AMY GELFAND, MD

Clinical Research Protocol

CHOCOlate MeLatonin for AdolescenT MigrainE:

The CHOCOLATE Study

Protocol Number:	CHOCOLATE.01
Version Date:	02/05/2018
Investigational Product:	Melatonin 1mg – 8mg, formulation by Good Day Chocolate
IND Number:	124,226
NCT Number:	NCT03597529
Development Phase:	Phase 2
Sponsor:	Amy Gelfand, MD Assistant Professor of Neurology and Pediatrics University of California, San Francisco 550 16th Street, Fourth Floor San Francisco, CA 94158
Funding Organization:	Funding is provided by the UCSF Pediatric Headache Program discretionary funds, and the product is donated by Good Day Chocolate
Principal Investigator:	Name: Amy Gelfand, MD Telephone: 415-885-7832 Fax: 415-353-2400 E-mail: Amy.Gelfand@ucsf.edu
Coordinating Center:	UCSF

Approval:

02/05/2018

Amy Gelfand M.D.
Assistant Professor of Neurology and Pediatrics, UCSF

Date

This confidential information about an investigational product is provided for the exclusive use of investigators of this product and is subject to recall at any time. The information in this document may not be disclosed unless federal or state law or regulations require such disclosure. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, with the obligation not to further disseminate this information.

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: **CHOCOLATE.01**

Protocol Title: **The CHOCOLATE Study: CHOCOlate MeLatonin for AdolescenT MigrainE**

Protocol Date: **02/01/2018**

02/01/2018

Investigator Signature *Date*

Amy Gelfand M.D.
Assistant Professor of Neurology and Pediatrics

Print Name and Title

Site Name UCSF Pediatric Headache Program

Address University of California, San Francisco (UCSF)

550 16th Street, Fourth Floor

San Francisco, CA 94158

Phone Number 415-885-7832

The CHOCOLATE Study: CHOCOlate MeLatonin for AdolescenT MigrainE

Principal Investigator	Amy Gelfand, MD Assistant Professor of Neurology and Pediatrics University of California, San Francisco San Francisco, CA
UCSF Co-Investigator	William Qubty, MD Assistant Professor of Neurology and Pediatrics University of California, San Francisco San Francisco, CA
Additional Support	Laura Dapkus- Study Coordinator Elaina Allen- Biostatistics

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LIST OF ABBREVIATIONS

AE	adverse event
CFR	Code of Federal Regulations
CRF	case report form
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
PI	Principal Investigator
SAE	Serious Adverse Experience
SAP	Statistical Analysis Plan
UCSF	University of California, San Francisco
US	United States
	VAS (Visual Analog Scale)
	ICHD (International Classification of Headache Disorders)

PROTOCOL SYNOPSIS

TITLE	The CHOCOLATE Study: CHOCOlate MeLatonin for AdolescenT MigrainE
SPONSOR	Investigator Initiated Study (Dr. Amy Gelfand)
FUNDING ORGANIZATION	Funding is provided by the UCSF Pediatric Headache Program discretionary funds, and the product is donated by Good Day Chocolate
NUMBER OF SITES	1
RATIONALE	Migraine is common in children and adolescents. It causes pain and suffering and disability. Acute medications exist but do not work for everyone and may cause side effects. Some patients and parents will prefer a natural supplement for acute treatment rather than a prescription or over-the-counter pharmacologic agent. Melatonin has recently been shown to be effective for migraine prevention in adults and some early work suggests it may also be effective for migraine prevention in children and adolescents. Some migraine treatments that are helpful as preventives can also be helpful acutely. This is a dose-finding study to begin to examine whether melatonin might also be helpful acutely for treating migraine in children and adolescents.
STUDY DESIGN	This pilot randomized trial is a dose-finding study to determine which dose of melatonin is most effective for treating acute migraine in children and adolescents who have episodic migraine. We will identify the most effective dose to pull forward into a future fully-powered placebo-controlled efficacy study. If both doses are equally effective, we will bring forward the best tolerated dose. If doses are equally well tolerated, we will bring forward the lowest effective dose, as this will minimize cost to families should this treatment become widely adopted.
PRIMARY OBJECTIVE	To determine a change in mean VAS score between baseline and 2-hr time point in low-dose vs. high-dose group.

