

Official Title: A Randomized, Double-Blinded, Placebo-Controlled, Cross Over Study Evaluating the Efficacy and Safety of Timolol Ophthalmic Solution as an Acute Treatment of Migraine

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# University of Kansas Medical Center Study Protocol

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**Study Title:** A Randomized, Double-Blinded, Placebo-Controlled, Cross Over Study Evaluating the Efficacy and Safety of Timolol Ophthalmic Solution as an Acute Treatment of Migraine

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## **I. Purpose, Background and Rationale**

### **A. Aim and Hypotheses**

Migraine is a common, disabling neurological disorder, affecting 10–12% of US population; 18% women and 6% men. [1]. The treatment of migraine headache includes preventive therapies and abortive therapies. There are several preventive therapies available with the goal to decrease the overall frequency and intensity of migraine attacks. The abortive medications are used during acute migraine episode. There are several medications like NSAIDs, triptans etc. that are used for migraine abortion.

Despite of the various migraine abortive therapies available, there is an ongoing need for novel therapies. Beta-blocker medications have been used for migraine prevention for a long time. However, their use for migraine abortion has not been well identified. In this study, we propose the use of topical beta-blocker eye drops for acute treatment of migraine headache. If successful beta-blocker eye drops will be a simple, painless and low cost acute treatment of migraine.

### **Specific aims**

- 1) To assess the efficacy (headache freedom at 2 hours) of Timolol 0.5% ophthalmic solution compared to placebo in acute treatment of migraine headache.
- 2) To assess the safety and tolerability of Timolol 0.5% ophthalmic solution in treatment of acute migraine headache.

### **Hypothesis:**

Oral beta-blockers are a class of medications frequently used to control blood pressure, angina, and heart irregularities. Certain oral beta-blockers such as propranolol and timolol are used on a daily basis to prevent migraines. However, propranolol and timolol tablets have not been shown to be effective as an acute treatment to stop attacks of migraine because of their longer onset of action. We propose that, since beta-blocker eye drops, unlike tablets are quickly absorbed through the covering of the eye and lining of the nose and can be detected in the bloodstream within minutes, can be beneficial and efficacious in the treatment of headache abortion.

Timolol is a non-selective beta-adrenoreceptor antagonist [7]. Oral timolol (20-30 mg daily) has been studied in 3 randomized controlled trials and have been found to reduce headache frequency by more than 50% when compared to placebo.[8-10] It has been approved by FDA for prophylactic use in migraine patients and had level A evidence to support this indication. The prophylactic benefit of beta-blockers in migraine treatment is not completely understood. It may be related to the effect of beta-blockers on central autonomic vascular tone center, which in turn modulate the cerebrovascular reactivity to sensory stimulation.[11] [12] Propranolol, a beta-adrenergic blocker modulates serotonergic transmission, regulates periaqueductal pathway activation and prevents central sensitization, normalizes neuronal excitability in the CNS, and blocks cortical spreading depression (CSD). Topical ocular beta blockers have been reported to be successful in retinal arteriolar spasm,

retinal migraines causing visual field defects, migraines causing oculomotor nerve palsy[14], and as abortive agents in migraine patients[4-6]. Topical timolol maleate solution 0.5% reaches a concentration of 0.5 ng/ml in the plasma within 4 hours of first dose after being used twice daily for 7 days [4].

Topical beta-blockers so far have been noted to be effective for acute migraine episodes only in case reports [4, 5] and a recent case series of 7 patients. [6] To date there have been several case studies of patients successfully using a beta blocker eye drop containing timolol to treat attacks of migraine, however, there have been no randomized controlled trials. We believe that this pilot study, to evaluate the efficacy and safety of a timolol eye drop for acute treatment of migraine headaches, will open doors for future trials and larger studies. If successful, this will be able establish the use of beta-blocker eye drops which is a simple, painless and low cost acute treatment of migraine.

To date, there have been several case studies of patients successfully using a beta-blocker eye drop containing timolol to treat attacks of migraine; however, there have been no randomized controlled trials. The aim of this study is to determine the efficacy of timolol eye drops for the acute treatment of migraine.

