]

Administration of acetaminophen 4g/day up to 12 months/ was well tolerated in the treatment of osteoarthritis of the hip or knee.[37]

6.2 Effects of Anticoagulants on Acetaminophen

Chronic oral acetaminophen use at a dose of 4000 mg/day has been shown to cause an increase in international normalized ratio (INR) in some patients who have been stabilized on sodium warfarin as an anticoagulant [38]

6.3 Naltrexone Hepatotoxicity Warning

Naltrexone packaging insert carries a warning for hepatotoxicity "Cases of hepatitis and clinically significant liver dysfunction were observed in association with naltrexone

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[36] FDA - Acetaminophen Overdose and Liver Injury — Background and Options for Reducing Injury (May, 2009) http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM164897.

[37] Anthony R. Temple, et al. Multicenter, randomized, double-blind, active-controlled, parallel-group trial of the long-term (6–12 months) safety of acetaminophen in adult patients with osteoarthritis. Clinical therapeutics February 2006Volume 28, Issue 2, Pages 222–235

[38] Gregory J. Hughes, et al., Effect of Acetaminophen on International Normalized Ratio in Patients Receiving Warfarin Therapy; Pharmacology and Drug Therapy, Volume 31, Issue 6, pages 591–597

hydrochloride exposure during the clinical development program and in the post-marketing period. Transient, asymptomatic hepatic transaminase elevations were also observed in the clinical trials and post-marketing period. When patients presented with elevated transaminases, there were often other potential causative or contributory etiologies identified, including pre-existing alcoholic liver disease, hepatitis B and/or C infection, and concomitant usage of other potentially hepatotoxic drugs." Placebo-controlled studies employing up to fivefold higher doses of REVIA (up to 300 mg per day) than that recommended for use in opiate receptor blockade have shown that REVIA causes hepatocellular injury in a substantial proportion of patients exposed at higher doses."

"An increase in naltrexone AUC of approximately 5- and 10-fold in patients with compensated and decompensated liver cirrhosis, respectively, compared with subjects with normal liver function, has been reported. These data also suggest that alterations in naltrexone bioavailability are related to liver disease severity."[39]

6.4 Vulnerability to Opioid Overdose

The naltrexone-packaging insert carries a warning for vulnerability to opioid overdose, "After opioid detoxification, patients are likely to have reduced tolerance to opioids. As the blockade of exogenous opioids provided by naltrexone hydrochloride wanes and eventually dissipates completely, patients who have been treated with naltrexone hydrochloride may respond to lower doses of opioids than previously used, just as they would shortly after completing detoxification."

6.5 Precipitated Opioid Withdrawal

"The symptoms of spontaneous opioid withdrawal (which are associated with the discontinuation of opioid in a dependent individual) are uncomfortable, but they are not generally believed to be severe or necessitate hospitalization. However, when withdrawal is precipitated abruptly by the administration of an opioid antagonist to an opioid-dependent patient, the resulting withdrawal syndrome can be severe enough to require hospitalization. Symptoms of withdrawal have usually appeared within five min of ingestion of REVIA and have lasted for up to 48 hours. Mental status changes including confusion, somnolence and visual hallucinations have occurred. Significant fluid losses from vomiting and diarrhea have required intravenous fluid administration. Review of post-marketing cases of precipitated opioid withdrawal in association with naltrexone treatment has identified cases with symptoms of withdrawal severe enough to require hospital admission, and in some cases, management in the intensive care unit. "

6.6 Depression and Suicidality

The naltrexone-packaging insert carries a warning for Depression and Suicidality, "Depression, suicide, attempted suicide and suicidal ideation have been reported in the post-marketing experience with naltrexone hydrochloride used in the treatment of opioid dependence. No causal

[39] CONTRAVE (naltrexone HCl and bupropion HCl) ExtendedRelease Tablets package insert (Initial U.S. Approval: 2014) http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/200063s000lbl.pdf

relationship has been demonstrated. In the literature, endogenous opioids have been theorized to contribute to a variety of conditions."

6.7 Potential Hepatotoxicity Risks of the Investigational Drug

Hepatotoxicity and potential Drug Induced Liver Injury (DILI) have been associated with both components of the investigational drug and may be an anticipated risk. [40, 41] Acetaminophen has a narrow safety margin; exceeding four grams per day can cause serious liver injury-even death. However, liver toxicity due to both acetaminophen and naltrexone is clearly dose-dependent.

The dose of [redacted] mg of acetaminophen contained in the investigational drug constitutes 8% of the daily maximum dose of 4000 mg. The dose of [redacted] mg of naltrexone contained in the Investigational drug is 4.5% of the 50 mg daily-approved dosage (used for treatment of opioid and alcohol dependence).

In this study, the study drug will be administered twice a day for a 12-week Treatment Period.

The low dosage of both constituents in ALLOD-2 significantly diminishes the likelihood of hepatotoxicity.

The OFIRMEV™ (acetaminophen for injection) package insert indicates, "Use caution when administering acetaminophen in patients with the following conditions: hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia (e.g., due to dehydration or blood loss), or severe renal impairment (creatinine clearance ≤ 30 mL/min)."

The mechanism of liver injury caused by acetaminophen is due to small amount of acetaminophen converted to a toxic metabolite - NAPQI (N-acetyl-p-benzoquinone imine). The toxic metabolite binds with liver proteins to cause cellular injury. The amount of toxic metabolite produced and the ability of the liver to remove this metabolite before it binds to liver protein influence the extent of liver injury. [42]

6.8 Hepatotoxicity Stopping Rules

Due to hepatotoxicity concerns with both components of the Investigational drug, to evaluate for potential drug induced liver injury (DILI), laboratory evaluation of liver function test will be conducted at baseline and 2-days after taking the study drug).

In the event of abnormal liver function tests, the following can be considered a basic guide for discontinuation of treatment. (Irrelevant for this single-dose study). In the event of abnormal LFT's with limits below, patients will be followed until abnormalities returns to normal or to the baseline state.

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[40] FDA - Acetaminophen: Background and Overview (29 2009) Available at: http://www.fda.gov/downloads/Advisor.../UCM175767.pdf

[41] Acetaminophen Overdose and Liver Injury - Background and Options for Reducing Injury, (May 22, 2009) http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM164897.

[42] FDA - Acetaminophen Overdose and Liver Injury — Background and Options for Reducing Injury (May 22, 2009) http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DrugSafetyandRiskManagementAdvisoryCommittee/UCM164897.

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)"

DILI may develop or progress even after the causative drug has been stopped. Results should be recorded on the case report form. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be DILI, indicating that liver injury was related to underlying liver disease.

One of the critical purposes of close observation is to gather additional clinical information to determine the most likely cause or causes of the observed abnormalities, and specifically, whether there is a cause other than the study drug, such as one of the following common causes. Other less common causes also may need to be considered.

Exclusion of the two ABCs (i.e., viral hepatitis A, B, or C; alcoholic or autoimmune hepatitis, biliary disorders, and circulatory disorders) as causes of liver injury should be attempted in all cases of suspected DILI, and the results should be recorded. There is a practical limit as to how much testing should be done to exclude less common liver diseases, such as acute Wilson's disease or alpha-1-antitrypsin deficiency.

Patient discontinued from the study based on abnormal LFTs, must be reported as an AE or SAE. The sponsor will be responsible for reporting to the FDA.

6.9 Management of Liver Transaminase Elevation

In general, an increase of serum liver enzymes to > 3x ULN should be followed by repeat testing within 24 to 48 hours of all four of the usual serum measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry about symptoms (i.e. including the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia). Patients must be closely observed according to the following:

Repeating liver tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or study drug has been discontinued and the patient is asymptomatic.

- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., International Normalized Ratio (INR).
- Considering gastroenterology or hepatology consultation.

The observation of the critical importance of altered liver function has been referred to informally as Hy's Law.

Briefly, Hy's Law cases have the following three components:

1. The drug causes hepatocellular injury, generally shown by more frequent 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control agent or placebo.
2. Among patients showing such aminotransferase elevations, often with aminotransferases much greater than 3xULN, some patients also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (serum alkaline phosphatase (ALP) activity >2xULN).

No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C, preexisting or acute liver disease, or another drug capable of causing the observed injury.

7 MANAGEMENT OF THE INVESTIGATIONAL DRUG

7.1 Investigational Drug Allocation, Dispensation, Labeling and Packaging

The study pharmacist will control the randomization scheme. The randomization code will not be revealed until after the data lockout.