SECONDARY OBJECTIVES	• To determine a change in mean VAS score between baseline and 2-hr time point in low-dose vs. high-dose group in the < 40 kg and the ≥40 kg subgroups. (We will also do sensitivity analyses of completers who were awake for the 2-hr time point). • To determine the tolerability/side effects of high-dose vs. low-dose in the group over all, and in weight-based strata. • To determine the proportion of participants who get to mild/no pain by 2 hrs (overall and by weight group), and who remain at mild/no pain from 2-24 hours • To determine the proportion of participants who get to mild/no of each of: pain, photophobia, phonophobia, nausea, vomiting at 30, 60, 90, and 120 minutes and 24 hours; both overall and in weight based strata. • To determine the proportion of parents/participants who found the treatment useful, and who preferred it over other treatments they'd tried. • Using logistic regression, we will examine for possible predictors of treatment efficacy (sex, age, nap, nap duration, etc). • To determine the proportion of participants who needed rescue medication between 2-24 hrs, both overall and by weight- based strata.
NUMBER OF SUBJECTS	100
SUBJECT SELECTION CRITERIA	Inclusion Criteria: 1. Meet ICHD criteria for episodic migraine in children and adolescents, with at least 1 migraine attack per month on average. 2. Age 3-17 years 3. Dissatisfaction with previous acute treatments, for one or more of the following reasons: a) One or more previously tried acute medications have not been effective, or adequately effective, b) previously tried acute treatments have caused side effects, or C) patient/family would prefer a natural supplement for acute treatment over medication treatment 4. If of driving age, teen participant agrees not to drive for at least 8 hours after treating with melatonin. Exclusion Criteria: 1. Allergy or intolerance to melatonin, or to chocolate. 2. Opioid or barbiturate overuse as defined in ICHD 3. Pregnant/lactating

TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Good Day Chocolate melatonin 1-8mg per attack, taken my mouth
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	N/A
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Participation duration depends on how long it takes to treat two migraine headache attacks. In total, it will take approximately 2-3 hours to complete the study. Enrollment will take place over 24 months.
CONCOMMITANT MEDICATIONS	Allowed: All Prohibited: N/A Acute migraine medications such as ibuprofen (Motrin), acetaminophen (Tylenol), naproxen (Aleve) or a triptan (for example, sumatriptan) may be taken during the study, but we will ask participants to try to wait 2 hours after they take the study treatment, in order to see if the study treatment is effective.
EFFICACY EVALUATIONS	VAS pain scores between baseline and 2-hr time point
PRIMARY ENDPOINT	To determine a change in mean VAS score between baseline and 2-hr time point in low-dose vs. high-dose group.
SECONDARY ENDPOINTS	• To determine a change in mean VAS score between baseline and 2-hr time point in low-dose vs. high-dose group in the < 40 kg and the ≥40 kg subgroups. (We will also do sensitivity analyses of completers who were awake for the 2-hr time point). • To determine the tolerability/side effects of high-dose vs. low-dose in the group over all, and in weight-based strata. • To determine the proportion of participants who get to mild/no pain by 2 hrs (overall and by weight group), and who remain at mild/no pain from 2-24 hours • To determine the proportion of participants who get to mild/no of each of: pain, photophobia, phonophobia, nausea, vomiting at 30, 60, 90, and 120 minutes and 24 hours; both overall and in weight based strata.

	• To determine the proportion of parents/participants who found the treatment useful, and who preferred it over other treatments they'd tried. • Using logistic regression, we will examine for possible predictors of treatment efficacy (sex, age, nap, nap duration, etc). • To determine the proportion of participants who needed rescue medication between 2-24 hrs, both overall and by weight- based strata.
OTHER EVALUATIONS	Headache Diary
SAFETY EVALUATIONS	Incidence of adverse events.
PLANNED INTERIM ANALYSES	Serious adverse events will be monitored by the PI and the UCSF IRB on an ongoing basis throughout the study.
STATISTICS **Primary Analysis Plan**	To detect a mean difference of 3 cm (SD 3) on the change in VAS between doses, an effect size that has been considered clinically meaningful in previous pediatric migraine work, we would anticipate needing 2-hour outcome data on 16 individuals per arm for subjects treating only one attack. However, we will be able to control within subject variability to a degree by having subjects treat two attacks, and thus will revise the estimate to needing outcome data on 12 per group. We will use generalized estimating equations (GEE) to compare mean change from baseline to 2-hour time-points in high-dose vs. low-dose, controlling for repeated measures.
Rationale for Number of Subjects	Assuming 15% drop-out, and adding an extra 20% data-loss for those who will be asleep at the 2-hour time point assessment, we anticipate needing to enroll 19 participants per dosing arm. As we wish to be able to perform this analysis both for the group overall (i.e. all "high dose" vs. all "low dose"), and for the <40 kg and ≥40 kg subgroups individually, we will need to enroll a total of 76 participants. 19 @ < 40 kg, given 1 mg at each of 2 attacks 19 @ < 40 kg given 4 mg at each of 2 attacks 19 @ ≥40 kg given 2 mg at each of 2 attacks 19 @ ≥40 kg given 8 mg at each of 2 attacks

