Title:

Treatment for post-concussive headache: A randomized, placebo-controlled, double blinded trial

Document Date:

March 31, 2023

NCT Number:

NCT04226365

CLINICAL RESEARCH PROTOCOL.

INVESTIGATIONAL PRODUCT(S):	Nortriptyline 10 mg oral daily
IRB NUMBER:	2019-83-LGHP
PROTOCOL(S) TITLE:	Treatment for post-concussive headache: A randomized, placebo-controlled, double blinded trial
CTA NUMBER:	NCT04226365
FUNDING SPONSOR(S):	Louise Von Hess Research Grant
MEDICAL DIRECTOR:	Laura DiPaolo, MD
ORIGINAL PROTOCOL DATE:	24 December 2019
VERSION NUMBER:	V8.0
VERSION DATE:	12 April 2022

Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRC	Clinical Research Coordinator
C-SSRS	Columbia-Suicide Severity Rating Scale
DHHS	Department of Health and Human Services
DSMC	Data Safety Monitoring Committee
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRPP	Human Research Protection Program
ICH	International Conference on Harmonization
IRB	Institutional Review Board
MP	Monitoring Plan
NCT	National Clinical Trial
NIH	National Institutes of Health
PCHSE	Post-Concussion Head Symptom Evaluation
PHQ-9	Patient Health Questionnaire
PI	Principal Investigator
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
UP	Unanticipated Problem
US	United States

1 STUDY SUMMARY

1.1 Synopsis

Title:	**Treatment for post-concussive headache: A randomized, placebo-controlled, double blinded trial**
Short Title:	Pediatric Concussion Outcomes
Study Description:	This is a randomized, placebo-controlled, double-blinded trial in which participants with a post concussive headache meeting inclusion criterion will be assigned to one of two treatment groups: placebo or nortriptyline, and will take the study drug as directed for the duration of the 4 week study. Each participant in both groups will be evaluated at week 0 and again each week for the next 4 weeks of treatment with a concussion survey that rates their symptoms. At the end of 4 weeks the study will be unblinded. It is hypothesized that the addition of nortriptyline to the standard headache treatments will result in more rapid decrease of symptom score than with placebo.
Objectives:	The purpose of this study is to investigate the impact of nortriptyline on recovery from post-concussive headache using a randomized, placebo-controlled, double-blinded trial.
Primary Endpoint:	Compare Post Concussive Symptom Inventory Score for headache between control and intervention groups
Secondary Endpoints:	Compare time to resolution of symptoms (specifically time until symptom-free for 48 hours), time to treatment termination, headaches days per month, time to return to prior activity level, time to return to full academic schedule between control and intervention group
Study Population:	The study will focus on adolescents between the ages of 13 and 18 years of age with recent minor head trauma without loss of consciousness with headaches symptoms persisting for greater than or equal to 4 weeks post trauma.
Phase:	Phase III
Description of Sites/Facilities	A primary care practice affiliated with Penn Medicine Lancaster General Health, which will refer eligible patients to Sports Medicine for further study enrollment consideration or consent patients. An outpatient practice affiliated with Penn Medicine Lancaster General Health dedicated to primary care Sports Medicine in Lancaster County, PA.
Enrolling Participants:	Patients are identified for the study after initial evaluation at an LGHP Sports Medicine office or after referral from an LGHP office to the Sports Medicine practice. Clinical research coordinator (CRC) will aid in identifying concussed patients who may be eligible for the study. Once determined eligible, the study will carried out solely through the Sports Medicine practice.
Description of Study Intervention:	Participants are randomly assigned to one of two treatment groups. The experimental group receives standard headache treatment including Tylenol, NSAIDs 2-3x/week, vestibular PT and daily nortriptyline 10mg oral. The

	control group also receives the standard headache treatment, but will instead be given a placebo, which will look physically identical to the nortriptyline capsule and be comprised of non-active pharmaceutical grade excipient.
Study Duration:	18 months
Participant Duration:	24 weeks

1.2 Key Roles and Study Governance

Role	Name and Address
Principal Investigator	Laura DiPaolo, MD LG Health Physicians Sports Medicine 51 Peters Road, Suite 200 Lititz, PA 17543
Co-Investigators	Patrick Moreno, MD LG Health Physicians Sports Medicine 51 Peters Road, Suite 200 Lititz, PA 17543
Statistician	Kellie Bresz 2110 Harrisburg Pike, Suite 315 Lancaster, PA 17602

1.3 Schema

Week 0	Screening, Randomization and baseline assessment
• Total n = 100 • Obtain informed consent • Screen potential participants by inclusion and exclusion criteria • Complete post concussive headache symptom evaluation score, PCSHE • Complete PHQ depression screening • Randomize to intervention group (n = 50) and placebo group (n=50) • Drug distribution to patient	
Week 1	CRC: Repeat PCSHE Assessment with patient via telephone
• Repeat post concussive headache symptom evaluation score with CRC via telephone	