The study drug is placed in sequentially numbered vials. Each vial contains two purple capsules, a size 3 (small) capsule and a size 0 capsule (large). Patients will be instructed to take the two capsules together. The vials have identical labeling and appearance. The capsules have the same appearance, weight, color, and sound the same when shaken. The site will administer the study drug vials sequentially.

The investigational drug vials were labeled according to Good Manufacturing Procedure guidelines. The medication vials label includes the following items: patient identifier, study drug name, dosage strength, lot number, protocol number, number of tablets, caution statement for Investigational Products, storage instructions, and sponsor identification.

The study drug will be kept in the site under proper conditions (in a locked cabinet in a temperature-controlled room). The vial number administered to each patient will be documented in a medication log.

The sites must save all empty packaging or packaging containing unused tablets for final disposition by the sponsor or sponsor representative.

Acute migraine rescue medications will not be provided by the study.

7.2 Receipt of Investigational Drug Supplies

The study drug will be delivered to the site and a chain of custody will be maintained.

Upon receipt of study product, the investigator or designee should ensure that the information on the packing slip matches the study product received. At a minimum, the recipient should verify the following: product identification, amount of product received, lot numbers, expiration dates,

physical product is in good condition, and proper maintenance of storage conditions during transport. A copy of shipping manifests will be kept in the regulatory folder.

Evidence of breakage, compromised storage, or product tampering should be reported to the sponsor immediately and the study product should be quarantined and maintained under the correct storage conditions until further instructions are given. Investigational drugs will not be dispensed until proper authorization that the enrollment process can begin.

7.3 Investigational drug Dispensation

A mechanism must be established to ensure that the investigational drug is dispensed only upon the order of the Clinical Investigator, as stated on FDA 1572 form. FDA 1572 Form is a binding document, whereby by completing and signing the FDA 1572 form the Investigator has certified that the study product is administered only to patients under his/her personal supervision or under the supervision of co-investigators responsible to him/her.

At randomization, The Investigator will assign the sequential vial number from the study drug container to a patient (using double-checking medication dispensation procedure, discussed below in more details) and document the vial number administered in the appropriate logs. Post-randomization, the vial I.D. number becomes the patient's study I.D. The Investigator will label each of the vials with the patient's birth year.

7.4 Double-Checking Procedure during Dispensation of the Study Drug

Double-checking medication dispensation is a means of reducing medication errors. Medication dispensation errors pose a threat to patient safety, and a risk to data integrity. Double-checking medication dispensation procedure involves two staff members; the responsibility of the second staff member is to conduct a verification of the work performed by the first.

Double-checking is required during two steps of the medication dispensation process. First, when removing the investigational drug vial from the medication container, and second, when the medication vial is dispensed to the patient. Two staff members, side-by-side, must ensure that all information on the medication vial is accurate with regard to patient and ensuring that the investigational drug vial is delivered, in person, to the positively identified patient. Once the two steps are complete, the staff members will co-initial the medication log.

7.5 Ensuring Compliance with the Investigational Drug and Reconciliation

The investigator is responsible for maintaining strict control over the investigational drug and maintains of an inventory log during the study, any discrepancies must be investigated, resolved, and documented. The Clinical Investigator must also ensure proper security and storage of the investigational drug.

Each time an investigational drug vial is dispensed or returned, the event will be documented in the medication log. The medication vials returned by the patient will be returned to the container.

At study completion, the investigational drug container will be retained at the study sites as part of the record.

7.6 Drug Accountability Monitoring

During routine visits, the trial monitor will assess the clinic's dispensing procedures, the patient compliance, and ensure proper drug storage and temperature log maintenance. The monitor will also verify that the Clinical Investigator or an authorized representative is the person dispensing the medication. Further, the monitor will confirm that all investigational drugs are accounted for, investigate any discrepancies, and resolve all items before site closure. There should be evidence that entries into the logs were made in real time (at the time the action took place). Any identified inappropriate practices will prompt retraining of site staff as needed. An auditor may conduct similar document reviews at any time. Documentation should support proper storage and security of the drug. In all, the documentation should provide a full and accurate explanation of drug handling from receipt through final disposition.

7.7 Investigational Drug Storage

The supply of investigational drug will be stored in a locked cabinet in a room with climate control maintaining the temperature within a range of 20°-25° C (68°-77° F). A temperature log must be maintained in the storage room and the temperature will be recorded once every working day. Access to trial drug will be limited to the Clinical Investigator and his/her designees. The Clinical Investigator must maintain an inventory record of the investigational drug received, dispensed, and returned.

7.8 Emergency Preparedness Measures for Investigational drug

Site SOPs will dictate preparedness for emergencies, such as power outages, floods, hurricanes, etc. to protect the integrity of the investigational drug and to minimize the impact of potential interruptions to the clinical trial.

7.9 Blinding and Emergency Un-Blinding

All study staff will be blind to treatment assignments. Sponsor's staff involved in data management, data analysis and trial monitoring will not have access to the randomization code during the trial.

In emergencies that involve patient safety, the identity of the investigational drug assignment can be revealed. Pharmacy staff charged with packaging the investigational drug will have access to the randomization. In the event of an SAE, the randomization assignment can be un-blinded by the study pharmacist, in a communication not shared with the sponsor, the study pharmacist will inform the necessary parties of the individual's name, patient I.D. number and randomization code assignment. The sponsor will report all relevant and required information to the FDA, IRB and all other required regulatory agencies. The Clinical Investigator is encouraged to contact the sponsor to discuss their rationale for un-blinding, although sponsor approval is not required prior to un-blinding. The Clinical Investigator will be able to obtain the code break information independent of the sponsor. When breaking the blinding code, the Clinical Investigator will fully document the date, time, the site staff involved, and the reason for the un-blinding in the source documentation. The Clinical Investigator must notify the sponsor of the un-blinding within 24 hours.

7.10 Drug Product Quality Complaints (PQC) Reporting

Product quality complaints can be issued by the study site staff, patient, regulatory agency, or other third party that alleges deficiencies or dissatisfaction related to identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness or performance of a drug product after it is released for distribution. Relevant examples include:

- Incorrect or missing labeling
- Packaging issues (e.g., damaged, dirty, crushed, missing product)
- Vial defects (e.g., under fill or overfill, no safety seal)
- Product defect (e.g., odor, chipped, broken, embossing illegible)
- Loss or theft of product

The Clinical Investigator must notify the sponsor within 24 hours of becoming aware of the product quality complaints.

7.11 Investigational Drug Return

At the end of the study, or as directed by the sponsor, all investigational drug, including unused, partially used, or empty vials, will be returned to a designee as instructed by the sponsor. Investigational drug will be returned only after the trial monitor has completed a final inventory to verify the quantity to be returned. The return of investigational drug must be documented and the documentation included in the shipment. At the end of the study, a final Investigational drug reconciliation statement must be completed by the investigator, or designee, and provided to the sponsor.

All Investigational drug inventory forms must be made available for inspection to the sponsor's representative (e.g. site monitor) and any authorized inspector from a regulatory agency. The investigator is responsible for the accountability of all used and unused study supplies at the clinic.

8 SAFETY AND ADVERSE EVENTS MANAGEMENT

8.1 Adverse Event Definition

Unanticipated problems involving risk to patients or others any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency, (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the Investigator's brochure, etc.)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places patients or others at greater risk of harm, (including physical, psychological, economic, or social harm).

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study Examples of AEs include symptoms of dizziness or nausea, or signs of bradycardia or hypotension. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the Clinical Investigator to be of clinical significance
- serious adverse event (SAEs)

An adverse event is classified as "serious" if it results in any of the following outcomes:

- death
- is life-threatening (an event in which the patient was at risk of death)
- inpatient hospitalization or prolongation of existing hospitalization
- persistent or significant disability/incapacity
- a congenital abnormality/birth defect
- is an important medical event
- note: SAEs includes conditions that do not require hospitalization but require intensive treatment at home or in the emergency room (e.g. severe allergic reaction, a seizure that did not result in inpatient hospitalization). Elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment should not be classified as SAE's.

  All adverse events that do not meet any of the criteria for serious, should be regarded as non-serious adverse events.