## **B. Background and Significance**

### 1. Study Significance:

Migraine and other benign recurrent headache disorders are a major public health problem, particularly among reproductive-aged women. They are associated with substantial personal suffering, disability, and societal expense. The impact of migraine is substantial because of its high prevalence, accompanying significant disability, and risk for other comorbidities. Data from the National Ambulatory Medical Care Survey (NAMCS), and the National Hospital Ambulatory Medical Care Survey (NHAMCS) indicate that headache is among the top 20 reasons for outpatient medical visits and among the top 5 reasons for ED visits. Several preventive and abortive medications are available for the treatment of migraine headaches. Despite of various treatments available, there seem to be an ongoing need for novel therapies.

It is known that ocular symptoms are commonly seen in classic migraine. Retinal spasm or elevated intra-ocular pressure may play a role in causing headaches for some patients. Perimetry study in migraine patients (compared to controls) have shown temporal visual field dysfunction in migraine subjects similar to early stages of glaucoma.[2] Migraine patients may also have retinal ischemic changes and optic nerve ischemia.[3] Topical beta-blockers so far have been noted to be effective for acute migraine episodes only in case reports [4, 5] and a recent case series of 7 patients. [6] The aim of this study is to evaluate the role of topical timolol 0.5% to treat acute migraine attacks and compare the efficacy and tolerability of this product with a topical placebo.

## **C. Rationale**

1. Certain beta-blockers medications like propranolol and timolol have been used as a preventive therapy for migraine headaches. Their safety and efficacy in the prevention of migraines has been well established. In this study we propose the use of topical beta-blocker eye drops for acute treatment of migraine attack. Since topical and local application beta-blocker eye drops are directly absorbed through the ophthalmic and nasolacrimal mucosa and enters the blood stream within minutes.
2. To date, there have been several case studies of patients successfully using a beta-blocker eye drop containing timolol to treat attacks of migraine; however, there have been no randomized controlled trials. The aim of this study is to determine the efficacy of timolol eye drops for the acute treatment of migraine
3. We believe that this pilot study, to evaluate the efficacy and safety of a timolol eye drop for acute treatment of migraine headaches, will open doors for future trials and larger studies. If successful, this will be able establish the use of beta-blocker eye drops which is a simple, painless and low cost acute treatment of migraine.

## **II. Research Plan and Design**

### **A. Study Objectives:**

A. The objective of this study is to assess the efficacy and response to treatment of acute migraines with timolol 0.5% eye drops as compared to placebo.

We will also assess the safety and tolerability of timolol eye drops in acute treatment of migraine headaches using patient satisfaction scale.

### **B. Study Type and Design:**

B. This is a randomized, double blind, crossover, placebo-controlled, study containing a screening visit, a double-blind treatment phase, and an end-of-study visit. The participating site is the University of Kansas Medical Center where eligible subjects in the age group of 18-65 years will be enrolled. A total of 26 subjects with 1-8 migraines per month will be enrolled in a randomized double blind fashion.

Power calculations were performed and we found that twenty six subjects are required to have a 90% chance of detecting, as significant at the 5% level, an increase in the primary outcome (benefit vs. failure) from 25% in the control group to 65% in the experimental group.

C.

D. The study will consist of two visits (Visit 1 Screening/ Randomization and Visit 2 End-of-Study). Subjects will treat two of their migraine attacks with either the study drug or placebo in a double blinded, randomized, crossover fashion within a period of 8 weeks. Subjects who do not have any migraines attacks in the given 8 weeks period will be dropped from the study. Eligible

subjects will be enrolled from their usual office visits. At the Screening/ Randomization visit, subjects will provide a detailed medical and headache history, concurrent medications, demographics, a physical examination will be performed, vital signs will be obtained, a urine pregnancy test will be obtained for female subjects with child bearing potential, and verification of inclusion/exclusion criteria will be completed. Since most of the above are done as a part of the routine office visit (except for urine pregnancy screen and verification of inclusion/ exclusion criteria), collection of these data points will not be repeated.

E.