Week 2	CRC and Provider: Repeat Assessment PCSHE and PHQ In office
• Repeat post concussive headache symptom evaluation score with CRC in the office	
• Perform study drug reconciliation via pill count	
• Repeat PHQ depression screening with provider	
Week 3	CRC: Repeat PCSHE Assessment with patient via telephone
• Repeat post concussive headache symptom evaluation score with CRC via telephone	
Week 4	CRC and Provider: Repeat Assessment PCSHE and PHQ In office/Unblinding
• Repeat post concussive headache symptom evaluation score with CRC in the office	
• Repeat PHQ depression screening with provider	
• Patients receiving "no benefit," (a change in PSCI by ≤ 2 points) will be offered a change in treatment strategy. Patients in the placebo arm who are receiving "no benefit" will be offered a transition to the experimental group. Patients in the experimental group will be offered different medical management options as per standard of care.	
Weeks 6, 12 and 24	CRC: Repeat PCSHE Assessment with patient via telephone
• Repeat post concussive headache symptom evaluation score with CRC via telephone • Treatment will be terminated once symptoms have resolved, and patients are returning to normal academic learning environment	
Refer to Appendix Section 12.1, Schedule of Activities	

2 INTRODUCTION AND RATIONALE

2.1 Study Rationale

Each year in the United States, greater than 500,000 children present to the Emergency Department for evaluation following traumatic brain injury (TBI) (Chloe et al, 2015). The majority of these visits meet criteria for mild TBI or concussion, but they may lead to chronic symptoms and even impairment (Kacperski et al., 2016). In primary care Sports Medicine, the primary concern is that of Sports Related Concussion (SRC). According to the 2017 Concussion in Sport Group (CISG) consensus statement, an SRC is a traumatic brain injury induced by biomechanical forces that typically leads to transient, functional impairment of neurological function (McCrory P et al., 2017). This may lead to a large constellation of symptoms, which often includes physical, psychological, and cognitive symptoms. Symptoms are considered "persistent" when their symptoms persist beyond 4 weeks (McCrory P et al., 2017), and this typically occurs between 10-30% of the time (Makdissi et al 2017). During initial assessment and outpatient follow-up, symptoms are routinely monitored using the symptom score on the validated form Sport Concussion Assessment Tool (SCAT 5) which measures 22 symptoms along a 7- point Likert scale (David et al, 2017). Headache is the most common post-concussion symptom and it may impact a patient's ability to sleep, perform in school, participate in athletics, or cope with stress (Kacperski et al., 2016). This ultimately complicates the athletes return to play. There is limited research focused on the treatment of posttraumatic headache, particularly with concussion or mild traumatic brain injury (Chloe et al., 2015). As a result, there are few specific guidelines or pathways created to manage post-traumatic headache (Chloe et al., 2015).

2.2 Background

Acute post-traumatic headaches are often treated with acetaminophen, ibuprofen (initiated after first 24 hours of injury), and physical therapy. Although symptoms often resolve by 1-week post-injury (Bernard et al., 2017), patients are often offered additional medication options if their symptoms persist greater than 4 weeks. A prospective cohort study in children in 2013 revealed 64% response rate in treatment groups including: amitriptyline, melatonin, topiramate, nortriptyline, Indomethacin, and flunarizin (Kacperski et al., 2013). These medications were chosen for patients based on specific risk factors, previous illness, and side-effect profiles. As a result, the study was not blinded to patient or physician (Kacperski et al., 2013). Given the lack of research in treatment for pediatric post-concussion headache, we have designed a randomized, placebo-controlled, double-blinded study focusing on the impact of nortriptyline. Nortriptyline has a superior side effect profile to that of other tricyclic antidepressants such as amitriptyline, but has never been studied in the treatment of post-traumatic headache. This study may provide insight into the use of nortriptyline for post-concussive headache, and may pave the way for more research of its kind.

2.2.1 Pharmacokinetics, Pharmacodynamics and Toxicology

Nortriptyline is FDA approved for the treatment of depression. Onset of action for depression treatment is 4-8 weeks. Absorption is rapid. This medicine extensively binds to plasma proteins. Metabolism is primarily hepatic. Excretion is via urine. (Pamelor [package insert], 2019)

Toxicities are mostly via exaggeration of pharmacologic activities, including CNS depression, seizurogenicity, sodium channel blockade, and alpha-adrenergic blockade. Mild to moderate toxicity produces symptoms such as drowsiness, sedation, tachycardia, hallucinoses, and other anticholinergic effects may be seen at lower doses. Severe toxicity could produce coma, seizures, QRS prolongation with ventricular dysrhythmias, respiratory failure. Toxicity of Nortriptyline could occur at greater than 2.5 mg/kg. (Pamelor [package insert], 2019)

2.2.2 Assessment for Potential Study Products Drug-Drug, Drug-Device, Device-Device Interactions

The risks of taking Tylenol, ibuprofen, or nortriptyline include any adverse reactions to the medications themselves. There are no known interactions between these medications. These are commonly used FDA approved medications with known side effect profiles.

2.2.3 Clinical Adverse Event Profile

The most common side effect of nortriptyline is constipation. Very rarely does this lead to paralytic ileus. Cardiovascular side effects are rare but include dysrhythmia, heart block, prolonged QT interval, and acute MI. Risks may be increased in those with preexisting cardiac disease. Use should generally be avoided in patients with Brugada syndrome or those suspected of having Brugada syndrome. In addition, patients with hyperthyroidism or who receive thyroid medications have an increased risk of cardiac arrhythmias. Nortriptyline should be used with caution with other CNS depressants, especially in the elderly due to increased risk of falls. Anticholinergic effects may aggravate urinary retention in patients with history of urinary retention. There is a rare side effect of SIADH. Hepatic side effects are rare including abnormal hepatic functions tests, jaundice. Caution with excessive alcohol use due to increased risk of suicidal ideation. Seizures may occur, especially in patients with a history of seizures, as nortriptyline may lower seizure threshold. When used with other serotonergic medications (eg, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, and St. John's wort) there is a risk of serotonin syndrome. Nortriptyline and its metabolites cross the human placenta and can be detected in cord blood. Tricyclic antidepressants may be associated with irritability, jitteriness, and convulsions (rare) in the neonate and thus caution advised during 3rd trimester. (Pamelor [package insert], 2019)