1 BACKGROUND

Migraine is common in children and adolescents. It affects 5% of children by age ten and prevalence increases further in adolescence. In addition to causing pain, migraine causes children and teens to miss school and can impact their school performance. While acute medications exist for treating migraine in children and adolescents, they do not work for all children and can cause significant side effects. In addition, some patients and parents prefer a natural supplement for acute migraine treatment rather than a prescription or over-the-counter pharmacologic agent (e.g. sumatriptan or ibuprofen). Additional safe, well- tolerated and effective acute migraine treatments are needed to help those who do not respond to existing therapies, experience significant side effects from existing therapies, or who prefer not to be taking prescription acute medications.

1.1 Overview of Non-Clinical Studies

Melatonin is a well-known and well-established substance, and there are no relevant non-clinical studies or safety concerns pertinent to using this drug for a migraine indication.

1.2 Overview of Clinical Studies

Melatonin is effective for migraine prevention in adults and data suggest it may also be effective for migraine prevention in children and adolescents. Our clinical experience suggests melatonin may also be helpful for treating *acute* migraine in children and adolescents, even among some who do not respond to other acute agents. There are several possible mechanisms by which melatonin might help migraine acutely. Melatonin may help children get to sleep, and sleep seems to be helpful in terminating migraine attacks. Melatonin may also have direct, acute analgesic effects. It has been used to treat acute procedural pain in children, without significant safety issues, even when administered at a high-dose of 10mg/kg IV to neonates who were undergoing endotracheal intubation (i.e. a dose of about 30 mg IV for a typical 3 kg neonate). There are melatonin receptors in both the thalamus (part of the ascending nociceptive pathway) and the periaqueductal grey (part of the descending anti-nociceptive pathway). There are also melatonin receptors in the hypothalamus, a part of the brain thought to be involved in generating migraine attacks. In animals, melatonin has been shown to decrease the amount of trigeminal nociceptive activation induced by cortical spreading depression, suggesting it could be effective acutely for migraine.

It is already established that certain agents that are traditionally thought of as useful for migraine prevention can also be useful for treating acute migraine—such as sodium valproate. The reverse also appears to be true, for example the NSAID naproxen is effective for acute migraine treatment but also can be effectively used as a migraine preventive. The question now arises whether melatonin—known to be effective for migraine prevention in adults and likely in children—can also be effective acutely for migraine.

This proposed pilot trial is a dose finding study to determine which dose of melatonin is most effective at treating acute migraine in children and adolescents who have episodic migraine. The

doses being studied here are well within the range of what has been safely studied in children before. We propose, depending on weight, to give between 1 mg and 8 mg of melatonin, once, at onset of headache. Each participant would treat two attacks. As noted above, neonates have safely been given 10mg/kg IV for peri-procedural pain management. Children undergoing auditory brainstem response tests were given 5-20 mg. Doses of 0.25-0.5 mg/kg have been given for MRI sedation—which would equate to about 15 mg for a 30 kg child. In another study, children were given 10 mg for MRI sedation. Our clinical experience suggests that for acute migraine treatment, 1-4 mg of melatonin would be adequate for children < 40 kg, and 2-8 mg for children and adolescents >40 kg. We propose to study a melatonin formulation that is an edible (i.e. chewable) milk-chocolate based formulation. We consider this formulation to have three potential advantages:

1. More rapid onset than a tablet/capsule formulation, potentially allowing for faster relief and in turn potentially a higher chance or relief, as treating when the pain is still mild has been shown to predict efficacy of other acute migraine treatments.
2. Young children who cannot yet swallow pills will be able to take this formulation.
3. Children who are nauseated during migraine attacks may still find a chocolate-based formulation palatable and be willing to take it during an attack.

2 STUDY RATIONALE

This pilot study is a dose finding study to determine what dose of melatonin seems effective for treating acute migraine in children and adolescents with episodic migraine. We will identify the most effective dose to pull forward into a future fully-powered placebo-controlled efficacy study. If doses are equally effective, we will bring forward the best tolerated dose. If equally well tolerated, we will bring forward the lowest effective dose, as this will minimize cost to families should this treatment become widely adopted.

2.1 Risk / Benefit Assessment

2.2 Very low risks to participating in this study, and inconvenience to the participant/family is minimized as most/all study activities can be completed from the participant's home.