F. Subjects who meet all inclusion and exclusion criterion will be identified and recruited through routine office visits. Subjects will be randomized in a double-blinded fashion to either the study medication arm or placebo arm. They will be sent home with one bottle of the drug, which will be either the study medication (0.5% timolol ophthalmic solution) or the placebo (0.9% normal saline solution). They will be provided instructions on proper administration of the eye drops. They will treat their first migraine attack with 1 drop of ophthalmic solution in each eye (either study medication or placebo, depending upon which study arm they are in). If they miss the eye in the first attempt, they may re-administer another drop. They will be asked to then blink rapidly for 3-5 seconds to promote absorption. After 15 minutes, if the migraine headache is still present, they can re-administer one drop in each eye. They will record their migraine pain level using the comparative pain scale (Appendix B) before administering the eye drops and 2 hours after treatment. They will also report their treatment satisfaction using the forms provided (Appendix C). After the treatment of their first migraine attack, the subjects will notify the study staff and will either come in to return the first bottle and forms or they will send in their medications and forms. Once the first bottle is received, we will either mail in using a service like FedEx or they will return to pick up their second bottle. At the interim visit, if the subjects decide to return their first bottle via mail, they will be contacted by the study staff via phone call, in order to report any changes in their concomitant medications or any adverse events. The subjects will treat their second migraine attack with the second drug and again report their migraine pain level using the comparative pain scale and also report treatment satisfaction. See table below.

**Table 1: Schedule of events**

<b>Procedure</b>	<b>Baseline Visit</b>	<b>Interim Visit</b>	<b>End of Study Visit</b>
Consent	X		
Demographics	X		
Medical History	X		
Concomitant Medications	X	X	X
Physical Exam	X		X
Vital signs	X		X
Urine pregnancy screen	X		X
Drug Dispensing	X	X	
Drug Accountability		X	X
Adverse events		X	X
Pain Questionnaire	X	X	X
Satisfaction Questionnaire	X	X	X
Data Entry	X	X	X

At any point, during the treatment of their migraine attacks with the study medications, rescue medications (like NSAIDs, triptans or their usual migraine abortive medications) can be taken 120 minutes after the study drug dose, if necessary. After treating their second migraine attack, the subjects will return for an end-of-study visit. This should occur within 7 days after treating their last qualifying migraine, or after 8 weeks of enrolling in the study (whichever comes first). The subject's diary information will be reviewed and all end-of-study visit procedures will be performed

Subjects will use a diary to collect all attack and safety data needed for data analysis. They will use the comparative pain scale to grade their migraine pain level before and at 2 hour after administration of study ophthalmic drops. They will be provided forms during each visit to record their pain score and treatment satisfaction. A safety monitor will be appointed and all adverse reactions will be reported, although we do not anticipate any adverse events given the short duration of the study and established safety of the drug. All data collected from the patients will be entered on a secured spreadsheet/ database. No patient identifiers will be used. Descriptive statistics will establish baseline characteristics and adverse event frequency. Data for the primary endpoint will be statistically analyzed via 2-tailed t-test. Data for the secondary outcome measures will be statistically analyzed for both within and between group changes via 2-tailed repeated measures ANOVA and or independent or dependent t-tests as appropriate. All ANOVAs will be followed by univariate post-hoc tests.

### **C. Sample size, statistical methods, and power calculation**

1. A total of 26 subjects will be enrolled. Eligible subjects in the age group of 18-65 years will be enrolled at the University of Kansas Medical Center. Subjects will be randomized on 1:1 ratio. They will treat their first migraine episode with the first drug (study drug or placebo, depending upon which group they are randomized to) and then will cross over to the second drug.
2. This will be a double-blinded study. The drug bottles (study drug and placebo) will be given to the subjects in unlabeled bottles.
3. A maximum of 26 subjects will be enrolled in the study. All data collected from the subjects will be entered on a secured spreadsheet/ database. Descriptive statistics will establish baseline characteristics and adverse event frequency. Data for the primary endpoint will be statistically analyzed via 2-tailed t-test. Data for the secondary outcome measures will be statistically analyzed for both within and between group changes via 2-tailed repeated measures ANOVA and or independent or dependent t-tests as appropriate. All ANOVAs will be followed by univariate post-hoc tests.
4. Study results:  
Primary outcome change in visual analogue pain scale (VAS) 120 minutes after dose showed a similar decreases for placebo and drug with a slightly wider 95% CI for placebo. Planned secondary analysis based on satisfaction (satisfactory and very satisfactory compared to neutral and unsatisfied) was negative by Chi-square  
Post-hoc analysis was 50% or greater decrease in VAS compared to < 50% decreased was negative by chi-square