8.2 Adverse Event Prompting Procedure

At each visit, including telephone visits, the Clinical Investigator must passively capture spontaneously reported adverse events and seek information from the patient regarding adverse events with use of an open-ended prompt, by directly asking: "Have you had any health concerns since the last time you were seen?" The patient should be questioned regarding AEs in a general way, without asking about existence of specific symptoms. Additionally, AEs will be captured when patients call the site from home reporting an AE. If appropriate or necessary, further evaluations shall be conducted.

8.3 Recording of Adverse Events

Information on all adverse events should be recorded in the source document immediately, and in the adverse event CRF. All clearly related signs, symptoms, and abnormal diagnostic

procedures results should be recorded in the source document, though they should be grouped under one diagnosis. All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

8.4 Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 28 days following the last administration of investigational drug.

8.5 Preexisting Conditions

A pre-existing condition is one that is present at the start of the study. A pre-existing condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

8.6 Post-study Adverse Event

All unresolved adverse events should be followed by the Clinical Investigator until the events have resolved. At the last scheduled visit, the Clinical Investigator should instruct each patient to report any subsequent event(s) that the patient, or the patient's personal physician, believes might reasonably be related to participation in this study. The Clinical Investigator should notify the study sponsor of any death or adverse event occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the Clinical Investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that has participated in this study.

8.7 Determination of Abnormal Laboratory Values as Adverse Events

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic

investigation, etc.

The investigator should evaluate the laboratory, vital sign, or ECG abnormalities, for clinical significance, they should be reported as AEs if they are symptomatic, lead to study drug discontinuation or require corrective treatment.

8.8 Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event. Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization, for diagnostic or elective surgical procedures for a preexisting condition.
- Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical Investigator.

8.9 Reporting of Serious Adverse Events and Unanticipated Problems

Investigators and the sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum, those events that must be reported are those that are:

- Related to study participation,
- Unexpected, and
- Serious or involve risks to patients or others (refer to definitions, section 7.1).

8.10 Clinical Investigator reporting and notifying the study sponsor

Any study-related unanticipated problem posing risk of harm to patients or others, and any type of serious adverse event, must be reported to the study sponsor by telephone within 24 hours of the event. To report such events, a Serious Adverse Event (SAE) form must be completed by the investigator and faxed to the study sponsor within 24 hours. The Clinical Investigator will keep a copy of this SAE form on file at the study clinic. Within the following 48 hours, the Clinical Investigator must provide further information on the serious adverse event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Serious Adverse Event form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing serious adverse events should be provided

promptly to the study sponsor

8.11 Categorizing Relationship of AE's to Investigational drug

Investigators will determine the relationship between each AE and the Investigational drug. The determination will reflect whether in the opinion of the Investigators

- A relationship exists
- Possibly exists, or
- Does not exist.

The outcome of AEs must be recorded on CRFs; outcome categories are as follows:

- Resolved, no sequelae
- Still present not being treated
- Still present and being treated
- Residual effects present but not treated
- Residual effects but being treated
- Death
- Unknown

Symptoms of the disease under study (migraine) should not be reported as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease. However, significant worsening of the symptoms should be recorded as an AE.

8.12 Non-Serious Adverse Events

All adverse events that are not identified as serious or life threatening is considered non-serious adverse events. Non-serious adverse events will be identified by severity and is recorded in the CRF patient to the pertinent severity scale. A new AE is recorded if and when a pre-existing AE worsens.

The medical assessment of severity is determined by using the following definitions:

- Mild: AE that is transient requiring only minimal treatment.
- Moderate: an AE that usually requires treatment, but poses no significant or permanent harm to the patient.
- Severe: AE that interrupts activities of daily living, and may require intensive treatment.

Non-serious adverse events must be reported to sponsor by the completion of the Adverse Event Form. Non-serious adverse events and non-serious suspected adverse reactions are reported to the sponsor periodically throughout the duration of the study. The Clinical Investigator must report this information to the sponsor within a maximum of 21 days of the recording of the non-serious suspected adverse event.

8.13 Other Reportable Events

The following events are also reportable to the sponsor:

- Any adverse experience, defined as an untoward or unfavorable medical occurrence in a human patient, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the patient's participation in research, whether or not considered related to the patient's participation in the research) that is considered:
    - Serious: Death; a life-threatening adverse drug experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability or incapacity; or a congenital anomaly or birth defect; and
    - Unexpected: Any adverse experience, the specificity or severity of which is not consistent with the current Clinical Investigator brochure or consent form; and
    - Possibly related: There is a reasonable possibility that the incident, experience, or outcome may have been associated with the procedures involved in the research; and
    - Is experienced by a participant in a trial
- Information that indicates a change to the risks or potential benefits of the research, in terms of severity or frequency, For example:
    - An interim analysis indicates that patients have a lower rate of response to treatment than initially expected.
    - Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected.
    - A paper is published from another study that shows that an group of your research study is of no therapeutic value.
- Change in FDA safety labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- Breach of confidentiality
- Change to the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research participant.
- Complaint of a participant when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- Protocol violation (meaning an accidental or unintentional violation from the IRB approved protocol) that in the opinion of the Clinical Investigator placed one or more patients at increased risk, or affects the rights or welfare of patients

8.14 Sponsor Reporting and Notifying the FDA

The study sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of AEs are referred to as IND safety reports. The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- Within 7 calendar days

Any study event associated with the use of the study drug that is:

- Unexpected,
- Fatal or life-threatening, and

- Within 15 calendar days Any study event associated with the use of the study drug, that is:
  - Unexpected, and
  - Serious, but not fatal or life-threatening

    -Or-

  - A previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

8.15 FDA Reporting Process and Sponsor Notifying Participating Investigators

Adverse events may be submitted on FDA Form 3500A or in a narrative format.

The sponsor is responsible of notifying all the investigators of any serious and/or unexpected adverse event associated with the use of the drug. Additionally, the sponsor is required to identify in the IND safety reports all previous reports concerning similar adverse events and to analyze the significance of current event in light of the previous reports.

8.16 Pregnancy Prevention and Counseling

Women of childbearing potential are defined as any female who has experienced menarche and who is NOT permanently sterile or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

The female patient who is premenopausal or postmenopausal less than 1 year, or have not had surgical sterilization (i.e., tubal ligation, partial or complete hysterectomy), must have a negative urine pregnancy test, be non-lactating, and commit to using 2 methods of adequate and reliable contraception throughout the study and for 28 days after taking the last dose of the study drug (e.g., barrier with additional spermicidal, intra-uterine device, hormonal contraception).

The Clinical Investigator will discuss with women of childbearing age before enrollment the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy, pregnancy prevention information, contraceptives in current use and guidelines for the follow-up of a reported pregnancy. The patient must sign an Informed Consent stating that the above - mentioned risk factors and the consequences were discussed with her.

During the trial, all women of childbearing potential should be instructed to contact the Clinical Investigator immediately if they suspect they might be pregnant. If pregnancy is confirmed, the investigational drug will be discontinued and the patient will be withdrawn from the trial.

Any pregnancy of a study participant must be reported to the sponsor within one business day. The study participant must be withdrawn from the study. Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the duty of the Clinical Investigator to obtain this information within 30 calendar days after the initial

notification and approximately 30-calendar days, post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Serious Adverse Event Form. An elective abortion is not considered a serious adverse event (SAE).

8.17 Abuse, Misuse, Overdose and Medication Error of Investigational Drug

Abuse, misuse, overdose or medication error regarding this study's Investigational drug must be reported to the sponsor following the SAE reporting procedure whether or not they result in an AE/SAE, however, the one business day reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose or medication errors unless these result in an SAE.

A medication error made regarding prescribing, dispensing, administration and/or use of an Investigational drug will be reported as a major protocol violation. Medication errors should be collected and reported only for the Investigational drug. The administration and/or use of an expired product should be considered as a reportable medication error, missing doses are not reportable as medication errors.

The potential for misuse or abuse of naltrexone or acetaminophen is low.

The definition of an overdose with the investigational drug for the purpose of this study is intake of more than 12 tablets per day (intentional or unintentional). This corresponds to consumption of more than 3900 mg of acetaminophen. Twelve tablets of the investigational drug contain 30 mg of naltrexone, which is lower than the 50 mg/day approved dose. The occurrence of an overdose with the investigational drug will managed as an emergency.

9 DATA HANDLING AND RECORD KEEPING

9.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the site study staff under the supervision of the Investigator. The Investigator must review all source documents and laboratory reports for accuracy and completeness. The investigator or designee must address any unanticipated problems that might occur.