2.2.4 Dosing Rationale

Nortriptyline is FDA approved for depression in adolescents. Adolescents may receive 30 to 50 mg/day orally in divided doses or single daily doses for treatment of depression. (Pamelor [package insert], 2019) Lower doses are typically used in the treatment of migraine prevention therefore this trial will investigate 10mg dosing to balance both the safety profile and efficacy for use of headache treatment.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

One potential rare but immediate and long-range risk of the study is increased suicidality. Antidepressants, including nortriptyline, can increase the risk of suicidal thinking and behavior in children, adolescents, and young adults with major depressive disorder and other psychiatric disorders within the first few months of therapy. Close monitoring is recommended for clinical worsening or suicidality. (Pamelor [package insert], 2019) Due to this known risk, participants with a known history of depression are excluded from the study. In addition, participants will be also be monitored after treatment initiation for increased suicidality with the PHQ questionnaire and the C-SSRS questionnaire, if applicable. The PHQ questionnaire is a validated study tool for ages 13-18 for evaluation of major depressive disorder (Johnson et al., 2002). Another risk of the study is that the patient's headache go untreated if in the placebo arm of the study.

2.3.2 Known Potential Benefits

Immediate potential benefits to the study include earlier return to play and return to the classroom post-concussion as post concussive headache can impede progress. There is also a potential benefit of decreased depressive symptoms post-concussion.

2.3.3 Assessment of Potential Risks and Benefits

The benefits of the study drug, nortriptyline, include improved symptom score post-concussion and earlier return to school and return to play. There is also the potential benefit of decreased depression because of the aforementioned earlier return to play but also as a direct effect of the drug itself. The rare but potential side effect of increased suicidality will be monitored with frequent follow up. It has been shown that frequent follow up, as is planned in this study design, decreases the risk of increased suicidality. Participants will be monitored with the PHQ, a depression screen validated in ages 13-18 (Johnson et al., 2002). If any participant screens positive to question 9 they will be evaluated by a primary care physician in the office and referred to either the Emergency Department or to their primary care doctor's office. The drug will be discontinued and they will drop out of the study.

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To investigate the impact of nortriptyline on recovery from post-concussive headache using a randomized, placebo-controlled, double-blinded trial	Post-Concussive Symptom Inventory (PSCI) score of 0-1 on the PCSHE concussion survey	There is currently no standard of care for treatment of post concussive headache despite its high prevalence and this will aid in determination of improvement of symptom severity
Secondary		
To assess headache days per month with treatment vs placebo	Number of headache days per month	To determine if treatment of post-concussive headache impacts return to play
To evaluate time to resolution of symptoms	Time to treatment termination	Given the lack of a current standard of care in treatment, this will help determine potential length of treatment with nortriptyline
Tertiary		
To compare return to prior activity level timeline in placebo vs. nortriptyline	Time to return to prior activity level	To determine if treatment of post concussive headache impacts return to prior activity level.
To compare return to academic timeline in placebo vs. nortriptyline	Time to return to prior academic schedule	To determine if treatment of post concussive headache impacts return to school

4 STUDY PLAN

4.1 Study Design

This trial is a randomized, double-blinded placebo-controlled phase III trial designed to evaluate the effect of nortriptyline on post concussive headache. Participants meeting inclusion criteria will be assigned to one of two treatment groups. Patients will be identified for the study after initial evaluation at an LGHP Sports Medicine office or at the LGHP Sports Medicine office after referral from an another LGHP office. Consenting will take place at Sports Medicine or Family Medicine practices while studyactivities will be performed at LGHP Sports Medicine, a single practice with multiple locations. CRCs will assist with identifying concussed patients who may be eligible for our study. At the time of enrollment, patients will have a meeting (in-person or telehealth) with a physician for concussion discussion/consenting, followed by another visit with a CRC to complete enrollment and randomization. The consent process may occur on paper, or electronically via REDCap. The visit with the physician may be in-person or via telehealth platform. For randomization, each participant will be de-identified and assigned a number. These numbers will be randomly assigned to one of the two treatment arms. The participants, CRC and the physicians carrying out evaluations will be blinded to the treatment groups, and the pharmacists will be unblinded. The experimental group will receive standard headache treatment (Tylenol, Ibuprofen 2-3x/week, vestibular PT) + nortriptyline. The control group will receive standard headache treatment (Tylenol, Ibuprofen 2-3x/week, vestibular PT) + placebo pill.

Participants will initially be enrolled on week 0, at which point they will be randomized to one of the two groups, and complete the "Concussion Intake Form" and the PCSHE survey. The PCSHE will be administered upon enrollment (week 0), and again each week for the initial 4 weeks of treatment. This will amount to 5 surveys. Surveys on weeks 1 and 3 will be completed with the help of a CRC over the telephone. The patients will fill out their surveys during scheduled office visits at LGHP Sports Medicine clinic on weeks 2 and 4. At these scheduled office visits the participants will also fill out the PHQ-A form for evaluation of increased suicidality on the medicine. The patient's scores on their PCSHE will be tracked for each week, particularly their rating of symptoms: headache, "pressure in head," and neck pain.

During the appointment on week 4, the CRC will un-blind the randomization and allow the physician to develop an appropriate treatment plan. It is hypothesized that the addition of nortriptyline to the standard headache treatments will result in more rapid headache recovery at 4 weeks when compared to placebo.

