

Manistee Partners:	Title: CLINICAL STUDY PROTOCOL		
Protocol Number: 17-MAN-001	Version Number: 1.1	Effective:12/21/17	Page: 1 of 13

A Phase II randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of bimatoprost in the treatment of episodic migraine.

Protocol #: 17-MAN-001

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Clinical phase: Phase II

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Manistee Partners:		Title: CLINICAL STUDY PROTOCOL	
Protocol Number: 17-MAN-001	Version Number: 1.1	Effective:12/21/17	Page: 2 of 13

Document History:

Version	Date	Replaces	Description of Changes
1.1	12/21/2017	1.0	Relaxation of exclusion criteria to permit enrollment of subjects currently taking antidepressants

Manistee Partners:		Title: CLINICAL STUDY PROTOCOL	
Protocol Number: 17-MAN-001	Version Number: 1.1	Effective:12/21/17	Page: 3 of 13

Protocol Signature Page

Approvals:

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Manistee Partners:		Title: CLINICAL STUDY PROTOCOL	
Protocol Number: 17-MAN-001	Version Number: 1.1	Effective:12/21/17	Page: 4 of 13

Investigators protocol signature page:

I confirm that I have read this protocol, I understand it and I will work according to this protocol and the ethical principles stated in the Code of Federal Regulations (CFR), title 45, part 46, as well as ICH E6, GCP guidelines, and applicable local and state laws and regulations of the study site for which I am responsible, whichever provides the greater protection of the individual. I will abide by the publication rules set forth in my agreement with Manistee Partners, LLC. I will accept the monitor’s inspection and overseeing of the study. I will promptly submit the protocol to the applicable Institutional Review Board for approval.

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Date

Manistee Partners:		Title: CLINICAL STUDY PROTOCOL	
Protocol Number: 17-MAN-001	Version Number: 1.1	Effective:12/21/17	Page: 5 of 13

Acronyms and Definitions:

NERHC – New England Regional Headache Center

Manistee Partners:	Title: CLINICAL STUDY PROTOCOL		
Protocol Number: 17-MAN-001	Version Number: 1.1	Effective:12/21/17	Page: 6 of 13

1. PURPOSE OF STUDY AND BACKGROUND

- a. Purpose: To assess the efficacy and safety of a topical prostaglandin F2 alpha analog (bimatoprost) applied to the fingernail bed in reducing frequency, severity, duration and disability of migraine headaches.
- b. Background: This study is important because it is estimated that 36 million people in the United States suffer from migraine headaches and this number may reach 1.2 billion worldwide. The global migraine evaluation survey found a 12% migraine prevalence worldwide and many patients suffer without adequate short-term treatment and/or long-term control (1). The annual value of loss productivity from migraine headaches in the United States is \$13 billion (1).

Prostaglandins are created from arachidonic acid and are part of the body's inflammatory response. They participate in a wide range of functions, such as contraction and relaxation of small smooth muscles, dilation and constriction of blood vessels, control of blood pressure and modulation of inflammation. Intravenous infusion of vasodilating prostaglandins (E2, E3, I2 and D2) has been shown to induce headaches, whereas non-vasodilating prostaglandins (F2 alpha) are not associated with headaches (2).

Hall, *et al.* (3) observed that treatment with topical prostaglandin F2 alpha analogs (applied either to the eye or fingernail bed) significantly reduced the frequency, severity and duration of headaches in migraine sufferers, as well as the migraine disability assessment score (MIDAS).

- c. Primary endpoint of the study: Does topical bimatoprost (a prostaglandin F2 alpha agonist) applied to the fingernail beds reduce the number of headache days per month in episodic migraineurs?
- d. Secondary endpoints: Does topical bimatoprost applied to the fingernail beds of episodic migraineurs (a) reduce severity of migraine headaches; (b) reduce duration of headaches; (c) improve the quality of life as measured by the MIDAS score and headache intensity assessment.

2. STUDY DESIGN

Study drug: Topical bimatoprost 0.03% solution is a prostaglandin F2 alpha analog. It is FDA approved for topical application to the eye in the treatment of glaucoma. Prostaglandins, including bimatoprost, have been used to topically treat glaucoma for 30+ years. When applied to the eye, bimatoprost is well tolerated and results in decreased intraocular pressure. Eye drop application can be associated with alteration in pigmentation of pigmented tissues and

Manistee Partners:	Title: CLINICAL STUDY PROTOCOL		
Protocol Number: 17-MAN-001	Version Number: 1.1	Effective:12/21/17	Page: 7 of 13

eyelash growth. It is rarely associated with intraocular inflammation, macular edema, bacterial keratitis, conjunctival hyperemia, conjunctival hemorrhage, eye irritation, eye pain, itchy eye, erythema of the eyelid, eyelid itchiness, instillation site irritation, punctate keratitis, visual blurring and visual acuity reduction. Eye drop application has also been associated with periorbital and lid changes including deepening of the eyelid sulcus (4). Topical application to the fingernail bed may be associated with a slight increase in fingernail growth.