9.2 Source Documentation Requirements

Data should be handled in accordance with GCP, U.S. federal regulations and local regulations (if applicable). All source documents should be filled out completely by the Clinical Investigator or the study coordinator and should be signed by the person collecting the data on that form. The Clinical Investigator will review, sign and dated the source documents. Whenever possible, source documents should not identify patients by name but by study I.D., such identifiers facilitate cross-indexing of the participant's data while protecting the patient's privacy.

Data entries into source/CRF documents should be made in blue or black ink. Corrections should be made with a single line through the entry and the change initialed and dated, original entries should remain legible (i.e., they should never be erased or covered with correction fluid to obscure the original entry); late entries should be initialed and dated at the time entered.

Source documents for patients who are screened but not enrolled must be retained following the same guidelines as other study source documents.

9.3 Data collection into Case Report Forms (CRF)

The sponsor will provide duplicate carbonless paper CRFs to collect the specific data needed to answer this study's research questions.

The investigators will enter the data on duplicate Case Report Forms (CRFs) and the field study monitors will review the CRFs for completeness and accuracy. The field study monitors will collect and forward the original copy of the CRF forms to the sponsor, the second copy will remain at the study site. The original copy of the CRF will be forwarded to the Sponsor's Data Management team, once the Sponsor's Data Management team receives the CRFs, receipt will be recorded, the original copy will be placed in Central Files and a working copy will be made and forwarded to the responsible data management staff for processing. Data items from the CRFs will be entered into the study database using double data entry with verification upon second entry.

Screened patients are defined as patients who signed the Informed Consent. Screened patients who discontinued prior to randomization will be recorded as screen failures. All screened patients including screened failures will be entered into a screening log, a separate CRF-like document. It will be processed like any other CRF page.

9.4 Data Entry Errors

Any change to a CRF entry once the data has been submitted requires the Investigator's signature, a comment explaining the reason the data was changed and completion of a Data Correction Form (DCF).

10 STATISTICAL METHODS

10.1 Management of the Statistical Analysis Plan

All staff involved with the analysis of the study will remain blinded until protocol violators are identified and the database is locked. A comprehensive Statistical Analysis Plan (SAP) will be prepared before the first patient is randomization. Prior to the un-blinding of the data, the SAP is finalized to reflect the protocol and any amendments. The sponsor or designee will perform the data analysis.

10.2 Sample Size Determination

To determine the sample size for the migraine prevention study the results of two previous studies were considered.

An IND double-blind clinical trial for back pain with naltrexone [redacted] mg/clonidine [redacted] mg bid captured data for concomitant headache/migraine. The table below shows the change in headache-day frequency from baseline to week 3 (last week of treatment). The results for headache days were statistically significant with naltrexone [redacted] mg/clonidine [redacted] mg group of 13 subjects and placebo of 10 subjects. We believe naltrexone/acetaminophen is even more

potent than naltrexone/clonidine.

The FDA, granted naltrexone/clonidine a breakthrough designation based on the IND study.

ANALYSIS OF CHANGE FROM BASELINE IN WEEKLY FREQUENCY TO WEEK 3 IN MIGRAINE SUBJECTS

		Weekly Frequency of Migraine Days			
Treatment	N	Baseline	WK3	Change (Standard Error)	p-value
Placebo	10	2.60	1.50	1.10 (0.85)	0.04284
ATNC05	13	3.85	0.00	3.85 (0.90)	

Groups	All Migraine Subjects
Method	t-Test, 2-sided
P Value	0.04284
Mean Difference	-2.75
Standard Error	± 0.88
95% Confidence Interval	(-0.050 to 5.550)

The second study was an acute migraine pilot study where naltrexone [redacted] mg/acetaminophen [redacted] mg (N=21) vs. naltrexone [redacted] mg/ [redacted] mg (N=9) headache pain free at 30-minute was 76% vs. 22%. Calculating[43] the sample size based on odds ratio of 76/22, yields 16 patients per group.

The study plans to enroll 24 patients per group to allow for greater power.

The migraine prevention study is a proof of concept study. The investigator hypothesizes a reduction in migraine headache days in the ALLOD-2 group versus the placebo group, for which 24 patients in each group can provide statistical significance.

10.3 Analysis Populations

The analysis populations will be as follows:

Screened patients: the screened patient's population consists of all the patients who signed the Informed Consent. Screen Failures are screened patients who were not randomized. The screened population includes screen failures and randomized patients.

Intent-to-treat (ITT) population: consists of all patients who were randomized who took the study drug, recorded baseline pain as moderate or severe, and had at least 1 post baseline efficacy evaluation. All efficacy analyses are conducted on the ITT population.

Safety patient population: consists of all patients who have received the investigational drug.

Per-Protocol population: consists of all patients who did not present with any major protocol deviations in accordance with the study specific inclusion/exclusion criteria. Determination of the per protocol analysis set is made before unbinding of the trial. Protocol deviations will not necessarily result in discontinuation of the trial. The per-protocol analysis population will be

[43] http://powerandsamplesize.com/

used for sensitivity analyses of the primary endpoint.

10.4 Statistical Analyses

All statistical analysis will summarize the number and percent of patients. Descriptive statistics by treatment group (mean, standard deviation, median, minimum, maximum, and confidence intervals) will be provided.

A headache day is defined as a calendar day during which a patient had a migraine headache lasting ≥30 minutes, a migraine headache is defined as moderate to severe headache with at least one migraine-associated symptom, i.e., light sensitivity, noise sensitivity, nausea.

Statistical analysis will be performed on patient reported data from the migraine diary, patient reported data from site visits, and data collected during site visits.

Analysis will be performed for the comparison of the reduction in the mean migraine headache days, headache days, 50% or more reduction in monthly migraine frequency, severity, duration, nausea severity, light sensitivity, noise sensitivity, and days of rescue medication intake from baseline to the last 28 days of the 12-week Treatment Period. Analysis will be performed for the comparison of the reduction in MIDAS, HIT-6, and PIRS-20 from baseline to End-of-treatment Visit.

10.5 Missing Data Imputation

Missing data imputation will be determined prior to data lockout.

10.6 Analysis of Patients Background Data

The analysis of the background data will include patient demographics, history of migraine, baseline migraine duration and characteristics, baseline concomitant medications, and baseline concomitant illnesses presented by treatment group.

10.7 Statistical Analysis of the Study Endpoints

Primary Endpoint	
1)	Change from baseline in the mean number of migraine/probable migraine headache days. Description: Probable migraine is defined by ICHD – 3 (beta version) criteria, is an attack fulfilling all but one of criteria A-D for migraine with or without aura, headaches must be moderate or severe and lasting ≥30 minutes. Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
Secondary Endpoints	
1)	Change from baseline in the mean number of headache days. Description: Headache days are defined as none-migraine headache days plus migraine headache days. Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
2)	Proportion of patients with 50% or more reduction in migraine/probable migraine headache days. Time Frame: From the 28-day baseline period to the last 28 days of the 12-week

	Treatment Period.
3)	Change from baseline in the mean migraine severity. Description: Measured on a 4-point (0-3) rating scale, (0=none, 1=mild, 2=moderate, 3=severe). Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
4)	Change from baseline in the mean migraine duration. Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
5)	Change from baseline in the mean nausea severity. Description: Measured on a 4-point (0-3) rating scale, (0=none, 1=mild, 2=moderate, 3=severe). Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
6)	Change from baseline in the mean number of acute migraine medications intake days. Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
7)	Proportion of patients "satisfied" or "extremely satisfied" with migraine prevention. Time Frame: week 12.
8)	Change from baseline in the mean migraine disability assessment scale (MIDAS). Time Frame: From baseline to week 12 of the Treatment Period.
9)	Change from baseline in the mean headache impact test (HIT-6). Time Frame: From the 28-day baseline period to the last 28 days of the 12-week Treatment Period.
10)	Change from baseline in the mean Pittsburgh Insomnia Rating Scale-20 (PIRS-20). Time Frame: From baseline to week 12 of the Treatment Period.
Safety Endpoints	
1)	Comparison of the proportion of patients who experienced adverse events, defined as any untoward medical occurrences, regardless of their suspected cause. Time Frame: A 12-week Treatment Period.
2)	Comparison of the proportion of patients who experienced treatment emergent adverse events. Time Frame: A 12-week Treatment Period.
3)	Comparison of the change from screening in the mean blood counts, hepatic, and renal function. Time Frame: A 12-week Treatment Period.
4)	Comparison of the change from screening in the mean systolic blood pressure, diastolic blood pressure, and pulse. Time Frame: A 12-week Treatment Period.