Patients receiving "no benefit," (a change in PSCI by ≤ 2 points), will be offered a change in treatment strategy after 4-6 weeks of treatment, per standard of care. Patients in the placebo arm who are receiving "no benefit" will be offered a transition to the experimental group. Patients in the experimental group will be offered different medical management options as per standard of care. Patients who noted improvement at 4 weeks will be offered continued

treatment. After 4 weeks, the study will become observational. Participants will continue to complete the PCSHE survey via telephone with the CRC at 6, 12 and 24 weeks.

Treatment will be terminated once symptoms have resolved, and as patients are returning to their academic learning environment. Patients will only return to their previous activity level once they are titrated off their medication. Of note: patients who recover from injury during summer months or during months when they are not in season will have individualized return to previous activity plans.

LGH Research Institute will initiate early discontinuation of the study if the magnitude of improvement noted in the experimental arm exceeds expectations in a way that threatens integrity and ethics of continuing as planned. Specific early discontinuation criteria include patient preference to discontinue, parental preference to discontinue and adverse reaction to medication including allergy and suicidality. Increased suicidality will be assessed using PHQ questionnaire, question 9.

4.2 Scientific Rationale for Study Design

A randomized placebo controlled double blinded trial was chosen for the evaluation of the efficacy of nortriptyline in post-concussive headache due to the lack of guidelines in the treatment of post concussive-headache, the most common post concussive symptom. Controlled studies of medications in post concussive headache are lacking and all medication use is considered off label.

Given the benefit previously seen in one study that included amitriptyline (Kacperski J et al., 2013), a TCA with nortriptyline as a metabolite, it is anticipated that nortriptyline will produce a shorter time to headache recovery.

In addition, the trial will be unblinded at 4 weeks and patients receiving no benefit will be offered a change in treatment strategy, as this would be offered after 4-6 weeks of treatment per standard of care.

4.3 Justification for Dose

Nortriptyline 10mg daily dosing was chosen, as the dose used in migraine prevention is lower than depression dosing. Therefore a lower dose is likely to have a similar affect in treating post-concussive headache while also decreasing potential side effect risk.

The pharmacy-supplied placebo capsule is matched in appearance to the nortriptyline 10mg treatment, and consists of an empty gel capsule and a non-active pharmaceutical grade excipient used as a filler.

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Appendix Section 12.1.

5 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Participants aged 13-21 years old
4. In good general health as evidenced by medical history and diagnosed with recent head trauma meeting ICHD-3 criteria for acute posttraumatic headache with symptom onset < 7 days from trauma
5. Ability to take oral medication and be willing to adhere to the medication regimen
6. No loss of consciousness OR loss of consciousness <30 minutes
7. Headache symptoms persisting ≥4 weeks post trauma
8. PCSHE score for headache + pressure in head + neck pain must be ≥ 3
9. After week 4 post-concussion at time of enrollment
10. Not currently receiving pharmacologic treatment for concussion aside from NSAIDs and acetaminophen.

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Focal neurological deficits following injury
2. Any acute abnormality on Computed Tomography (if obtained)
3. History of known seizure disorder. Or moderate or severe TBI
4. Current uncontrolled psychiatric illness given the potential side effects of the study drug (at investigator discretion). Current suicidal ideation as screened for on PHQ on intake
5. A personal history of Brugada syndrome
6. Known allergic reaction to nortriptyline
7. Current pregnancy
8. Positive COVID-19 test in prior 14 days

5.3 Lifestyle Considerations

During this study, participants are asked to:

- Refrain from consumption of over the counter supplements.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Due to the importance of post-concussive timeline in this study, individuals who do not meet the criteria for participation in this trial (screen failure) will not be rescreened for the same concussion.

5.5 Strategies for Recruitment and Retention

Patients will be identified initially by age and a history of recent head minor head trauma. Patients will be identified either at the study site, LGHP Sports Medicine outpatient practice, or will be referred to LGHP Sports Medicine from another LGHP affiliated office. Recruitment materials may also be shared with non-LGH practices and will still require identification/screening at LGH. CRCs will complete a thorough review of the Sports Medicine office records to identify patients being treated for concussion who would meet the criteria. Anticipated number of patients screened for the study is at least 150, with a target enrollment of 100 patients. Patients at LGHP Sports Medicine practice will be provided with an information form on concussions and information about the study around their 2-week concussion visit and provided with the consent form to review. Patients who are seen at an LGHP affiliated office will be referred to the Sports Medicine office.

If the patients consent (if age 18 or older) or their parents' consent (age 13-17), they will be given the concussion intake form to evaluate for inclusion and exclusion criteria, as well as informational material regarding the study. A CRC will call the patient at 2 weeks post-concussion to confirm that symptoms are still present, answer questions and verify that the patient is still interested in moving forward with the study. If patients meet the criteria at their 4-week post-concussion visit, they will be randomized to either the placebo group or the nortriptyline group. Patients will be followed up weekly either via phone or in the office as per standard of care in concussion follow up, however this frequent follow up will aid with also aid with study retention.

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

Nortriptyline is a tricyclic antidepressant with FDA approval for use in the treatment of depression. The exact mechanism of action of Nortriptyline is unknown. It is known that Nortriptyline intervenes with the transfer, release, and storage of catecholamines. It blocks the effects of acetylcholine, 5-hydroxytryptamine and histamine.