Headaches (but not the more severe and debilitating frequent migraine headaches) are reported as a potential systemic adverse side effect in 1-5% of patient's taking topical bimatoprost ophthalmic solution administered to the eye (4). Headaches may rarely occur with many medications. However, the greater than 80% positive response rate with reduction in headache frequency and severity documented in the study by Hall, et al. (3) using topical bimatoprost to the fingernails represents a significantly greater benefit without meaningful added risk to study patients.

- a. Study treatment group: This will be a 16-week double-blind, randomized, placebo-controlled parallel group trial of prophylactic bimatoprost in up to 80 patients with episodic migraine. There will be a 1:1 randomization across the two groups, bimatoprost and placebo. Randomization will be done using a computer random number generator. Randomization assessment of the subjects will be done blind to treatment assignment. Based on a review of placebo-control trials of migraine, we assume a 20% difference in changes from baseline in monthly headache frequency for a calculation of sample size. With a power of [80%, significance of this level of 5% (one-sided) and an effect size of 0.8 (large), the sample size requirement is 30 in each group.
- b. Treatment regimen: Bimatoprost 0.03% solution and a placebo will be placed in ophthalmic bottles. Treatment and placebo groups will place one drop (approximately 25 µl) once daily on the nail bed (lunula) of each of four fingers on the non-dominant hand. The drops will be allowed to air dry. No nail polish is to be used during the trial. This compares to one drop (approximately 25 µl) of 0.03% solution being FDA- approved for administration once daily into each of two eyes for treatment of glaucoma.
- c. Study visits: The study will consist of four visits for each patient: a screening visit (V1), week -4; randomization visit (V2), week 0; a compliance visit (V3), week 6; an end-point visit (V4), week 12. A compliance phone call assessment will be made to each participant at week 3 and week 9.
- d. Study duration: The study will continue for 16 weeks and each participant will be expected to participate in the full extent of the study.

Manistee Partners:	Title: CLINICAL STUDY PROTOCOL		
Protocol Number: 17-MAN-001	Version Number: 1.1	Effective:12/21/17	Page: 8 of 13

3. CRITERIA FOR SUBJECT SELECTION

- a. Number of subjects: Eighty subjects are expected to participate.
- b. Gender of subjects: Male and female patients will be admitted to the study. There will be no gender restriction, except pregnant and lactating females will be excluded.
- c. Age of subjects: The age range will be 18-65 years. Migraine manifestation and treatment is more complex and variable in children and adolescents. General medical issues and transportation availability can become problematic for people over age 65. Therefore, the age range of 18-65 has been selected.
- d. Racial and ethnical profile: There are no restrictions based on race or ethnic origin.
- e. Inclusion criteria: Inclusion for study will be diagnosis of episodic migraines based on International Classification of Headache Disorders (ICHD) II criteria and experiencing headaches for 4-14 days per month, the internationally accepted definition of “episodic migraine” patients. All our patients will be screened to make sure they do not have other medical conditions that are causing their migraines. The subjects in the study will already be taking medications as recommended by their primary physician. Patients will be permitted to use stable doses of up to three different standard migraine preventive drugs for at least three months before study onset. Patients will be allowed to treat acute migraine headaches as usual and they must show compliance (at least 80%) with a headache diary during the four-week run-in phase.
- f. Exclusion criteria: Exclusion criteria are significant liver or renal dysfunction, on treatment for inflammatory bowel disease, medication over-use for headaches according to the ICHD II criteria, use of antipsychotics in the past month, recent (in the past six months) history of alcohol or drug abuse, allergy to bimatoprost and its compounds, severe comorbid psychiatric illness, severe infection, malignancy, severe cardiovascular disease, neurodegenerative disorders, pregnancy and lactation, and sexually active women of child bearing age who do not use any method of contraception.
- g. Vulnerable subjects will not be included
- h. Consent: All subjects will read and sign the appropriate form approved by the Asentral Review Board (IRB). This study will be conducted in accordance with the principles of Good Clinical Practice and with the US Food and Drug Administration (FDA) guidelines for safety monitoring, as well as the last revisions of the Declaration of Helsinki. The study will also be registered in www.clinicaltrials.gov.
- i. Subject Identification Number: Before subjects begin participation in any study-specific activities/procedures, Manistee requires a copy of subject information. Each subject who enters into the screening period for the study shall sign and date the informed consent and receive a unique, randomly assigned subject identification number. The subject identification number will be used to identify the subject

Manistee Partners:	Title: CLINICAL STUDY PROTOCOL		
Protocol Number: 17-MAN-001	Version Number: 1.1	Effective:12/21/17	Page: 9 of 13

throughout the clinical study and will be used on all study documentation related to that subject.