## **D. Subject Criteria (See Vulnerable Populations appendix, if applicable):**

### **1. Inclusion criteria:**

Potential subjects must meet the following criteria at the screening visit to enter this study:

- Male or female, between the ages of 18 to 65 years
- Diagnosis of migraine, with or without aura, according to ICHD-2 criteria (Appendix A) for at least 1 year prior to screening; experience an average of 1 to 8 migraines per month.
- Females must be practicing an effective method of birth control before entry and throughout the study, or be surgically sterile, or be postmenopausal
- Females of child-bearing potential must have a negative urine pregnancy test
- Subjects should be able to demonstrate the ability to properly administer study medication
- Subjects should be able and willing to read and comprehend written instructions and complete the diary information required by the protocol
- Subjects must be capable, in the opinion of the Investigator, of providing informed consent or assent to participate in the study
- Subjects (and their legally acceptable representatives, if applicable) must provide an informed consent indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study

### **2. Exclusion criteria:**

Potential subjects who meet any of the following criteria will be excluded from entering this study:

- Inability to distinguish other headaches from migraine
- Experiences headache of any kind at a frequency greater than or equal to 15 days per month
- Current use of medication for migraine prophylaxis that has not been stable (no dose adjustment) for 30 days prior to screening
- Chronic opioid therapy for headaches (> 3 consecutive days in the 30 days prior to screening)
- Hemiplegic migraine
- History, symptoms or signs of ischemic cardiac, cerebrovascular or peripheral vascular syndromes. Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort, vasospastic forms of angina such as the Prinzmetal variant), all forms of myocardial infarction and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks. Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, Raynaud syndrome
- History of glaucoma and/or current treatment with prescription eye drops
- History of naso-lacrimal duct ("tear duct problem" to patients) obstruction or surgery for such
- Active treatment by ophthalmologist or optometrist for any severe ophthalmic disease or problem
- Any physical problems or co-ordination difficulty or eye avoidance sensitivity ("squeezer") that would preclude proper installation of eye drops in either or both eyes
- History of uncontrolled asthma, COPD, or reversible airway disease which in the opinion of the investigator would be worsened by the use of beta blockers
- History of clinically symptomatic bradycardia, congestive heart failure, or hypotension
- Uncontrolled Diabetes Mellitus
- Uncontrolled Hyperthyroidism

- History (within 2 years) of drug or alcohol abuse as defined by DSM-IV criteria
  - Systemic disease, which in the opinion of the Investigator, would contraindicate participation
  - History of a neurological or psychiatric condition, which in the opinion of the Investigator would contraindicate participation
  - History of hypersensitivity or intolerance to beta-blockers eye drops
  - Pregnant or lactating women
  - Have taken any investigational medication within 12 weeks before randomization, or are scheduled to receive an investigational drug
  - Subjects, who in opinion of the Investigator, should not be enrolled in the study because of the precautions, warnings or contra-indications sections of the timolol Package Insert
3. Withdrawal/Termination criteria: Although we do not anticipate any adverse events, subjects who experience any adverse effect from the study drug will be withdrawn from the study. Since the study drug will be used only once there will be no need to taper the drug dose. There wont be any tests necessary upon withdrawal from the study. Also, subjects who do not have any migraines attacks in the given 8 weeks period will be dropped from the study.
4. The study subject will not participate in another research study while participating in this study.