The package insert for Nortriptyline will be provided to the IRB.
The placebo in this study is matched in appearance to the nortriptyline 10mg treatment, and consists of an empty gel capsule and a non-active pharmaceutical grade excipient used as a filler.

6.1.2 Dosing and Administration

Patients will be provided either nortriptyline 10mg capsules or placebo-matched capsules containing a non-active pharmaceutical grade excipient. The capsules are to be taken by mouth. They will be advised to take the pills at nighttime as sleepiness is a potential side effect of nortriptyline.

Patients will continue on either the 10 mg nortriptyline or the placebo daily for 4 weeks until the study is un-blinded. At that time, patients receiving "no benefit," (a change in PSCI by ≤ 2 points), will be offered a change in treatment strategy, as this would be offered after 4-6 weeks of treatment per standard of care. Patients in the placebo arm who are receiving "no benefit" will be offered a transition to the experimental group. Patients in the experimental group will be offered different medical management options as per standard of care. For patients who noted improvement at 4 weeks, they will be offered continued treatment. After 4 weeks, the study will become observational and will no longer be experimental. Surveys will continue at week 6, then at month 3 and at month 6. Once patients have resolution of symptoms, they will be titrated off the medication.

Patients are advised to take a missed dose as soon as they remember as per standard of care with nortriptyline. If it is almost time for the next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.

The placebo pill is a matched capsule. Dosing, timing of administration, and missed doses are to be handled the same.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and accountability

The nortriptyline and matched placebo will be provided by the Lancaster General Health Inpatient Pharmacy. The pills will be packaged and labeled in matched bottles, 28 pills per bottle. Randomized numbers will be created to denote placebo vs. nortriptyline bottles. Labels associated with each pill bottle will be created to assist with logging the pills into the pharmacy, out of the pharmacy, into the LGHP Sports Medicine office (study site) and out when given to study participants.

6.2.2 Formulation, Appearance, Packaging, and Labeling

The Lancaster General Health Inpatient Pharmacy will provide compounded investigational products for the study, to include both encapsulated nortriptyline 10 mg capsules and placebo-matched capsules. Encapsulated nortriptyline capsules will consist of an empty gel capsule and a commercially available 10mg nortriptyline capsule. Placebo-matched capsules will consist of an empty gel capsule and non-active pharmaceutical grade excipient. Both the encapsulated nortriptyline product and the placebo product will be matched in appearance to aid in maintaining the blinding process. Investigational products will be securely stored within the inpatient pharmacy until dispensation, and will be stored per the required temperature range as defined by FDA-approved package labeling. Investigational products will be distributed and stored in a vial labeled with randomized numbers generated via the study-specific REDCap database. Assignment of the randomized numbers will be defined and stored in the REDCap database, and will only be accessible to study team personnel, including the clinical research coordinators and the pharmacist. Upon dispensation and distribution, vials will also be labeled with a standard prescription label per regulatory requirements.

6.2.3 Product Storage and Stability

The study drug will be stored and managed by the Lancaster General Health Inpatient Pharmacy in compliance with departmental policy and federal regulations. All investigational drug products will be stored in a locked, secure environment that is separate from routine drug inventory, with limited access for essential personnel. All investigational drug products will be stored according to storage requirements for FDA approved drugs.

When storage of investigational drug product occurs within The Department of Pharmacy, electronic, continuous monitoring of investigational drug storage temperatures will be utilized via an institutional-based temperature monitoring system.

When study drug is transported from the Inpatient Pharmacy to LGHP Sports Medicine, all study drug will be stored in a temperature monitored cooler in compliance with departmental policy.

6.2.4 Preparation

The Lancaster General Health Inpatient Pharmacy will be encapsulating the placebo and nortriptyline capsules in a matched capsule as to make them indistinguishable.

6.3 Measures to Minimize Bias: Randomization and Blinding

Each patient will be de-identified and assigned a study number. These numbers will be randomly assigned to one of the 2 treatment arms at an equal ratio. The study drug will be built into the electronic medical record, Epic, to help minimize risk of drug interactions if a patient were to go to another doctor during the study.

At 4 weeks, LGH Research Institute will un-blind the study to investigate improvement in the experimental vs. placebo group.

If a patient were to screen positive on the PHQ question 9 for suicidality they would be terminated as a study participant and thus un-blinded at that time to permit proper treatment by a physician.

If there is an emergency the participant can call the Research Institute, whose number they have been provided.

6.4 Study Intervention Compliance

A study drug reconciliation will be performed at weeks 2 and weeks 4, the in-office evaluations. A telephone call will be made to the consenting adult the business day prior to the study appointment where drug reconciliation is scheduled to occur. The patients will bring their pill containers and they will be counted by the CRCs to evaluate for missed pills. A patient will be considered compliant if they have taken 75% of the pills.

6.5 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements. As per exclusion criteria, patients on antidepressants are excluded from the study due to potential harmful drug-drug interactions.