10.8 Safety Analysis Considerations

Vital signs and laboratory data (hematologic, hepatic and renal function) will be obtained at baseline, and 2-7 days post-dose.

10.9 Adverse Event Classification

The Medical Dictionary for Regulatory Activities (MedDRA) Classification system will be used to classify AEs. TEAE is defined as an AE that emerged or worsened during treatment. The TEAE will be classified by treatment, seriousness, severity, system organ class, and relationship to the study drug. An event occurring more than once in the same patient will be counted only once. Deaths, SAEs, and treatment discontinuation due to AEs will be tabulated.

10.10 Interim Analysis

Interim analysis will not be performed.

11 STUDY ADMINISTRATION

11.1 Study Oversight

The Investigator is responsible for study oversight, including monitoring safety, ensuring that the study is conducted according to the protocol and ensuring data integrity. The Investigator will review the data for safety concerns and data trends at regular intervals, and will promptly report to the sponsor and the IRB any unanticipated problem, protocol violation, or any other significant event that arises during the conduct of the study.

11.2 Responsibilities of the Study Sites

Each study site is responsible for enrolling trial patients, executing the trial protocol, collecting trial data, complying with regulatory requirements, and providing clinical oversight. The sponsor will support the sites through this process and facilitate training and implementation of trial. Sites selected for this trial are required to have prior experience with pain studies, familiarity with pain assessment instruments, and dedicated research staff.

The study site staff must include a designated Investigator (Medical Doctor or Doctor of Osteopathy), a clinical research coordinator (CRC) and an on-site phlebotomist. The site is required to have an electrocardiogram machine, accessibility to LabCorp blood sample submission, high-speed internet and a locked storage area as described below.

The Clinical Investigator is required to disclose any financial arrangement during the trial and for 1 year after, pertaining to any significant equity interest in the sponsor as defined in 21 CFR 54 2(b). As compensation for participation in the trial, the sponsor pays the Clinical Investigator the sums set out in the payment schedule attached to the Clinical Investigator agreement.

11.3 Investigator Responsibilities

The Investigator has the overall responsibility for all aspects of the study clinic. The Investigator has the following administrative and clinical responsibilities:

- Providing patients information about the trial and obtaining the Informed Consent from the trial patients
- Compliance of the study site with regulatory requirements and trial documentation, including this Protocol

- Performance of trial procedures in accordance with this Protocol
- Completion of required training, including attending any trial investigator's meetings and human patient protection training
- Provision of sufficient training and support for study site staff
- Reporting of all Serious Adverse Events (SAEs) within 24 hours of local event awareness (but no later than the next business day) to the sponsor with full written report to follow
- Review of and timely response to all of the sponsor's communications
- Review of all CRFs and signature where required
- Review of and timely response to all of sponsor's communications

11.4 Responsibilities of the Clinical Research Coordinator (CRC)

The CRC has the primary responsibility of implementing the protocol. This includes the following administrative and clinical responsibilities:

- Maintaining updated contact information for each trial patient
- Complete / update CRFs
- Performance of trial procedures according to the protocol
- Maintaining contact with patients and following up on missed labs or visits
- Completion of required training, including human patient protection training
- Review of and timely response to all of sponsor's communications
- monitoring of investigational drug inventory

11.5 Regulatory Requirements, Essential Document and Archiving

This trial is subject to regulatory requirements both for the protection of human patients through the Institutional Review Board structure and for the regulation of investigational drugs through the Food and Drug Administration.

All key data must be recorded in the patient's medical records. The Clinical Investigator must permit authorized representatives of the sponsor, respective national or local regulatory authorities, the IRB, and auditors to inspect facilities and to have direct access to original source records relevant to this trial, regardless of media. Original source data will include, and are not limited to patient's medical file, and original clinical laboratory reports and ECG reports.

It is the Investigator 's responsibility to retain essential study documents for at least 2 years after the last approval of a marketing application in their country, and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational drug, (in accordance with 21 CFR 312.62(c)). These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the Clinical Investigator as to when these documents no longer need to be retained. In addition, if

applicable the sponsor (or designee) will send a list of treatment codes by trial patient, to the Clinical Investigator after the clinical database for this trial has been un-blinded.

11.6 Emergency Preparedness Measures for Study Records

Site SOPs will dictate preparedness for emergencies, such as power outages, floods, hurricanes, etc. to protect the integrity of the study records and to minimize the impact of potential interruptions to the clinical trial.

11.7 Institutional Review Board

Each study site is required to obtain approval from the Schulman IRB or local IRB (if applicable) prior to initiation of any collection of patient data. The Institutional Review Board for this trial is Schulman IRB, 4445 Lake Forest Drive, Suite 300, Cincinnati, OH 45242.

In addition to approval for planned trial activities, the IRB and the sponsor must be informed of all protocol deviations, violations, and adverse events. This protocol, and the Informed Consent document and any subsequent amendments is reviewed and approved by the trial's IRB or local IRB (if applicable). The Investigator(s) will submit periodic reports and inform the IRB of any reportable adverse events per ICH guidelines and local IRB standards of practice.

11.8 Essential Documents

The following essential documents must be retained at the study site, must be accurately maintained, and may be verified during trial monitoring visits:

Clinic-specific documents:

- The protocol and all protocol amendments
- All versions of IRB approved consent documents
- IRB documentation, approvals, and correspondence
- Investigator brochure, product label, or drug information sheet
- FDA Form 1572
- Financial disclosure forms
- Study communication
- Delegation of responsibilities log
- Documentation of clinical research and study training
- Screening and enrollment log
- Study product records (e.g., pharmacy logs)
- GCP certificate for the investigators
- Medical license
- Serious Adverse Events (SAEs)/Unanticipated Problems
- Protocol deviations
- Documentation of clinical site monitoring visits

Patient-specific documents:

- Completed case report forms
- Data correction forms
- Progress notes
- Source documents, (e.g., lab reports, ECG tracings, x-rays, radiology reports, etc.)
- Signed consent documents
- Migraine Diary forms completed by the participant

In the case of any serious adverse events, the study sites will report such occurrences to the sponsor within 24 hours. The sponsor is responsible for all reporting to the Food and Drug

Administration.

11.9 Investigator Meetings

A face-to-face investigator's meeting will be held, site PIs and one study coordinator are invited and strongly encouraged to attend. The sponsor will facilitate travel and will cover the associated costs.

At the meetings, key components of the trial design and implementation will be presented and site staff will have the opportunity to meet and ask questions of sponsor study team.

11.10 Training of Study Site Staff and Routine Contact with the Sponsor's Study Team

The Investigator will ensure that all study site staff are familiar with the trial Protocol and operating procedures. All trial staff must also maintain up-to-date human patients training. A site initiation visit by the sponsor will take place after the approval by IRB, and prior to the first patient's enrollment into the trial. The visit will ensure investigators fully understand their responsibilities and the responsibilities of the staff. It is the PI's duty to ensure that all staff involved in this trial is appropriately trained to ensure compliance with this protocol. The Investigator will maintain records of all site staff trainings and records regarding the qualifications of site staff.

Throughout the trial duration, study site staff will be in close communication with the sponsor. In addition to the reporting requirements, study sites are encouraged to contact the sponsor with problems, questions, suggestions, or concerns. The sponsor will also be contacting the study sites to check on recruitment and retention of patients, resolve questions on any trial data issues and inform sites of updated participant information.

11.11 Trial Monitoring Plan

The overall goal of the monitoring plan is to provide oversight to ensure adequate protection of the rights, welfare, and safety of human patients and the quality of the clinical trial data submitted to the FDA. The monitoring plan will employ risk-based monitoring strategies, which focus the sponsor's oversight activities on preventing or mitigating important and likely risks to data quality, to processes critical to human patient protection and trial integrity.