#### **E. Specific methods and techniques used throughout the study**

##### 1. Laboratory test:

The subjects will be identified and enrolled from the neurology office visits. Once identified, they will be consented. Since they will be enrolled from the office visit, most data points like medical history, concomitant medications, vital signs and physical examination will not be repeated as this will be collected as a part of their neurology office visit. A urine pregnancy screen will be performed in female subjects in the childbearing age groups to ensure that they are not pregnant. Once enrolled, they will then be randomized in a double blind fashion into a study drug arm or placebo arm. They will be demonstrated on how to instill eye drops and will be sent home with one bottle of the drug with instructions to treat their migraine attack with the drug (either the study medication or placebo, based on their randomization). They will treat their first migraine attack with the drug and record their migraine pain level using the comparative pain scale and treatment satisfaction score using the satisfaction scale. All the scoring forms will be provided to them at their visit. After the treatment of their first migraine attack, they will return the drug bottle (either in person or via mail). They will then receive the second bottle (either in person or via FedEx) and will be instructed to treat their second migraine attack with the drug. They will again rate their migraine pain score using the comparative pain scale and the treatment satisfaction score using the satisfaction scale. Subjects will then return for an end of study visit. Vital signs, physical examination,

and a repeat urine pregnancy screen (in child bearing age group female subjects) will be obtained and recorded. The urine pregnancy screen will be done using a urine dipstick method. No specimens will be stored. All data collected will be entered on a secured spreadsheet/ database.

**Table 1: Schedule of events**

<b>Procedure</b>	<b>Baseline Visit</b>	<b>Interim Visit</b>	<b>End of Study Visit</b>
Consent	X		
Demographics	X		
Medical History	X		
Concomitant Medications	X	X	X
Physical Exam	X		X
Vital signs	X		X
Urine pregnancy screen	X		X
Drug Dispensing	X	X	
Drug Accountability		X	X
Adverse events		X	X
Pain Questionnaire	X	X	X
Satisfaction Questionnaire	X	X	X
Data Entry	X	X	X

**F. Risk/benefit assessment:**

1. Physical risk

We do not anticipate any physical risk to the study subjects. A safety monitor will be appointed in case of any adverse events.

2. Psychological risk

The study subjects may not have adequate pain relief with the study drug and the placebo. To minimize this risk, at any point during the treatment of their migraine attacks with the study medications, rescue medications (like NSAIDs, triptans or their usual migraine abortive medications) can be taken 120 minutes after the study drug dose, if necessary.

3. Social risk

We do not anticipate any social risk.

4. Economic risk

Study subjects will be enrolled from their usual office visits. However, for the interim (if they decide to return to pick up the second drug) and end of study visit they will be compensated with a nominal subject honorarium amount which may not be enough to cover their travel expense if they live far off.

5. Potential benefit of participating in the study

- a. The individual subject participating in the study will benefit from the treatment if the study drug is effective in aborting their migraine attack and provide pain relief.
- b. If the study drug is efficacious and safe in treating migraine headaches in study subjects, the medication can potentially be used for migraine patient population from which the subjects are drawn.
- c. If successful this pilot study will open doors for future trials and larger studies that will be able establish the use of beta blocker eye drops which is a simple and low cost acute treatment of migraine.

**G.**

**G. Location where study will be performed:** Neurology clinics located at Landon Center of Aging, 3599 Rainbow Blvd, Kansas City, KS; Indian Creek Neurology Clinic located at 10777, Nall Avenue, Overland Park, KS and the Spine Center Neurology Clinic located at 3901, Rainbow Blvd, Kansas City, KS.

**H. Collaboration (with another institution, if applicable):**

**I. Single IRB Review for a Multi-site study (if applicable)**

1. For which sites will KUMC serve as the IRB of record?  
Neurology clinics located at Landon Center of Aging, 3599 Rainbow Blvd, Kansas City, KS; Indian Creek Neurology Clinic located at 10777, Nall Avenue, Overland Park, KS and the Spine Center Neurology Clinic located at 3901, Rainbow Blvd, Kansas City, KS
2. Indicate which study activities will occur at each site. If all study procedures will be identical across study sites, state this.  
Subjects who meet all inclusion and exclusion criterion will be identified and recruited through routine office visits at each of the above sites. They will be randomized in a double-blinded fashion to either the study medication arm or placebo arm.
3. Describe how you will assess the capacity of each site to perform the research (e.g., expertise, staffing, space, equipment, etc.) If applicable, include site evaluation tools in your IRB submission.  
Since the subjects will be identified and recruited through routine office visits, each of the above sites are fully equipped neurology clinics. The subjects will be identified and enrolled by physicians during the office visits. The clinic rooms, office ancillary staff and equipment will be used just like a regular neurology clinic visit.

