METFORMIN FOR THE PREVENTION OF MIGRAINE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY

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METFORMIN FOR THE PREVENTION OF MIGRAINE: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY

Funding Sponsor: Migraine Research Foundation

Study Product: Metformin

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List of Abbreviations

LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IND	Investigational New Drug Application
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure

Study Summary

Title	Metformin for the Prevention of Migraine: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study
Running Title	MPEM
Protocol Number	
Phase	Clinical study phase II
Methodology	Randomized, double-blind, placebo-controlled, crossover design
Overall Study Duration	12 months
Subject Participation Duration	32 weeks
Single or Multi-Site	Single
Objectives	Metformin is a safe, well-tolerated AMPK activator that has demonstrated efficacy in preclinical animal models of migraine and chronic pain. The objective of the MPEM Study is to determine if metformin will reduce the number of migraine days per month in patients with high-frequency migraine.
Number of Subjects	40
Diagnosis and Main Inclusion Criteria	Age 18-65 years Diagnosis of migraine with or without aura according to the ICHD-IIIb (2013) 5-25 migraine days per month
Study Product, Dose, Route, Regimen	Metformin 500mg twice daily orally x 11 weeks, the first week of each 12 week treatment period, patients will receive metformin 250mg twice a day or matching placebo. At week 2, the dose will be increased to metformin 500mg twice a day or matching placebo. In case of intolerable side effects, the dose will be reduced to 250mg twice a day.
Duration of Administration	12 weeks
Reference therapy	Matching placebo

Statistical Methodology	The primary end point is the number of migraine days per month during treatment with metformin vs placebo. The secondary end point is the percentage of patients with >50% reduction in migraine days per month (response rate). Mean 4-week migraine frequency for patients receiving metformin vs placebo treatment will be assessed by using the Hills-Armitage method. Response rate will be assessed by using the McNemar test.

1 Introduction

This is a clinical research protocol for a human research study. This document is a protocol for a human research study. This study will be carried out in accordance with the applicable United States government regulations and Mayo Clinic research policies and procedures.

1.1 Background

Migraine is the third most prevalent disease in the world (Vos, 2012). Preventive treatment is indicated in about 40% of individuals with migraines. Although 4 treatments are FDA-approved for prevention of migraine, none were designed to prevent migraine, efficacy is modest, and all have significant adverse-event profiles. As a result, less than 1/3 of migraine sufferers with who are candidates for prevention receive drug treatment and of those who are treated, more than 85% have discontinued the preventive drug within one year. . Medications designed to prevent migraine by addressing disease pathophysiology likely will have improved efficacy and increased tolerability compared with currently available therapies.

Migraine pain is associated with the activation and sensitization of peripheral meningeal nociceptors. As a result, approximately 75% of patients with migraine will have cephalic allodynia during an attack. mTORC1/MAPK are involved with the sensitization of nociceptors, resulting in chronic pain (Price, 2012). AMPK is a negative modulator of the mTORC1/MAPK pathways (Price, 2012) and therefore may be a novel target for the preventive treatment of migraine.

Metformin is a widely available, safe drug used to treat diabetes mellitus; it also is a powerful activator of AMPK. Preclinical data demonstrates efficacy of metformin in animal models of migraine, suggesting that it blocks hyperalgesia and the transformation to chronic pain.

Metformin has been studied in oncologic research as a novel anticancer drug for many types of cancers including prostate, breast, ovarian, and endometrial cancer. Many studies of metformin in nondiabetic patients with cancer have shown tolerability and lack of hypoglycemia at therapeutic doses up to 1,500 mg daily (Dilokthornsakul, 2013; Laskov, 2014).

Micromedex and prior studies as documented in the protocol, metformin alone does not cause hypoglycemia.

- Micromedex:
  Hypoglycemia has not been reported at usual doses in monotherapy. Hypoglycemia may occur if caloric intake is insufficient, if strenuous exercise occurs without adequate intake of calories, if other glucose lowering agents are used concurrently, or in combination with ethanol use.

We will instruct patients regarding eating well and not using any other glucose lowering agents or drink ethanol during the study.