In this study, patients will be permitted to take Tylenol and ibuprofen in addition to the study drug or placebo. The risks of taking Tylenol, ibuprofen, or nortriptyline include any adverse reactions to the medications themselves. There are no known interactions between these medications. These are commonly used FDA approved medications with known side effect profiles. Given the risk of rebound headaches with the use of NSAIDs, the use of ibuprofen will be limited to 3 times per week. Tylenol will be permitted per dosing guidelines 10 to 15 mg/kg/dose orally every 4 to 6 hours as needed.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation from the study intervention, placebo vs. nortriptyline, does not mean discontinuation from the study, and remaining study procedures will be completed as indicated by the study protocol is a patient agrees. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

At the time of study intervention discontinuation, if a patient is willing to continue surveys the observational data from the surveys will be continued based on the study timeline. If a patient is discontinued from the study for new onset suicidal ideation after initiating the drug, attempts will be made to follow them for both the concussion survey and the PHQ. Patients will still be allowed to voluntarily discontinue based on preference. A dedicated Case Report Form (CRF) page should capture the date and the specific underlying reason for discontinuation of study intervention or participant discontinuation/withdrawal.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request or with parental request for patients ages 13-17. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Significant non-compliance as defined as taking less than 75% of the study pills or filling out less than 3 of the initial 5 study surveys
- Increased suicidality as noted on question 9 of the PHQ as continued participation would be a danger to the health of the patient
- If a participant meets an exclusion criterion (either newly developed or not previously recognized) EXCEPT that of depression as this is a common problem in post-concussive syndrome

The reason for participant discontinuation or withdrawal from the study will be recorded in REDCap and EPIC. Participants who sign the informed consent form and are randomized and initiated in the study but subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

7.3 Lost To Follow-Up

A participant will be considered lost to follow-up if he or she fails to complete 2 or more scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within one week and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENT AND PROCEDURES

8.1 Safety and Other Assessments

The screening and enrollment process to determine study participation eligibility include the following procedures/evaluations:

- A detailed history including past medical history, current medications, allergies, family history (focusing on Brugada syndrome) and social history (school participation) to identify inclusion and exclusion criteria
- Physical examination to include height and weight, cardiovascular, pulmonary, and a targeted neurological exam looking for any focal neurological deficits.
- The concussion intake form
- Informed consent

The above intake and consenting process will be performed by an LGHP Sports Medicine physician within the 2 weeks prior to study initiation. Randomization will be performed by a CRC at 4 weeks post-concussion which corresponds to week 0 of the study. Physicians will assist in the completion of surveys at the in-office visits, including the PHQ. All positive screens to question 9 on the PHQ will be managed by the physician in the office and the appropriate course of action will be taken per standard of care. The reminder of the surveys on week 1 and week 3 over the phone to be performed by a CRC.

Assessment of adverse events will be at all weekly visits. In addition, participants with any concerns or potential adverse events will have the ability to call the Research Institute at all times.

8.2 Adverse Events and Serious Adverse Events

8.2.1 Definition of Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. Concurrent illnesses or injuries should be regarded as adverse events.

A pre-existing condition should be recorded as an adverse event if the frequency, intensity or the character of the condition changes.

8.2.2 Definition of Serious Adverse Events (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that, in the view of the investigator is:

- fatal
- life-threatening
- requires or prolongs hospital stay

- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the participant and may require intervention to prevent one of the other serious outcomes noted above. In this study specifically, suicidal ideation would count as an important medical event.

8.2.3 Classification of an Adverse Event

8.2.3.1 Severity of Event

For adverse events (AEs) not included in the protocol defined grading system, the following guidelines will be used to describe severity.

- Mild – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.2.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to nortriptyline assessed by the clinician who examines and evaluates the participant based on temporal relationship and their clinical judgment. The degree of certainty about causality will be graded using the categories below.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to nortriptyline administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the nortriptyline (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory re-challenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the nortriptyline, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.

- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely to be related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to nortriptyline administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the nortriptyline) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- Unrelated – The AE is completely independent of nortriptyline administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.2.3.3 Expectedness

The clinical investigators will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the nortriptyline.

8.2.4 Time Period and Frequency for Event Assessment and Follow-Up

- No AEs will be collected as solicited events.
- Unsolicited events will be captured in the EMR by the CRC or PI.
- Time period of collection will be 6 months

Safety will be assessed by monitoring and recording potential adverse effects at each study visit. Participants will be monitored by medical histories, physical examinations and questionnaires. If a grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible.

At each contact with the participant, the investigator will seek information on adverse events by non-directive questioning and, as appropriate, by examination. Adverse events may also be detected when they are volunteered by the participant during the screening process or between visits, or through physical examination, laboratory test, or other assessments. Information on all adverse events will be recorded in the source documentation. To the extent possible, adverse events will be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event.

As much as possible, each adverse event or follow-up information will be evaluated to determine:

1. Severity grade (CTCAE Grade 1-5)
2. Duration (start and end dates)
3. Relationship to the study treatment or process – Reasonable possibility that AE is related: No (unrelated/ not suspected) or Yes (a suspected adverse reaction). If yes (suspected) - is the event possibly, probably or definitely related to the investigational treatment?
4. Expectedness to study treatment or process – Unexpected – if the event severity and/or frequency is not described in the investigator brochure (if applicable) or protocol.
5. Action taken with respect to study or investigational treatment or process (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
6. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
7. Whether the event is serious

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

8.2.5 Adverse Event Reporting

Reporting Period

Adverse events will be reported from the time of informed consent until study completion.

Investigator Reporting: Local Reporting Requirements

The investigator will report AEs and SAEs to the IRB/EC of record and other local regulatory groups per the local requirements.

8.2.6 Serious Adverse Event Reporting

The study clinician will immediately report any serious adverse event to the IRB, whether or not considered nortriptyline related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the nortriptyline caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the nortriptyline and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the IRB.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the

participant is stable. Other supporting documentation of the event may be requested by the IRB and should be provided as soon as possible.

The study investigator will be responsible for notifying the Food and Drug Administration (FDA), as applicable of any unexpected fatal or life-threatening suspected adverse reaction per applicable regulations.