4. Describe how the lead investigators will ensure that all participating sites use the IRB-approved version of the protocol, consent, recruitment materials and other study documents.  
We will make sure that all the participating sites and all study investigators are following the IRP protocol. Each site will have the protocol, consent forms, exam forms and other forms (pain scale and patient satisfaction scale).
5. Describe how the lead investigators will communicate with and disseminate new information to other sites (e.g., training meetings, regularly-scheduled conference calls, notifications, etc.)  
Routine meetings and /or conference calls will be conducted to communicate with all study personnel. Any new data or information pertinent to the study will be discussed during these meetings and phone calls.
6. Describe how the lead investigator will assess protocol compliance, unanticipated problems and adverse events at other sites.  
We do not anticipate any adverse events in this study. A safety monitor will be appointed for any adverse events, if any.
7. Name the member of the KUMC study team who will be the point of contact to coordinate oversight and communication with the sites.  
Andrew Heim, Laura Herbelin and Dipika Aggarwal, MD

**J. Community-Based Participatory Research (if applicable)**

1. Participants and the nature of their involvement:  
Drs Carl Migliazzo and John C. Hagan III are ophthalmologists in the community who are also involved in the study. They will serve the roll to identify subjects in their office and refer them to the neurology clinic for evaluation and enrollment into the study.
2. Cultural issues: We do not anticipate any cultural issues.
3. Origin of the research question: N/A
4. Risks and Benefits: N/A
5. Study Description and Process: N/A
6. Return of results: N/A
7. Sustainability: N/A

**K. Personnel who will conduct the study, including:**

1. Indicate, by title, who will be present during study procedure(s): Study personnel including Co-PI and Co-I; Deetra Ford, MD; Brennen Bittel, DO ; Patrick Landazuri, MD; Vernita Hairston, MD; Fred Sachen, MD; Dipika Aggarwal, MD (PI), Laura Herbelin
2. Primary responsibility for the following activities, for example:
  - a. Determining eligibility: Study personnel
  - b. Obtaining informed consent: Study personnel
  - c. Providing on-going information to the study sponsor and the IRB: Dipika Aggarwal, MD, Andrew Heim and Laura Herbelin
  - d. Maintaining participant's research records: Study personnel
  - e. Completing physical examination: Study personnel
  - f. Taking vital signs, height, weight: The ancillary clinic staff including the Medical Assistant and LPNs
  - g. Drawing / collecting laboratory specimens: No blood draws are needed for the study.
  - h. Performing / conducting tests, procedures, interventions, questionnaires: Study personnel
  - i. Completing study data forms: Study personnel
  - j. Managing study database: Study personnel

**L. Assessment of Subject Safety and Development of a Data and Safety Monitoring Plan**

1. Elements of the plan include:
  - a. Persons/groups who will review the data (study team; independent safety monitor, data monitoring committee or formal DSMB) Study personnel
  - b. Data/events that will be reviewed - All collected data will be reviewed
  - c. Frequency of review - Once a month
  - d. Types of analyses to be performed
  - e. Safety-related triggers that would cause the PI to stop or alter the study  
We do not anticipate any safety related triggers that would cause the study to be stopped or altered
2. We do not anticipate any adverse events in the study. In case of any unanticipated problems we will have a safety monitor appointed for the study. Any adverse event from the drug will be treated in timely fashion. The subject will be withdrawn from the study in case of any adverse events.
3. The subject will be withdrawn from the study in case of any adverse events to ensure safety.