1.2 ***We will educate patients on the symptoms of hypoglycemia including sweating, weakness, tachycardia, tremor, and feelings of nervousness and/or hunger. If they experience these symptoms, the patient can take 4 oz (120 mL) fruit juice; 6 ounces of non-diet soda; or a tablespoon (15 mL) of honey or table sugar. This process may be repeated in 10 to 15 minutes. If there is no improvement, they will be advised to seek immediate medical help.*** **Investigational Agent**

Metformin is a widely available, safe drug used to treat diabetes mellitus; it also is a powerful activator of AMPK. Preclinical data demonstrates efficacy of metformin in animal models of migraine, suggesting that it blocks hyperalgesia and the transformation to chronic pain.

Metformin has been studied in oncologic research as a novel anticancer drug for many types of cancers including prostate, breast, ovarian, and endometrial cancer. Many studies of metformin in nondiabetic patients with cancer have shown tolerability and lack of hypoglycemia at therapeutic doses up to 1,500 mg daily (Dilokthornsakul, 2013; Laskov, 2014).

1.3 Preclinical Data

Preliminary experiments in the laboratories of Drs. Greg Dussor and Ted Price have shown that application of the proinflammatory cytokine interleukin-6 (IL-6) to the dura of rats produces allodynia that lasts for 24 hours and is resolved by 48 hours (Figure 1) (Yan, 2012). However, they remain sensitive to normally nonnoxious stimuli such as small changes in pH (here, the application of a pH 6.8 solution to the dura). As shown in Figure 1, only rats that received IL-6 responded to subsequent pH 6.8 stimulation, even though they were all free from allodynia. This shows that an initial headache-like event in rats can prime the nociceptive system to subsequent,

normally subthreshold events. Mechanisms that mediate priming of the dural-afferent nociceptive system in rats may similarly sensitize the analogous system in humans and contribute to the pain of migraine. This could promote development of headaches in response to events that would be considered nonnoxious in those without headaches. Next, rats were given metformin (200 mg/kg, saline vehicle, administered intraperitoneally) the day before and the day of the IL-6 injection. Metformin administration attenuated the initial allodynia due to IL-6, but more importantly, it prevented development of the primed state (Figure 2). Rats treated with metformin did not have allodynia with pH 6.8 stimulation at the 72-hour time point. These data suggest that metformin treatment may have efficacy against individual headache attacks and that it may treat sensitization of the dural-afferent nociceptive system present between migraine attacks.

1.4 Clinical Data to Date

This will be the first clinical data exploring the use of metformin in high-frequency migraine.

1.5 Dose Rationale and Risk/Benefits

Metformin is a widely available, safe drug used to treat diabetes mellitus; it also is a powerful activator of AMPK. Preclinical data demonstrates efficacy of metformin in animal models of migraine, suggesting that it blocks hyperalgesia and the transformation to chronic pain.

Metformin has been studied in oncologic research as a novel anticancer drug for many types of cancers including prostate, breast, ovarian, and endometrial cancer. Many studies of metformin in nondiabetic patients with cancer have shown tolerability and lack of hypoglycemia at therapeutic doses up to 1,500 mg daily (Dilokthornsakul, 2013; Laskov, 2014).

2 Study Objectives

Study Objective 1: To compare the reduction in the number of migraine days per month during 12 weeks of treatment with metformin vs placebo (primary end point).

Hypothesis: Metformin treatment will significantly reduce the number of migraine days per month compared with placebo.

Study Objective 2: To compare the response rate (percentage of patients with a >50% reduction in migraine days per month) during 12 weeks of treatment with metformin vs placebo (secondary end point).

Hypothesis: The response rate to metformin will be significantly greater than the response rate to placebo.

Study Objective 3: To determine the safety and tolerability of metformin in patients with migraine.

Hypothesis: Metformin treatment will be safe and well tolerated, with limited adverse effects.

3 Study Design

3.1 General Design

We will obtain approval from the Mayo Clinic Institutional Review Board, and all patients will provide written, informed consent before study enrollment.

This will be a single-center, double-blind, randomized, placebo-controlled, crossover study.

After study enrollment, patients will be randomized to the Metformin study drug group or the placebo group. The Principal Investigator or patient can't choose the study group. The patient will have an equal chance of being assigned to the Metformin group. Neither the patient or the Principal Investigator will know which study group they are participating in. In case of an emergency, this information will be available.