8.2.7 Reporting Events to Participants

If there is a data breech, the CRC will make every effort to notify the participant. They will send a letter and make a phone call recorded in the EMR notifying participant and/or parents, as applicable about such.

8.2.8 Reporting of Pregnancy

Pregnancy, in and of itself, is not regarded as an AE. When a pregnancy has been confirmed in a participant, and the fetus is exposed to study drug and/or process (maternally or paternally), the study intervention will be discontinued while continuing safety follow-up, requesting permission to follow pregnant women to pregnancy outcome.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

8.3 Unanticipated Problems

8.3.1 Definition of Unanticipated Problems (UP)

Human Research Protections Program (HRPP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.3.2 Unanticipated Problem Reporting

Unanticipated problems (UPs) such as:

- Post-marketing withdrawal of a drug, device, or biologic used in a research protocol due to safety concerns.
- FDA ban of a drug, device, or biologic used in a research protocol due to safety concerns.
- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the participant to remain on the study
- Premature closure of a study (e.g., due safety, lack of efficacy, feasibility, financial reasons, etc.) should be reported by the investigator to the reviewing Institutional Review Board (IRB) and to the Data Monitoring Committee DMC/lead principal investigator (PI). The UP report will include the following information:
- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported as any other SAE.
- Any other UP will be reported to the IRB and to the DSMC within 72 hours of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and HRPP within 72 hours of the IRB's receipt of the report of the problem from the investigator.

9 STATISTICAL CONSIDERATIONS.

9.1 Statistical Hypotheses

- Primary Endpoints: The primary outcome is % of patients with no headache (score of 0-1 on headache question) and 5 measures for each patient (baseline and weeks 1-4).

- Secondary Endpoints: The secondary endpoints to be evaluated include time to resolution of symptoms (specifically time until symptoms free for 48 hours), time to treatment termination, headaches days per month, time to return to prior activity level, time to return to full academic schedule

9.2 Sample Size Determination

Power calculations and time required to complete enrollment are based on unique visits presenting with the post-concussive headache diagnosis at LGHP Sports Medicine. For 80% power with a two-sided alpha of 0.05, and using a likelihood ratio test, the sample size is calculated to be 50 per group with a 1:1 assignment ratio, or 100 total participants.

9.3 Statistical Analyses

9.3.1 General Approach

The study team will use appropriate statistical techniques to calculate the percent reduction in pertinent questionnaire scores and confidence intervals for these measures. A dose-response analysis will be performed to determine if a relationship is observed between participants' level of adherence and their change in lab values from before and after the pharmacological intervention. Time to resolution of symptoms (specifically time until symptoms free for 48 hours), time to treatment termination, headaches days per month, time to return to prior activity level, time to return to full academic schedule will all be evaluated following the pharmacological intervention.

Exploratory analyses may be done to look at patterns of adherence over the course of the study, predictors of adherence, etc.

Descriptive statistics using appropriate comparative models will be used to assess homogeneity of demographics and any differences in outcomes between the control and intervention groups.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent and Other Informational Documents Provided To Participants

Consent forms describing in detail the nortriptyline, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering nortriptyline. Consent materials will be submitted with this protocol.

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB) approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and their parent or guardian and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants and their parent or guardian will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or guardian or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. If the participant is under 18 years old, the participant will sign the Child Assent form while their parent or guardian signs the Parental Consent form. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice.

A copy of the informed consent document will be given to the participants and their parent or guardian for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The option for remote consent will facilitate enrolling participants who opt to use telehealth appointments or in situations where the consenting physician and participant are in different locations. Should remote consent be utilized, the consenter will confirm that all parties are viewing a copy of the consent and follow the previously mentioned standard consent process. The witness and participant or participant's parent/guardian will sign the consent. The consent will then be scanned or faxed to the provider for them to sign and send back using one of the aforementioned methods.

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated by the PI if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants and the Institutional Review Board (IRB), and they will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB and/or Food and Drug Administration (FDA).

In terminating the study, the Principal Investigator will assure that adequate consideration is given to the protection of the participants' interests.

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval.

All research activities will be conducted in as private a setting as possible.

Authorized representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participants' contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for 6 years as dictated by the HRPP.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the on secure servers or in REDCap, a HIPAA compliant database management system. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at LGH Research Institute.

10.1.4 Safety Oversight

Safety oversight will be under the direction of a Data and Safety Monitoring Committee (DSMC) composed of individuals with the appropriate expertise, who work at Lancaster General Health. The committee will include a pediatric physician, a Sports Medicine advance practice provider, and a behavioral health expert in addition to a biostatistician. In addition, the principal investigator will attend committee meetings to address protocol. As the principal investigator, they are the person most familiar with the drug protocol and in the best position to address questions about it. However, they will not participate in any votes about study continuation or termination.

The first meeting of the committee will take place once the 50 participants have been enrolled or after 6 months, whichever occurs first. Thereafter, the committee will meet biannually to review accumulated safety data and ad hoc to review or address any adverse events. The principal investigator will be aware of all adverse events that may occur in the study and will be responsible to call ad hoc meetings of the DSMC if necessary. Specific safety outcomes to be monitored include:

- Related complications within 6 months of study intervention
- Other unanticipated events

10.1.5 Clinical Monitoring

Site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by the Research Institute.
- On-site monitoring will occur annually and will include a random review of certain data
- The Research Institute will be provided copies of monitoring reports within 30 days of visit.