Monitoring strategies will include the appropriate use of technological to meet statutory and regulatory requirements.[44]

The sponsor's monitoring activities will focus on the following critical data elements and processes:

- Verification that Informed Consent was obtained appropriately
- Adherence to protocol eligibility criteria designed to exclude individuals for whom the investigational drug may be less safe than the protocol intended and to include

[44] Guidance for Industry Oversight of Clinical Investigations - A Risk-Based Approach to monitoring Available at: http://www.fda.gov/downloads/Drugs/Guidancs/UCM269919. Accessed March 3, 2015.

only patients from the targeted study population for whom the test article is most appropriate

- Procedures for documenting appropriate accountability and administration of the Investigational drug (e.g., ensuring the integrity of randomization at the site level)
  - Conduct and documentation of procedures and assessments related to study endpoints
  - Protocol-required safety assessments
  - Evaluating, documenting and reporting serious adverse events, patient deaths and withdrawals, especially when a withdrawal may be related to an adverse event
- Conduct and documentation of procedures essential to trial integrity, such as ensuring the study blind is maintained, both at the site level and at the sponsor level, as appropriate

The monitor will visit the site at regular intervals throughout the study according to the clinical monitoring plan to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations.

The CRC and Investigator must be available to the trial monitor during the monitoring visit. Any egregious activity involving patient safety or lack of adherence to Good Clinical Practice (GCP) as required by federal guidelines may require reporting to the relevant IRBs and governmental regulatory agencies. A report of any findings will be provided to the site for all monitoring encounters.

During the trial, the sponsor will have regular contact with the site to ensure protocol adherence and to provide additional support and training. The sponsor will also ensure the timely recording of CRFs.

The Clinical Investigator will allow the trial monitor to inspect the clinical, laboratory and pharmacy facilities. The Clinical Investigator and staff are expected to cooperate with the Trial monitor, to be available during a portion of the monitoring visit to answer questions and to allow the trial monitor to conduct inspections. It is essential that the trial monitor have access to all trial and patient-related documents at any time these are requested. The CRFs and corresponding original patient source documents must be fully available for review by the trial monitor to verify data accuracy and adherence to trial protocol. The trial monitor will adhere to all requirements for patient confidentiality.

11.12 Auditing and Inspecting

The investigator will permit study-related monitoring, audits and inspections by the IRB, the sponsor or government regulatory bodies direct access to all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.). The investigator will give his/her permission to examine, analyze,

verify, and reproduce any records and reports that are important to the evaluation of a clinical study. Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities.

11.13 Clinical Trial Agreement

The Investigator at each study site will comply with all the terms, conditions, and obligations of the clinical trial agreement. Should any discrepancy arise between this clinical trial protocol and the clinical trial agreement, the terms of the clinical trial protocol shall prevail regarding the conduct of the trial and the treatment of patients. In all other respects, not relating to trial conduct or treatment of patients, the terms of the clinical trial agreement shall prevail. Study sites will be reimbursed for successful completion of milestones as outlined in the clinical trial agreement.

11.14 Confidentiality of the Protocol

The contents of this protocol are confidential. The Investigator, Investigator's staff and the IRB will not disclose or use, in whole or in part, any of the contents, amendments of this protocol or results of this study to others, for any purpose other than reviewing or performing the study absent prior written authorization from the sponsor.

11.15 HIPAA, Disclosure and Confidentiality

All sites, laboratories and other entities involved in this study must, if applicable, comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The confidentiality of records that may be able to identify patients is protected in accordance with applicable laws, regulations, and guidelines. After patients have consented to take part in the trial, the sponsor, and/or its representatives' review their medical records and data collected during the trial. Others including the following may in addition review these records and data: independent auditors who validate the data on behalf of the sponsor, third parties with whom the sponsor may develop, register, or market the investigational drug, national or local regulatory authorities, and the IRB(s). The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of patients' identities.

Patients are identified using a unique identifying number. However, laboratory blood procedures will require identifying information such as name initials, gender, and date of birth. The name initials and date of birth will not be transferred to the case report form. After patients are enrolled in the trial, all laboratory specimens, evaluation forms and reports that leave the site will be identified only by study Identification Number (ID) to maintain patient confidentiality.

All records will be kept in a locked file cabinet. Data entered into online forms are identified using patient I.D. numbers. Clinical information will not be released without written permission from the patient, except as necessary for monitoring by the FDA, the Office for Human Research Protections (OHRP), the sponsor or the sponsor's designee.

Information about study patients will be kept confidential and managed according to the requirements of the Health Information Portability and Accountability Act (HIPAA). Those regulations require a signed patient authorization informing the patient of the following:

- The personal health information (PHI) to be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- To whom the data may be disclosed and the reasons for this disclosure
- The rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the Investigator , by regulation, retains the ability to use all information collected prior to the revocation of patient authorization.

For patients who have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the patient is alive) at the end of their scheduled study period.

11.16 Inspection Procedures, Study Timetable and End of Study

A government regulatory authority may conduct an inspection during the study or after its completion. If an inspection is requested by a regulatory authority, the Clinical Investigator must immediately inform the sponsor that a request has been made.

The sponsor will notify the investigators when the study recruitment is complete. The study may be terminated at individual sites if the study procedures are not being performed according to GCP or if recruitment is slow. The sponsor may also terminate the entire study prematurely if concerns for safety arise within this trial.

12 DUTIES OF THE SPONSOR AND THE INVESTIGATORS

12.1 Recruitment/Retention and GCP Compliance by the Investigator

Each co-investigator is fully responsible for fulfilling all of the obligations of an investigator as identified in 21 CFR 312.60. Thus under 21 CFR 312.3(b), each co-investigator is an investigator, and as such must sign a separate 1572.

The Clinical Investigator is required to conduct the study in accordance with the International Conference on Harmonization (ICH) good clinical practice (GCP) guidelines. The Clinical Investigator is responsible for providing appropriate facilities, trained staff, and to demonstrate ability to recruit the required number of suitable patients within the agreed recruitment period prior to committing to participate in the trial. The Clinical Investigator will maintain a list of appropriately qualified persons to whom he/she has delegated significant trial-related tasks.

12.2 Study Staff Training

All study staff will receive training on all aspects of the protocol, to include:

- Study objectives
- Inclusion/exclusion criteria
- Protocol deviations
- Patient visit schedule
- Screening, treatment and end of study/early termination visits
- Laboratory evaluations

- Investigational drug
- Treatment timelines
- Safety monitoring and stopping rules
- Treatment interruptions or discontinuation

All study staff will receive training in the following areas of clinical operations:

- Communication
- Site visits
- Investigator responsibilities
- Good clinical practice (GCP)
- Essential document collection and storage
- IRB reporting requirements
- Audits
- Informed consent procedures

12.3 Protocol Adherence and Investigator Agreement

The investigator/designee(s) are required to adhere to the protocol as detailed in this document. The Clinical Investigator is responsible for enrolling only those patients who have met protocol eligibility criteria. A clinical study agreement will be signed by the Clinical Investigator to confirm willingness to comply with the study protocol.

In the event of an investigator's decision to terminate or suspend the trial, the Clinical Investigator is required to inform the IRB and the sponsor immediately, and provide them with detailed written explanation. The Clinical Investigator will return all Investigational drug and other study materials to the sponsor.

12.4 Reimbursement and Insurance

Prior to starting the study, the Clinical Investigator will sign a clinical study agreement with the sponsor. Financial aspects and patient insurance for the trial will be documented in the agreement between the sponsor and the investigator.

12.5 Study Modification/Discontinuation or Suspension/Termination by the sponsor

The study may be modified or discontinued at any time by the IRB, the sponsor or government agencies as part of their duties to ensure that research patients are protected.

The sponsor may suspend or terminate the study or part of the study at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable regulatory agencies and IRBs/IECs are notified as appropriate.

12.6 Public Posting of Study Information

This study will be registered and regularly updated on the ClinicalTrials.gov registry, in accordance with all relevant regulations. Information included in the registry may include participating investigators' names and contact information.

12.7 Publication Policy

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

All publications or presentations arising from the results of this study must be reviewed and approved in writing by the sponsor, at least 30 business days in advance of the publication submission. The review is aimed to protect the sponsor's proprietary information, existing either at the date of the beginning of the study or produced during the study. This permits the sponsor to review submitted publications for accuracy and verification that protected information is not inadvertently disclosed to allow for additional patent protection, establishment of co-authorship, and to provide relevant supplementary information.

Publication or presentation of data collected as a result of this study (directly or indirectly) is considered a joint publication by investigator(s) in all study sites. The initial publication is based on data collected from all analyzed patients, not the individual investigator(s). Absent agreement by all other investigators and the sponsor, investigators agree not to present data gathered individually prior to the full initial publication.