Patients will undergo a 2-hour oral glucose tolerance test to confirm the absence of diabetes mellitus. Subjects will then keep a paper headache diary for 4 weeks to establish baseline characteristics, including number of migraine days per month, number of moderate to severe headache days per month, and number of days per month of acute medication use. The 4-week baseline period will be followed by 2 treatment periods of 12 weeks each, separated by a

washout period of 4 weeks (total study duration, 32 weeks). During the washout period, we will washout the study drug x 4 weeks.

For the 12-week treatment periods, subjects will receive either metformin 500mg twice daily or matching placebo twice daily. During the first week of each 12 week treatment period, patients will receive metformin 250mg twice a day or matching placebo. At week 2, the dose will be increased to metformin 500mg twice a day or matching placebo. In case of intolerable side effects, the dose will be reduced to 250mg twice a day.

Subjects will have 7 clinic visits. Routine laboratory studies and a pregnancy test will be performed at enrollment and week 20. Abnormal kidney or liver function will exclude subjects. Pregnancy will exclude subjects. General and neurologic examinations will be performed during 2 of the 7 visits. At each visit, subjects will receive medication for the period until the next visit. A paper headache diary will be used for the trial. For every day that the subject has a headache of any type, she or he will record headache characteristics, associated features, and medications used.

The Screening Visit, visit #1, week 0, will be 60 minutes. During this visit, we will do some tests and procedures to confirm study subjects are eligible to take part in this research study such as: review medical history, physical exam, including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates), draw a blood sample, 2 hour glucose tolerance test, urine pregnancy test, provide the study subject instructions for completion of the headache diary and provide headache diary.

Visit #2, week 4, will take about 30 minutes. At this visit we will: review the headache diary and provide the participant with a new supply of study drug.

Visit #3, week 10, will be a phone visit and will take about 15 minutes. At this phone visit we will: Review the headache diary.

Visit #4, week 16, will take about 30 minutes. At this visit we will: Review the headache diary and collect any unused study drug.

Visit #5, week 20, will take about 30 minutes. At this visit we will: review interim medical history, conduct a physical exam including height, weight, and "vital signs" (blood pressure, temperature, heart and breathing rates), collect blood sample, pregnancy test, review the headache diary and provide a new supply of study drug.

Visit #6, week 26, will be a phone visit and will take about 15 minutes to review the headache diary.

Study Closeout Visit

Visit #7, week 32, will take about 30 minutes. At this visit we will: review and collect the headache diary, and collect any unused study drug. The primary end point is the number of migraine days per month during treatment with metformin vs placebo. The secondary end point is the percentage of patients with >50% reduction in migraine days per month (response rate). Adverse events will be recorded. Mean 4-week migraine frequency for patients receiving metformin vs placebo treatment will be assessed by using the Hills-Armitage method. Response rate will be assessed by using the McNemar test.

The statistician will create Web-based case report forms using REDCap. Study coordinators will record data using REDCap forms.

3.2 Primary Study Endpoints

The primary end point is the number of migraine days per month during treatment with metformin 500mg BID vs placebo for 12 weeks.

3.3 Secondary Study Endpoints

The secondary end point is the percentage of patients with >50% reduction in migraine days per month (response rate).

3.4 Primary Safety Endpoints

To determine the safety and tolerability of metformin in patients with migraine.
Hypothesis: Metformin treatment will be safe and well tolerated, with limited adverse effects.

4 Subject Selection Enrollment and Withdrawal

4.1 Inclusion Criteria

Inclusion criteria are as follows: 1) age 18-65 years, 2) a diagnosis of migraine with or without aura for >1 year according to the International Classification of Headache Disorders-IIIb (2013), and 3) 5-25 migraine days per month on average during the preceding 3 months. Women of reproductive ability must use a reliable form of contraception beginning 3 months before study enrollment, throughout the study, and for at least 1 month after study completion.