A subject is considered enrolled when the Principle Investigator or Sub-Investigator decides that the subject has met all eligibility criteria and is randomized. The Principle Investigator or Sub-Investigator is to document this decision date and enter it in the subject's medical record and on the enrollment case report form (CRF).

The subject identification number will remain constant throughout the entire clinical study; it will not be changed after initial assignment, including if a subject is rescreened. This number will not include any identifiers for the subject.

4. METHODS AND PROCEDURES

- a. Study Drug: The study drug will be sourced, labeled, and packaged in 3 ml sterile ophthalmic bottles by Boulevard Compounding Pharmacy, a licensed pharmacy, located in Worcester, Massachusetts. It will be stored there at room temperature in a locked cabinet until needed for distribution at the clinical test site. The pharmacy will label each bottle with a unique number, assigned to a unique subject identification number, according to the Sponsor's computer-generated randomization code. The study site will be responsible for recording the study drug code on each subject's case report form.
- b. Study Visits and Duration: The study will be a 16-week double-blind, randomized placebo-control parallel-group trial of prophylactic bimatoprost in patients with migraine. The study will consist of a 4-week baseline after which the patients will be treated for 12 weeks. The patients will come in four visits: a screening visit (V1), week -4; a randomization visit (V2), week 0; a compliance visit (V3), week 6; an end-treatment visit (V4), week 12. Compliance phone call assessments will be made to each participant at week 3 and week 9.
 - i. The screening visit (V1) will consist of informed consent, eligibility and exclusion criteria, medical and psychiatric history, concomitant medications, height, weight, vital signs, physical and neurological examination, review of daily diary and dispensing of diaries. Urine tests for drug use, blood sampling for blood chemistries and EKG will be performed.
 - ii. The randomization visit (V2) consists of diary collection, diary review and, where necessary, correction by the subject, health status changes, concomitant medications, MIDAS questionnaire, dispensing of daily diaries and study medication. At the end of the randomization visit, but before medication is dispensed, it will be established that the subject meets eligibility and exclusion criteria.

Manistee Partners:	Title: CLINICAL STUDY PROTOCOL		
Protocol Number: 17-MAN-001	Version Number: 1.1	Effective:12/21/17	Page: 10 of 13

- iii. The compliance visit (V3) consists of diary collection and review and, when necessary, correction by the subject, study medication accountability, medication administration compliance, health status changes, adverse occurrences, concomitant medications and dispensing of study medication as necessary.
 - iv. The end treatment (V4) consists of diary and study medication collection, diary review and, where necessary, correction by the subject, study medication accountability, medication administration compliance, health status changes, adverse event occurrences, concomitant medications, and MIDAS questionnaire.
 - v. The week 3 and week 9 phone calls will be made to each participant to confirm compliance with medication usage, diary completion, health status changes, adverse medical events, and concomitant medications will be addressed.
- c. Data analysis and data monitoring: Patients will be instructed to record in a diary the number of headache attacks per day and the headache intensity, duration, disability level, associated symptoms and medications taken. The headache diary will be filled out every day of the month, even on days when the patient has no headache (see diary form).

The Migraine Disability Assessment Scale (MIDAS) is a five-item instrument developed to measure migraine related disability and functional consequences. It is divided into four categories based on the score of: 0-5, minimal disability; 6-10, mild disability; 11-20, moderate disability; greater than 20; severe disability. Reliability and validity of MIDAS questionnaires have been well established

- d. Primary outcome: The primary outcome measures will be the difference in the average change from the 4-week baseline period in the number of migraine headache days with moderate or severe intensity compared to weeks 9-12 between the two groups.

A migraine headache day is defined as any calendar day on which a headache which meets criteria A, B and C listed below occurs.

- A. Headache has at least two of the following:
 - i. Unilateral location
 - ii. Pulsating quality
 - iii. Moderate or severe pain intensity
 - iv. Aggravated by or causing avoidance of routine physical activity (*e. g.*, walking or climbing stairs)
- B. At least one of the following:
 - i. Nausea and/or vomiting
 - ii. Photophobia and phonophobia

Manistee Partners:	Title: CLINICAL STUDY PROTOCOL		
Protocol Number: 17-MAN-001	Version Number: 1.1	Effective:12/21/17	Page: 11 of 13