Publication by investigators of any results or data collected or obtained throughout the course of this study is prohibited absent prior written authorization from the sponsor.

13 ETHICS/PROTECTION OF HUMAN PATIENTS

13.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report. As well as with the ethical principles, and guidelines for the Protection of Human Patients of Research, as drafted by the US National Commission for the Protection of Human Patients of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

The research participant rights and safety are protected through the Informed Consent approval of the clinical trial protocol by the Institutional Review Board (IRB), oversight by the FDA and ongoing monitoring of the trial.

13.2 Institutional Review Board

The protocol, Informed Consent form(s), recruitment materials and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form will be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes will be implemented in the study.

13.3 Informed Consent Process

Informed consent is a process that will be initiated prior to the individual agreement to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to patients and their families, if applicable. A consent form describing in detail the study procedures and risks is given to the participant Consent forms is IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the Informed Consent document prior to any study-related assessments or procedures.

Patients will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed Informed Consent document must be given to the patients for their records. The rights and welfare of the patients are protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the research record.

13.4 Participant Confidentiality

Participant confidentiality will be strictly held in trust by the investigators, study staff, the sponsor and their agents. This confidentiality is immediate to cover testing of biological samples and genetic tests in addition to any study information relating to patients.

The study protocol, documentation, data, and all other information generated will held in strict confidentiality. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The trial monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study patients. The clinical study site will permit access to such records.

14 APPENDICES

14.1 Appendix 1: The International Classification Of Headache Disorders-3 (Beta version)

1.1 Migraine without aura

Diagnostic criteria:
A. At least five attacks[1] fulfilling criteria B-D
B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)[2;3]
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 (eg, 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

Diagnostic criteria:
A. At least two attacks fulfilling criteria B and C
B. One or more of the following fully reversible aura symptoms: Visual, Sensory, Speech and/or

language, Motor, Brainstem, Retinal

C. At least two of the following four characteristics:

1. At least one aura symptom spreads gradually over ≥5 min, and/or two or more symptoms occur in succession
2. Each individual aura symptom lasts 5-60 min[1]
3. At least one aura symptom is unilateral[2]
4. The aura is accompanied, or followed within 60 min, by headache

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

1.5 Probable migraine

Previously used term: Migrainous disorder.

Coded elsewhere: Migraine-like headache secondary to another disorder (symptomatic migraine) is coded according to that disorder.

Description: Migraine-like attacks missing one of the features required to fulfil all criteria for a subtype of migraine coded above, and not fulfilling criteria for another headache disorder.

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A-D for 1.1 Migraine without aura, or all but one of criteria A-C for 1.2 Migraine with aura

B. Not fulfilling ICHD-3 criteria for any other headache disorder

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

Comment: In making a headache diagnosis, attacks that fulfil criteria for both 2. Tension type headache and 1.5 Probable migraine are coded as the former in accordance with the general rule that a definite diagnosis always trumps a probable diagnosis. However, in patients who already have a migraine diagnosis, and where the issue is to count the number of attacks they are having (for example, as an outcome measure in a drug trial), attacks fulfilling criteria for 1.5 Probable migraine should be counted as migraine. The reason for this is that mild migraine attacks, or attacks treated early, often do not achieve all characteristics necessary for a migraine attack diagnosis but nevertheless respond to specific migraine treatments.

1.3 Chronic migraine

Description: Headache occurring on 15 or more days per month for more than three months, which, on at least 8 days per month, has the features of migraine headache.

8.2 Medication-overuse headache (MOH)

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 three 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[1]

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

Note:

1. Patients should be coded for one or more subtypes of 8.2 Medication-overuse headache according to the specific medication(s) overused and the criteria for each below. For example, a patient who fulfils the criteria for 8.2.2 Triptan-overuse headache and the criteria for one of the subforms of 8.2.3 Simple analgesic-overuse headache should receive both these codes. The exception occurs when patients overuse combination-analgesic medications, who are coded 8.2.5 Combination-analgesic-overuse headache and not according to each constituent of the combination-analgesic medication.
Patients who use multiple drugs for acute or symptomatic treatment of headache may do so in a manner that constitutes overuse even though no individual drug or class of drug is overused; such patients should be coded 8.2.6 Medication-overuse headache attributed to multiple drug classes not individually overused.
Patients who are clearly overusing multiple drugs for acute or symptomatic treatment of headache but cannot give an adequate account of their names and/or quantities are coded 8.2.7 Medication-overuse headache attributed to unverified overuse of multiple drug classes until better information is available. In almost all cases, this necessitates diary follow-up.
Comments:
8.2 Medication-overuse headache is an interaction between a therapeutic agent used excessively and a susceptible patient. Among those with a previous primary headache diagnosis, most have 1. Migraine or 2. Tension-type headache (or both); only a small minority have other primary headache diagnoses such as 3.3 Chronic cluster headache or 4.10 New daily persistent headache.
The diagnosis of 8.2 Medication-overuse headache is extremely important clinically. Approximately half of people with headache on 15 or more days per month for more than three months have 8.2 Medication-overuse headache. Evidence shows that the majority of patients with this disorder improve after discontinuation of the overused medication, as does their responsiveness to preventative treatment. Simple advice on the causes and consequences of 8.2 Medication-overuse headache is an essential part of its management. An explanatory brochure is often all that is necessary to prevent or discontinue medication overuse. Prevention is especially important in patients prone to frequent headache.

However, the behaviour of some patients with 8.2 Medication-overuse headache is similar to that seen with other drug addictions, and the Severity of Dependence Scale (SDS) score is a significant predictor of medication overuse among headache patients.

14.2 Appendix 2: Four-Point Likert Scale for Assessing Headache Pain and Nausea

Rating	Pain Level
0	No headache pain
1	Mild headache pain, interfering little with Activities of Daily Living (ADLs)
2	Moderate headache pain, pain interfering significantly with ADLs
3	Severe headache pain, disabling; unable to perform ADLs

14.3 Patient Global Impression of Change (PGIC)

Since the start of the treatment, my overall status is: (Please check only one choice)				
Date:	Date:	Date:	Date:	Date:
Visit 3	Visit 4	Visit 5	Visit 6	Visit 7

1. Very much worse 2. Much worse 3. Minimally worse 4. No change 5. Minimally improved 6. Much improved 7. Very much improved	1. Very much worse 2. Much worse 3. Minimally worse 4. No change 5. Minimally improved 6. Much improved 7. Very much improved	1. Very much improved 2. Much improved 3. Minimally improved 4. No change 5. Minimally worse 6. Much worse 7. Very much worse	1. Very much improved 2. Much improved 3. Minimally improved 4. No change 5. Minimally worse 6. Much worse 7. Very much worse	1. Very much improved 2. Much improved 3. Minimally improved 4. No change 5. Minimally worse 6. Much worse 7. Very much worse

14.4 Appendix 3: Criteria for Identifying Laboratory Values of Potential Clinical Relevance

	Test	Range	Rule	Value
Hepatic Function	TBL mg/dL	0 – 1.2	> 1.5 × ULN	≥ 2.0 mg/dL*
	ALP IU/L	39 - 117	> 1.5 x ULN	≥ 234 IU/L
	AST (SGOT) IU/L	0 – 40	> 2 x ULN	≥ 80 IU/L
	ALT (SGPT) IU/L	0 - 44	> 2 x ULN	≥ 88 IU/L
Renal Function	BUN mg/dL	6 - 24	> 1.5 × ULN	≥ 36 mg/dL
	Creatinine mg/dL	0.67 – 1.27	> 1.5 × ULN	≥ 2.0 mg/dL
LabCorp Normal Range ULN = upper limit of the laboratory reference (normal) range. BUN = blood urea nitrogen; TBL= Total bilirubin (serum) ALP = alkaline phosphatase; AST (SGOT) = aspartate transaminase (serum glutamic-oxaloacetic transaminase); ALT (SGPT) = alanine transaminase (serum glutamic-pyruvic transaminase) * limit criteria are not applicable for patients documented to have Gilbert's syndrome				

14.5 Appendix 4: Limits for baseline vital signs values

Measure	Low Value	High Value
Heart Rate	< 50 bpm	> 100 bpm
Systolic Blood Pressure	< 90 mmHg	> 180 mmHg
Diastolic Blood Pressure	< 50 mmHg	> 105 mmHg
Baseline values must be in the above ranges		