### **III. Subject Participation**

#### **A. Recruitment:**

1. Subjects in the age group of 18-65years will be recruited from the neurology clinics at the University of Kansas Medical Center located at Landon Center of Aging, 3599 Rainbow Blvd, Kansas City, KS; Indian Creek Neurology Clinic located at 10777, Nall Avenue, Overland Park, KS and the Spine Center Neurology Clinic located at 3901, Rainbow Blvd, Kansas City, KS.
2. Recruitment will be conducted by the study personnel (physicians)
3. N/A
4. N/A

**B. Screening Interview/questionnaire:** No specific screening interview or questionnaire will be performed. Subjects will be identified and enrolled during their neurology office visit.

#### **C. Informed consent process and timing of obtaining of consent**

- 1 Physicians (PI and Co-I)
- 2 A detailed verbal and written informed consent will be provided to the subjects. They will then be given some time to go over the details and make a thoughtful decision. All questions will be answered by the study personnel providing the consent.
- 3 The study personnel (physicians, PI and Co-I) will determine whether the subject (age 18-65years) is able to give an informed consent.

**D. Alternatives to Participation:** None

**E. Costs to Subjects:** Subjects will be identified and enrolled from their office visit. The subject's insurance company will pay for costs of clinical care just like any usual office visit. The only test which will be done as a part of the study, is the dipstick urine pregnancy screen the cost of which will be budgeted in the study budget.

**F. How new information will be conveyed to the study subject and how it will be documented:** Any new information made available will be conveyed to the subjects at either their in person visits or via phone calls.

**G. Payment, including a prorated plan for payment:** Subject honorarium/shipping: The end of study visit is not a clinic visit but a research visit. We will provide subjects \$25 to offset the cost of travel and food for this visit. For the interim visit, for the subject who can return to pick up their medication, we are offsetting the cost of travel and food for this visit by providing subjects \$25.

**H. Payment for a research-related injury:** None anticipated

### **IV. Data Collection and Protection**

#### **A. Data Management and Security:**

1. All data will be collected from the subjects and will be entered on a secure spreadsheet/ database. The study personnel will have access to this database.
2. All subject data will be de-identified and entered in a secure database.
3. Human subjects will be identified through coded information. No personal identifiers will be used.
4. Research coordinators
5. N/A
6. Data will be stored in a secure server.
7. None
8. None

**B. Sample / Specimen Collection:** No samples will be collected or stored as a part of the study.

**C. Tissue Banking Considerations:** None

**D. Procedures to protect subject confidentiality:** None

**E. Quality Assurance / Monitoring**

1. All data will be verified prior to entering in the database to ensure reliability.
2. No

## **V. Data Analysis and Reporting**

**A. Statistical and Data Analysis:** All data collected from the patients will be entered on a secured spreadsheet/ database. No patient identifiers will be used. Descriptive statistics will establish baseline characteristics and adverse event frequency. Data for the primary endpoint will be statistically analyzed via 2-tailed t-test. Data for the secondary outcome measures will be statistically analyzed for both within and between group changes via 2-tailed repeated measures ANOVA and or independent or dependent t-tests as appropriate. All ANOVAs will be followed by univariate post-hoc tests.

**B. Outcome:** The primary end point of the study is to compare differences in headache severity at 120 minutes between study medication and placebo. A statistically significant pain relief in the study medication arm when compared to the placebo arm will determine success of the study. The secondary end point will be to assess the safety and subject satisfaction with treatment.

**C. Study results to participants:** Once the study results are available, they will be conveyed to the subjects either in person during their regular office visit or via telephone calls

**D. Publication Plan:** We plan to publish the study upon completion and results available.

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## **APPENDIX I: VULNERABLE POPULATIONS**

- I.** N/A
- II. Cognitively or decisionally impaired individuals:** Subjects with history of an underlying neurological or psychiatric condition which in the opinion of the investigator would contraindicate participation will be excluded from the study
- III. Children:**
- IV. Pregnant women:** Pregnant women will be excluded from the study
- V. Prisoners:** We do not foresee any prisoners to be enrolled in the study.
- VI. Students and/or Employees:**
  - A.** None
  - B.** None
  - C.** We will identify and enroll subjects in the age groups of 18-65 years.