- iii. Typical aura (*i. e.*, visual, sensory, or speech/language) accompanying or
- iv. Within 60 minutes before headache begins
- C. Duration of headache lasting 2 hours or longer on a calendar day unless an acute, migraine-specific medication (*i. e.*, triptan or ergot derivative) was used after the start of the headache, in which case no minimum duration to be specified.
- e. Secondary outcomes: Secondary outcome measures will be:
 - i. Percentage reduction in the average weekly number of migraine headaches comparing baseline to weeks 9-12.
 - ii. Change in the MIDAS score comparing baseline to weeks 9-12.
 - iii. Change in severity of headaches comparing baseline to weeks 9-12.
 - iv. Change in duration of headaches comparing baseline to weeks 9-12
- f. Data recording: All data will be collected in the form of the written diaries and case report forms. No data will be collected electronically. All original data documents will be photocopied and provided to the Sponsor for data analysis. At the conclusion of the study all data documents will be scanned and converted into electronic files for secure archival storage; all the original paper documents will be stored in a locked cabinet.
- g. Data review and analysis: All study data will remain blinded to both the patients and all investigators at the NERHC. Manistee Partners will have access to unblinded data throughout the trial as it is accrued. Interim data analysis will be undertaken at a midpoint of the trial.
- h. Data storage and confidentiality: All data will be stored on a secure server in a secure file for a period of 5 years.
- i. Transition from research participation: At the termination of the study (V4), each subject will be returned to their usual care. There will be no compassionate use extension or rollover of placebo group to treatment group.

5. RISK BENEFIT ASSESSMENT

- a. Risk category: There is minimal risk associated with this study.
- b. Potential risks: The most likely potential risk to the study is that participants may notice a slightly more rapid rate of fingernail growth. There are no other anticipated side effects.
- c. Protection against risks: The study, with V3 and V4 visits and phone call assessment at three weeks and nine weeks, will allow for assessment of adverse occurrences or health status changes.

Manistee Partners:	Title: CLINICAL STUDY PROTOCOL
Protocol Number: 17-MAN-001 Version Number: 1.1	Effective:12/21/17 Page: 12 of 13

- d. Potential benefits for subjects: Potential benefits include reduction in migraine frequency, severity and duration of headaches.
- e. Alternatives to participation: All patients will continue to use their program of alternative therapies and course of action for treatment of migraine headaches. If a subject elect not to participate in the study, their primary care practitioner and/or neurologist can continue to prescribe accepted methods of treatment for migraine headaches.
- f. Patient entry and withdrawal procedures: Once a Subject enters the clinical trial they can withdraw at any time.

6. SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT

- a. Method of subject identification and recruitment: Subjects will be identified from the data base and files of NERHC, Inc. Data Mining will be performed.
- b. Subject capacity: Only those patients with the capacity to give informed consent will be included in this study.
- c. Debriefing procedures: No psychological information will be withheld from the subjects.
- d. Consent forms: See attached.
- e. Documentation of consent: The Principal investigator is responsible for ensuring that valid consent is obtained and documented for all subjects.
 - i. Process: NERHC, Inc. will provide each subject a consent to review in a private location. They will be asked to write down any questions he/she must review with study staff. Any questions study staff is unable to answer the PI will provide the information to the subject. Once all questions are answered, the subject will sign the consent to participate in the clinical trial and witnessed by the person obtaining the consent. No study procedures will be performed prior to the consent being obtained.
- f. Cost to subject: No charge or expenses associated with the study will be accrued to the subjects. The sponsor will pay for the study drug, performance of the clinical trial and statistical analysis.
- g. Payment for participation: Each subject will who completes the full study will receive up to a total of \$450.00 if they complete this study. If they do not complete the study, for any reason, they will be paid for the study visits they do complete according to the following schedule: \$150.00 for Visits 1 and 4, \$75.00 for Visits 2 and 3. They will be paid at the time their participation in the study ends

Manistee Partners:	Title: CLINICAL STUDY PROTOCOL		
Protocol Number: 17-MAN-001	Version Number: 1.1	Effective:12/21/17	Page: 13 of 13

7. ETHICS

The study will adhere to the requirements of the Asestral Review Board (IRB), ICH GCB guidelines and the Declaration of Helsinki and the study will be HIPPA compliant.

8. STUDY CLOSURE

The study will close once last subject is completed.

9. PUBLICATION

Presentations at medical, neurology and ophthalmology symposia are anticipated along with possible submission for publication in peer and non-peer reviewed journals.

10. REFERENCES

1. Marcher DB, *et al.*, The Headache Management Trial: A Randomized Study of Coordinated Care. *Headache*. 2008 Oct; 48(9): 1294-310.
2. Antonova M. Prostaglandins and Prostaglandin Receptor Antagonism in Migraine. *Dan Med J*. 60 (5), B4635. 5 2013.
3. Hall LB *et al.* The Effect of Topical Prostaglandins on Migraine Headaches. Poster Presentation at the Association for Research in Vision and Ophthalmology Annual Meeting, May 2017.
4. [Package Insert for Lumigan 0.03%](#). Allergan, Inc.