4.2 Exclusion Criteria

Exclusion criteria are as follows: 1) a diagnosis of diabetes mellitus or polycystic ovarian syndrome, 2) overuse of acute migraine treatments, 3) failure to respond to 3 or more previous preventive drug treatments, 4) change in dose of migraine-preventive medication within 2 months of beginning the baseline diary phase, 5) initiation of cranial nerve blocks within 2 months of beginning the baseline diary phase, 6) initiation of Botox within 12 months of beginning the baseline diary phase, 7) significant somatic or psychiatric disease, 8) known alcohol or other substance abuse, and 9) pregnant or breastfeeding.

4.3 Subject Recruitment, Enrollment and Screening

Subjects will be recruited from the outpatient Mayo Headache Clinic, Mayo Women's Health Clinic, Mayo Community Internal Medicine, and the Mayo Clinic- Arizona State University Neurology Clinic. The Headache Clinic employs 6 headache specialists and 1 fellow which is sufficient staffing to support this proposal and recruitment of patients with high-frequency migraine within 6 months.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Subjects may withdraw from the study prior to that subject completing all of the study related procedures for the following reasons:

- Subject safety issues
- Failure of subject to adhere to protocol requirements
- Subject decision to withdraw from the study (withdrawal of consent)

4.4.2 Data Collection and Follow-up for Withdrawn Subjects

Even though a subject has withdrawn from the study, it may be important to collect some follow-up or survival data on such subjects throughout the protocol defined follow-up period. Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study drug. If a subject withdraws consent to participate in the study, for subject safety reasons, we will make every effort to obtain permission to collect follow up information.

5 Study Drug

5.1 Description

The study drug will be a tablet containing metformin 250mg or matching-placebo. The first week of the 12 week treatment period a tablet containing metformin 250mg will be used or matching placebo, 1 tablet twice daily. After the first week, 2 tablets of metformin 250mg (total of metformin 500mg) or 2 tablets of matching placebo twice daily x 11 weeks.

5.2 Treatment Regimen

The study drug will be a tablet containing metformin 250mg or matching-placebo. The first week of the 12 week treatment period a tablet containing metformin 250mg will be used or matching –placebo, 1 tablet twice daily. After the first week, 2 tablets of metformin 250mg (total of metformin 500mg) or 2 tablets of matching placebo twice daily x 11 weeks.

This will be followed by a 4 week washout period following which the patients will be crossed over to the other arm taking either of metformin or matching placebo x 12 weeks. The first week of the 12 week treatment period a tablet containing metformin 250mg will be used or matching – placebo, 1 tablet twice daily. After the first week, 2 tablets of metformin 250mg (total of metformin 500mg) or 2 tablets of matching placebo twice daily x 11 weeks.

5.3 Method for Assigning Subjects to Treatment Groups

A statistician will create a randomized treatment allocation schedule by using a computerized random-number generator. The randomized treatment allocation schedule will be stored using the REDCap randomization module.

5.4 Preparation and Administration of Study Drug

The Mayo Clinic Pharmacy will allocate patients to the metformin-placebo sequence or the placebo-metformin sequence in a 1:1 ratio. Study drug, both metformin and matching-placebo will be prepared and distributed to subjects. Pharmacy would not be blinded.
The study drug will be stored and dispensed from the Research Pharmacy

- [redacted]

5.5 Subject Compliance Monitoring

Subject compliance with study drug regimen will be monitored during study visits.

5.6 Prior and Concomitant Therapy

A list of all current medications will be recorded for all subjects including preventive headache medications and as needed headache medications.

Subjects are allowed to use preventive headache medications during the study, however, there must have been no change within 2 months of beginning the baseline diary phase. In addition, subjects that have failed to respond to 3 or more previous preventive drug treatments will be excluded.

Subjects are allowed to use as needed headache medications for rescue treatment. However, subjects may not overuse these medications. Overuse is defined by the ICHD-3b criteria for medication overuse.

5.7 Packaging

- The study drug and any comparator agent will be compounded into capsules
- Bottles containing 336 capsules
- Study drug will NOT be shipped.
- The study drug or comparator will be labeled with drug name, Lot #, preparation date, quantity and statement
- Study drug or comparator will be labeled "Caution: Existing Drug--Limited by Federal (or United States) law to investigational use."