3 STUDY OBJECTIVES

3.1 Primary Objective

To determine a change in mean VAS score between baseline and 2-hr time point in low-dose vs. high-dose group.

3.2 Secondary Objectives

- To determine a change in mean VAS score between baseline and 2-hr time point in low-dose vs. high-dose group in the < 40 kg and the ≥40 kg subgroups. (We will also do sensitivity analyses of completers who were awake for the 2-hr time point).

- To determine the tolerability/side effects of high-dose vs. low-dose in the group over all, and in weight-based strata.
- To determine the proportion of participants who get to mild/no pain by 2 hrs (overall and by weight group), and who remain at mild/no pain from 2-24hours
- To determine the proportion of participants who get to mild/no of each of: pain, photophobia, phonophobia, nausea, vomiting at 30, 60, 90, and 120 minutes and 24 hours; both overall and in weight based strata.
- To determine the proportion of parents/participants who found the treatment useful, and who preferred it over other treatments they'd tried.
- Using logistic regression, we will examine for possible predictors of treatment efficacy (sex, age, nap, nap duration, etc).
- To determine the proportion of participants who needed rescue medication between 2-24 hrs, both overall and by weight- based strata.

4 STUDY DESIGN

4.1 Study Overview

This randomized pilot trial is a dose finding study to determine which dose of melatonin is most effective for treating acute migraine in children and adolescents who have episodic migraine. Participants will be randomized to a higher-dose or a lower-dose, stratified by weight (< 40 kg and ≥40 kg). They will treat 2 acute headache attacks and will complete a symptom diary for those 2 attacks and then return the diary to the study center. Randomization will be done in blocks of 4 to ensure equal group size and will be stratified by weight (< 40 kg or ≥40 kg).

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

To determine in a randomized trial which dose of melatonin, “high dose” vs. “low dose”, is more effective at two-hours for acute migraine head pain in children and adolescents who have episodic migraine.

5.2 Secondary Efficacy Endpoints

- To determine a change in mean VAS score between baseline and 2-hr time point inlow-dose vs. high-dose group in the < 40 kg and the ≥40 kg subgroups. (We will also do sensitivity analyses of completers who were awake for the 2-hr time point).
- To determine the tolerability/side effects of high-dose vs. low-dose in the group over all, and in weight-based strata.
- To determine the proportion of participants who get to mild/no pain by 2 hrs (overall and by weight group), and who remain at mild/no pain from 2-24hours
- To determine the proportion of participants who get to mild/no of each of: pain, photophobia, phonophobia, nausea, vomiting at 30, 60, 90, and 120 minutes and 24 hours; both overall and in weight based strata.
- To determine the proportion of parents/participants who found thetreatment

useful, and who preferred it over other treatments they'd tried.

- Using logistic regression, we will examine for possible predictors of treatment efficacy (sex, age, nap, nap duration, etc).
- To determine the proportion of participants who needed rescue medication between 2-24 hrs, both overall and by weight- based strata.

5.3 Safety Evaluations

Although there is substantial safety data for the use of melatonin in children and adolescents (as cited above), safety will be carefully monitored throughout this study by review of the headache diary forms by the investigator team.

6 SUBJECT SELECTION

6.1 Study Population

Subjects ages 3-17 inclusive with a diagnosis of episodic migraine who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Meet ICHD criteria for episodic migraine in children and adolescents, with at least 1 migraine attack per month on average.
2. Age 3-17 years
3. Dissatisfaction with previous acute treatments, for one or more of the following reasons: a) One or more previously tried acute medications have not been effective, or adequately effective, b) previously tried acute treatments have caused side effects, or C) patient/family would prefer a natural supplement for acute treatment over medication treatment.
4. If of driving age, teen participant agrees not to drive for at least 8 hours after treating with melatonin.

6.3 Exclusion Criteria

1. Allergy or intolerance to melatonin, or to chocolate.
2. Opioid or barbiturate overuse as defined in ICHD
3. Pregnant/lactating

7 CONCURRENT MEDICATIONS

There are no concurrent medication restrictions except as above in the exclusion criteria..

7.1 Allowed Medications and Treatments

Standard therapy for migraine is allowed except for treatments noted in the exclusion criteria described above. Acute migraine medications such as ibuprofen (Motrin), acetaminophen (Tylenol), naproxen (Aleve) or a triptan (for example, sumatriptan) may be taken during the

study, but we will ask participants to try to wait 2 hours after they take the study treatment, in order to see if the study treatment is effective.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Randomization will be done in blocks of 4 to ensure equal group size and will be stratified by weight (< 40 kg or ≥40 kg).