10.1.6 Quality Assurance and Quality Control

All monitoring and audits are to be performed according to ICH GCP E6 (R2).

LGH will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, and data are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing, and inspection by local and regulatory authorities.

10.1.7 Data Handling and Record Keeping

10.1.7.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the principal investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into REDCap a 21 CFR Part 11-compliant data capture system provided by The Research Institute. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.7.2 Study Records Retention

Study documents should be retained for 6 years. No records will be destroyed prior to that time.

10.1.8 Protocol Deviations

The PI and the study team should document all scenarios where the protocol is not followed and provide, in particular:

- Who deviated from the protocol
- What was the deviation
- When did the deviation occur
- How did the deviation happen
- What is the impact of the deviation
- A root cause analysis of why the deviation occurred

If the assessment results in a determination that any of the following are potentially affected, the deviation would be considered of significant impact:

- having the potential to adversely affect participant safety; OR
- increases risks to participants; OR
- adversely affects the integrity of the data; OR
- violates the rights and welfare of participants, OR
- affects the participant's willingness to participate in research.
- there is a potential for an overall impact on the research that should be shared with the IRB for consideration and development of next best steps to address it

10.1.9 Publication and Data Sharing Policy

After completion of the study and analysis of the data, a manuscript for publication will be written with the principal investigator as the lead author. The manuscript will be targeted for publication in a Sports Medicine journal.

10.1.10 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 Additional Considerations

The study will not begin until it has received approval from the LGH Institutional Review Board (IRB). Any changes to the protocol or consent form that represent potential changes to the risk-benefit ratio or an increase in what is required of participants will be submitted to the IRB as an amendment for review before it is implemented (unless a delay in implementation would compromise participant safety).

10.3 Protocol Amendment History

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale.

Version	Date	Description of Change	Brief Rationale
2.0	July 7		

Version	Date	Description of Change	Brief Rationale
3.0	June 28	Updated procedure, study drug storage and transportation, included telehealth visits, adding electronic consent, included language to allow for multiple LGHP Sports Medicine locations, added exclusion for prior COVID-19 diagnosis	Better operational flow, reflect growth of LGHP Sports Medicine, adapt to workflows created during COVID-19 pandemic
4.0	December 29	Removed references to study "sponsor", updated DSMC personnel, changed "subject" to "participant" for consistency, made grammatical corrections, clarified some statements for accuracy	
5.0	February 2, 2022	Placebo composition change, updated Co-Investigators and LGHP affiliated offices who refer to LGHP Sports Medicine	Change of placebo composition due to supply chain variability, inclusive language of referral offices to better reflect LGHP Sports Medicine referral system and provider's practice schedule outside of the Sports Medicine Clinic
6.0	April 12, 2022	Updated exclusion criteria #5 to indicate expansion of criteria	Change to allow for more participants to safely enroll if determined by provider.
7.0	February 24, 2023	Updated inclusion/exclusion criteria, removed requirement of participant involvement in sport activity, added the ability for consent to take place at family medicine locations.	Change to allow for more participants to safely enroll in the study
8.0	March 31, 2023	Added language to indicate that recruitment materials can be shared with non-LGH practices	To allow for additional patients to be referred to LGH for potential study identification.

11 REFERENCES

1. Chloe MC ,Blume HK. “Pediatric Posttraumatic Headache.” Journal of Child Neurology. 2105;31(1)76-85., doi: 10.1177/0883073814568152
2. c
3. McCrory P, Meeuwisse W, Dvořák J, et al. “Consensus statement on Concussion in Sport- the 5th international conference on Concussion in Sport Held in Berlin, October 2016.” Br J Sports Med 2017;51:838–847.
4. Makdissi M. et al. “Approach to investigation and treatment of persistent symptoms following sport-related concussion: a systematic review.” British Journal of Sports Medicine 2017;0:1-12. doi:10.1136/bjsports-2016-097470
5. Davis GA, et al. “Sport Concussion Assessment Tool- 5th Edition.” Br J Sports Med 2017;**0**:1–8. doi:10.1136/bjsports-2017-097506SCAT5
6. Bernard, C. et al. “Do Concussive Symptoms Really Resolve in Young Children?” Journal of Head trauma Rehabilitation. 2017; 32(6)413-424., doi: 10.1097/htr:0000000000000298.
7. Kacperski J, et al. “Characteristics of post-traumatic headaches in children following mild traumatic brain injury and their responses to treatment: a prospective cohort.” Developmental Medicine and Child Neurology. 2013;55(7)636-641., doi: 10.1111/dmcn.12152
8. Pamelor [package insert]. Hazelwood, MO: Mallinckrodt Inc; 2019.
9. Johnson, J. et al. "The patient health questionnaire for adolescents: Validation of an instrument for the assessment of mental disorders among adolescent primary care patients." Journal of Adolescent Health, 2002; 30 (3) 196-204. doi:10.1016/S1054-139X(01)00333-0.

12 APPENDIX

12.1 Schedule of Activities (SoA)

	Screening	Enrollment	Week 1	Week 2	Week 3	Week 4	Week 6	Week 12	Week 24
Eligibility	x								
Preview informed consent/assent/HIPAA	x								
Review and sign informed consent/assent/HIPAA		x							
Medical history/demographics		x							
Height, weight, BMI		x							
Randomization		x							
Study drug distribution		x							
Study drug reconciliation				x		x			
Headache Survey (PCHSE)		x	x	x	x	x	x	x	x
Suicide Screen (PHQ-9, CSSRS is applicable)		x		x		x			
Un-blind						x			