5.8 Masking/Blinding of Study

Patients will be allocated to the metformin-placebo sequence or the placebo-metformin sequence at random in a 1:1 ratio. The statistician will create the randomized treatment allocation schedule by using a computer random number generator. The randomized treatment allocation schedule will be concealed by storing it on the REDCap Randomization Module. The Mayo Clinic Pharmacy will allocate patients to treatments using the REDCap Randomization Module.

5.9 Receiving, Storage, Dispensing and Return

5.9.1 Receipt of Drug Supplies

The drug will be obtained or delivered from Cardinal Health or PCCA to the pharmacy at each investigative site.

Upon receipt of the of the study treatment supplies, an inventory must be performed and a drug receipt log filled out by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipping

invoice. Any discrepancies, damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator must be notified immediately of any discrepancies, damaged or unusable products that are received.

5.9.2 Storage

No special handling requirements

5.9.3 Dispensing of Study Drug

The Mayo Clinic Pharmacy will allocate patients to the metformin-placebo sequence or the placebo-metformin sequence in a 1:1 ratio.

Regular study drug reconciliation will be performed to document drug assigned, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

5.9.4 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug dispensed, drug returns, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be documented and investigated, prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

6 Study Procedures

After study enrollment, patients will undergo a 2-hour oral glucose tolerance test to confirm the absence of diabetes mellitus. Subjects will then keep a headache diary for 4 weeks to establish baseline characteristics, including number of migraine days per month, number of moderate to severe headache days per month, and number of days per month of acute medication use. The 4-week baseline period will be followed by 2 treatment periods of 12 weeks each, separated by a washout period of 4 weeks (total study duration, 32 weeks). For the 12-week treatment periods, subjects will receive either metformin 500mg twice daily or matching placebo twice daily.

During the first week of each 12 week treatment period, you will receive metformin 250mg twice a day or matching placebo. At week 2, the dose will be increased to metformin 500mg twice a day or matching placebo. In case of intolerable side effects, the dose will be reduced to 250mg twice a day.

Subjects will have 7 clinic visits. Routine laboratory studies and a pregnancy test will be performed at enrollment and week 20. Abnormal kidney or liver function will exclude subjects. Pregnancy will exclude subjects. General and neurologic examinations will be performed during 2 of the 7 visits. At each visit, subjects will receive medication for the period until the next visit.

7 Statistical Plan

7.1 Sample Size Determination

This will be a single-center, double-blind, randomized, placebo-controlled, crossover study. Crossover designs have been used successfully in migraine trials (Olesen, 1981). Prior migraine trials have suggested that a sample size of 34 patients has 80% power to detect a mean reduction in migraine days of 1.25 days per month, with α=0.05[Q^1] (σ 2.5, ρ 0.5; Hauge, 2009; Silberstein, 2004; Sorensen, 1986). We will enroll 40 subjects to account for an estimated 15% dropout rate.

7.2 Statistical Methods

The primary end point is the number of migraine days per month during treatment with metformin vs placebo. The secondary end point is the percentage of patients with >50% reduction in migraine days per month (response rate). Mean 4-week migraine frequency for patients receiving metformin vs placebo treatment will be assessed by using the Hills-Armitage method. Response rate will be assessed by using the McNemar test. The frequency of adverse events during metformin treatment will be compared to that during placebo treatment by using the McNemar test.

Descriptive Statistics

Univariate descriptive statistics and frequency distributions will be calculated, as appropriate for all variables.

Handling of Missing Data

Patients will be included in the primary analysis on the basis of intention to treat. Migraine frequency will be calculated using all available follow-up data and converted to units of frequency per four weeks.

Multiplicity

There is a single primary outcome measure. If the primary analysis is statistically significant, the secondary outcome measure will be assessed in order to facilitate interpretation of clinical importance.

Interim Analysis

There will be no interim analysis for early stopping due to efficacy.

7.3 Subject Population(s) for Analysis

All-treated population: Any subject randomized into the study that received at least one dose of study drug employing an intention-to-treat analysis.

8 Safety and Adverse Events

8.1 Definitions

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that results in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e.

publications, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**

- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, not listed in the Investigator's Brochure, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Adverse Event

An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event

Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the sponsor-investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

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

Adverse Event Reporting Period

For this study, the study treatment follow-up period is defined as 32 weeks following the initiation of study treatment.

Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

General Physical Examination Findings

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.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report, to the investigator, any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if active management necessary requiring a change of dosage, or dosing schedule, discontinuation of study treatment or additional follow-up.

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 an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported 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.

8.2 Recording of Adverse Events

At each contact with the subject, the study team must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic, laboratory or procedure results should recorded in the source document.

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 ultimately determined that the study treatment or participation is not the probable cause. Serious adverse events that are still ongoing at the end of the study period must be followed up, to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be at least possibly related to the study treatment or study participation should be recorded and reported immediately.

8.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The investigator will evaluate the event and determine the necessary follow-up and reporting required.

8.3.1 Investigator reporting: notifying the Mayo IRB

The investigator will report to the Mayo IRB any UPIRTSOs and Non-UPIRTSOs according to the Mayo IRB Policy and Procedures.

According to Mayo IRB Policy any serious adverse event (SAE) which the Principal Investigator has determined to be a UPIRTSO must be reported to the Mayo IRB as soon as possible but no later than 5 working days after the investigator first learns of the problem/event.

Adverse events will be reported in an adverse event worksheet to be entered in the research database:

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment)
- Date of Resolution:

The investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

8.4 Unmasking/Unblinding Procedures

If unmasking/unblinding of the study drug is needed for subject safety, this will be performed. The study coordinator and the investigational pharmacy will determine if the subject was using

placebo versus active drug. This will be documented in the research database. In most cases, the unmasking/unblinding will be part of managing an SAE, and will be reported with the SAE. However, in cases where unmasking/unblinding was not associated with an SAE, such actions should be reported in a timely manner.

8.5 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 10 "Study Monitoring, Auditing, and Inspecting"). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9 Data Handling and Record Keeping

9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

9.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.3 Case Report Forms

The statistician will create Web-based case report forms using REDCap. Study coordinators will record data using REDCap forms. The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded.

Data Management

The statistician will create Web-based case report forms using REDCap. Study coordinators will record data using REDCap forms.

Data Processing

The REDCap project will be hosted on the Mayo Clinic intranet. The study coordinators will record the data on the REDCap forms. The statistician will download the data from the REDCap server.

Data Security and Confidentiality

All study data will be collected by the research team, reviewed by the PI, and stored in secure, locked files and/or databases in order to protect it from inadvertent loss or improper access. All laboratory specimens, evaluation forms, reports, and other records will be identified by coded number only to maintain subject confidentiality. Information gained from this study that can be

linked to the subject's identity will not be released to anyone other than the investigators, the subject and the subject's physician. All the information obtained in connection with these studies will remain confidential as far as possible within state and federal law. The results of these studies will be published in scientific journals without identifying the subjects by name.

Data Quality Assurance

Source document verification will be performed to ensure that the database accurately reflects data on the CRFs.

Data Clarification Process

9.4 Records Retention

The investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents. There will be a subject code master list that will be stored so as to protect subjects'confidentiality. Case Report Forms will be coded. There will be no subject names or other directly identifiable information will not appear on any reports, publications, or other disclosures of clinical study outcomes.

The investigator will retain the specified records and reports for;

1. Up to 2 years after the marketing application is approved for the drug; or, if a marketing application is not submitted or approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the FDA has been so notified. OR
2. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy" http://mayocontent.mayo.edu/research-policy/MSS_669717

Whichever is longer

10 Study Monitoring, Auditing, and Inspecting

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to

all the study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of 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.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices.

11 Ethical Considerations

This study is to be conducted according to United States government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted local Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study. The decision of the IRB concerning the conduct of the study will be made in writing to the sponsor-investigator before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the Approved IRB consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or the subject's legally authorized representative, and the individual obtaining the informed consent.

12 Study Finances

12.1 Funding Source

This study is financed through a grant from the Migraine Research Foundation.

13 Publication Plan

The primary investigator, Amaal Starling, MD, holds the primary responsibility for publication of the result of the study. The trial will be registered on ClinicalTrial.gov prior to subject recruitment and enrollment. We will post the results of the study within 12 months of final data collection for the primary outcome.

Link to protocol registration site for ClinicalTrials.gov: https://register.clinicaltrials.gov/ .

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