14.6 Appendix 5: List of Narcotic Pain Medications (Painkillers)

Generic	Brand Name
Buprenorphine	Buprenex, Butrans transdermal patch
Butorphanol	Stadol

Codeine	
Hydrocodone	
Hydromorphone	Dilaudid, Dilaudid-5, Dilaudid-HP, Hydrostat IR, Exalgo ER
Levorphanol	Levo-Dromoran
Meperidine	Demerol
Methadone	Dolophine, Methadose
Morphine	Astramorph PF, AVINZA, Duramorph, Kadian, M S Contin, MSIR, Oramorph SR, Rescudose, Roxanol
Nalbuphine	Nubain
Oxycodone	OxyContin, Roxicodone, Oxecta
Oxymorphone	Numorphan
Pentazocine	Talwin
Propoxyphene	Cotanal-65, Darvon
Tapentadol	Nucynta
Tramadol	Ultram
Tramadol and Acetaminophen	Ultracet
Combinations	
Butalbital, acetaminophen, caffeine, and codeine	Fioricet with Codeine
Hydrocodone and Ibuprofen	Hydrostal IR, Vicoprofen
Morphine/Naltrexone	Embeda
Pentazocine/Naloxone	Talwin NX
Acetaminophen and Codeine	Capital with Codeine, Margesic #3, Phenaphen with Codeine, Tylenol with Codeine
Dihydrocodeine, Acetaminophen, and Caffeine	DHCplus
Hydrocodone and Acetaminophen	Allay, Anexsia 5/500, Anexsia 7.5/975, Dolacet, Dolagesic, Duocet, Hycomed, Hydrocet, Hydrogesic, HY -PHEN, Lorcet 10/975, Lorcet-HD, Lortab, Panacet 5/500, Panlor, Stagesic, T-Gesic, Ugesic, Vicodin, Zydone
Oxycodone and Acetaminophen	Endocet, Percocet, Roxicet, Roxilox, Tylox; Xartemis XR
Pentazocine and Acetaminophen	Talacen
Propoxyphene and Acetaminophen	Darvocet -N 50, Darvocet -N 100, E-Lor, Propacet 100
Aspirin, Caffeine, and Dihydrocodeine	Synalgos-DC
Aspirin and Codeine	Empirin with Codeine
Hydrocodone and Aspirin	Damason-P, Lortab ASA, Panasal 5/500
Oxycodone and Aspirin	Endodan, Percodan, Percodan- Demi, Roxiprin
Pentazocine and Aspirin	Talwin Compound
Propoxyphene, Aspirin, and Caffeine	Darvon Compound-65, PC -Cap, Propoxyphene Compound-65

14.7 Appendix 6: List Opiate Antagonists Medications [45]

Generic	Brand Name
Nalmefene (injectable solution)	Revex
Alvimopan*	Entereg

[45] List of Pain Relief Medications, NSAIDs Available at: http://www.emedexpert.com/lists/pain-meds.shtml.

Naloxone*	Narcan
Methylnaltrexone bromide*	Relistor
Naltrexone*	Vivitrol, ReVia®

14.8 Appendix 7: List Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Generic	Brand Name
Bromfenac	Prolensa, Bromday
Diclofenac	Cataflam, Voltaren, Zipsor
Diflunisal	Dolobid
Etodolac	Lodine, Lodine XL
Fenoprofen	Nalfon
Flurbiprofen	Ansaid
Ibuprofen	Advil, Cramp End, Dolgesic, Excedrin IB, Genpril, Haltran, Ibren, Ibu, Ibuprin, Ibuprohm, Ibu -Tab, Medipren, Midol IB, Motrin, Nuprin, Pamprin-IB, Q-Profen, Rufen, Trendar
Indomethacin	Indocin, Indocin SR, Tivorbex
Ketoprofen	Actron, Orudis, Oruvail
Ketorolac	Toradol, Sprix
Meclofenamate	Meclomen
Mefenamic Acid	Ponstel
Meloxicam	Mobic
Nabumetone	Relafen
Naproxen	Aleve, Anaprox, Anaprox DS, EC -Naprosyn, Naprelan, Naprosyn
Oxaprozin	Daypro
Phenylbutazone	Cotylbutazone
Piroxicam	Feldene
Sulindac	Clinoril
COX-2 Inhibitors	
Celecoxib	Celebrex
Non-Narcotic Analgesics	
Acetaminophen	Tylenol
Combinations	
Butalbital, Acetaminophen, and Caffeine	Femcet, Fioricet, Esgic, Esgic-Plus
Butalbital, Aspirin, and Caffeine	Fiorinal

14.9 Appendix 8: List of the Study's Clinical Laboratory Evaluations

Category	Parameters
Hematologic test	Complete blood count
Liver function tests	aminotransferase (AST [SGOT]), alanine aminotransferase (ALT [SGPT]), alkaline phosphatase aspartate, total bilirubin
Renal function tests	blood urea or blood urea nitrogen (BUN), creatinine
Urine drug screen	cocaine, marijuana, opiates, methamphetamines, and/or Oxycodone

Urine pregnancy test	Qualitative hCG

14.10 Appendix 9: Blood Collection Procedure

The site will collect a Non-fasting blood samples every visit except Visit 2 and Visit 6.

Blood specimen collection instruction:

1. Collect blood into one serum separating tube (SST) (LabCorp: red and black tiger top tube) and one lavender top tube).
2. Mix blood by gently inverting the tube(s) 5-10 times.
3. Affix completed I.D. labels to the tubes. Be sure labels correspond to the requisition form.
4. The blood tube I.D. label includes the following information: study account number, protocol number, and patient's initials, visit number, patient study ID, collection date, and collection time.
5. Allow blood to clot upright at room temperature for 30 min UNSPUN SPECIMENS MAY NOT SIT LONGER THAN 45 MIN
6. CENTRIFUGE at 1100 – 1300 g for 10-15 min at room temperature.
7. Do not remove top of SST. Tube is to be sent in "as is" after centrifugation. Do not send un-centrifuged specimens. Do not submit hemolyzed serum (occurrence of pinkish tinge to serum component)
8. The patient's study ID, gender and year of birth must match the information on the lab requisition slip. This ensures that lab results are attached to the correct participant.

14.11 Appendix 10: Blood pressure procedure instructions [46]

Approved equipment for measurement of blood pressure includes annually calibrated mercury manual sphygmomanometer or certified calibrated automatic device provided by the study clinic.

A number of factors related to the patient can cause significant violations in measured blood pressure. These include room temperature, exercise, alcohol or nicotine consumption, positioning of the arm, muscle tension, bladder distension, talking, and background noise. The patient should be asked to remove all clothing that covers the location of cuff placement. The patient should be comfortably seated, with the legs uncrossed, and the back and arm supported, such that the middle of the cuff on the upper arm is at the level of the right atrium (the mid-point of the sternum). Measurements made while the patient is on an examining table do not fulfill these criteria and should preferably be made while the patient is seated in a chair. The patient should be instructed to relax as much as possible and to not talk during the measurement procedure.

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[46] Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: From the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension. 2005; 45(1):142-61.

The "gold standard" device for office blood pressure measurement has been the mercury sphygmomanometer, it is recommended that, if available, a properly maintained mercury sphygmomanometer be used for routine office measurements. Mercury sphygmomanometers are critical for evaluating the accuracy of any type of non-mercury device.

14.12 Appendix 11: Pulse Measurement Procedure [47]

Resting heart rate is an easily measurable cardiovascular parameter, but is subject to high variability. Studies focusing on heart rate should take into account all possible sources of variability, including the resting period before measurement, environmental conditions, method of measurement (pulse palpation vs. electrocardiogram), number of readings, duration of measurement, position of the body, and nature of the observer. To minimize the effects of these confounding factors, the measurement of this clinical variable should be strictly standardized. Exercise, alcohol, nicotine, and coffee should be avoided in the hours preceding measurement. Readings should preferably be taken by pulse palpation while the patient is comfortably seated in a chair with legs uncrossed. The room should be at a comfortable temperature and background noises should be avoided. The patient should refrain from talking during the procedure, and at least 5 min should elapse before the first reading is taken.

15 ATTACHMENTS: STUDY FORMS

[47] Recommendations on how to measure resting heart rate available at: http://www.medicographia.com/2010/07/recommendations-on-how-to-measure-resting-heart-rate/.