8.2 Blinding

This is an open label study and there is no blinding

8.3 Formulation of Test and Control Products

8.3.1 Formulation of Test Product

Chocolate melatonin pieces, developed by Good Day Chocolate

Table 1: Formulation of melatonin

	Melatonin
Active Ingredient, mg/mL	Melatonin 1mg per piece
Other ingredient, mg/mL	Chamomile extract

8.3.2 Formulation of Control Product

There is no control product, all participants will receive chocolate melatonin.

8.3.3 Packaging and Labeling

Study drug is supplied in bulk from the manufacturer to the study team. The investigator team will place 1-8 pieces into each pill bottle, as determined by the randomization scheme. Each participant will receive two study treatment bottles—one for attack 1 and one for attack 2. The study team will label these bottles with the study ID number, and the attack they are intended for: i.e. “Attack 1” or “Attack 2” or “Extra” (in case they drop some or decide to treat a different attack). Participants randomized to receive either 1mg or 2mg will receive 4 extra pieces. Those randomized to 4mg or 8mg will get 8 extra pieces.,

Supply of Study Drug at the Site

Good Day Chocolate has donated the chocolate melatonin and the site will store it in a locked cabinet at room temperature.

8.3.4 Dosage/Dosage Regimen

19 participants @ < 40 kg, given 1 mg at each of 2 attacks
19 @ < 40 kg given 4 mg at each of 2 attacks
19 @ ≥40 kg given 2 mg at each of 2 attacks
19 @ ≥40 kg given 8 mg at each of 2 attacks

8.3.5 Dispensing

The investigators will give the participants the study bottles at their clinic visit, or the study bottles will be sent to them.

8.3.6 Administration Instructions

The study team will instruct the participant and a parent as to how and when to take the study chocolates.

8.4 Supply of Study Drug at the Site

Good Day Chocolate will send the chocolate to the site and the site will repackage the chocolate pieces into study pill dispending bottles.

8.4.1 Storage

The study bottles will be stored in a locked cabinet at room temperature.

8.5 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The principal investigator will verify these documents throughout the course of the study.

8.6 Measures of Treatment Compliance

Participants will be asked how many chocolate pieces they took for each attack and they will be asked how many of the Extra Pieces were either dropped/thrown away and how many were kept for a future or other attack.

9 STUDY PROCEDURES AND GUIDELINES

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated

by the subject's parent or legal guardian. Age appropriate assent will be obtained from the child or adolescent prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

Pertinent concomitant medication and concurrent therapies will be documented at Baseline/Screening. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

Demographic information (date of birth, sex, race) will be recorded at Screening.

9.1.3 Medical History

Relevant medical history will be recorded at Screening.

9.1.4 Physical Examination

Participants will have had physical examinations performed as part of their clinical care at the UCSF Pediatric Headache program. No additional physical examinations will be needed for study purposes.

9.1.5 Vital Signs

See 9.1.4

9.1.6 Adverse Events

Participants and parents will be able to report adverse events at any time during the study. Duration (start and stop dates and times), severity/grade, outcome, treatment and relation to study drug will be recorded on the case report form (CRF).

9.1.7 Pregnancy Determination

During enrollment, female subjects who are of childbearing age will be asked if they could be pregnant.

10 EVALUATIONS BY VISIT

10.1 Visit 1

Baseline data will be collected by either an investigator and/or the study coordinator either in-person in the clinic, via a recommendation by their doctor or another member of the study team, or via phone for those enrolling remotely. All participants will have already been verified to meet ICHD criteria for episodic migraine. Headache duration, history, preventive medication use pattern, acute medication use pattern, aura status, family history, associated symptoms, comorbidities, pregnancy status and other variables will be assessed via questioning either in the clinic, chart review or via phone/text.

Participants will be instructed to treat two migraine attacks with their assigned melatonin dose. For those randomized to either 1mg or 2mg, they will receive 4 extra pieces in case they drop or lose any, or would like to use a different headache to track in the event that they take the melatonin and then something comes up where they are unable to track that headache for 24 hours.

For those randomized to 4mg or 8mg, they will receive 8 extra pieces. Participants are instructed that they are able to keep any unused pieces for a future attack but will be asked to return the empty bottles. Families will be asked to write down on the front cover of the headache diary how many of the extra pieces were either kept for later attacks, or were lost/dropped/thrown away. Alternatively, the study team will ask the families and record this for them. The diary asks how many chocolate pieces were taken for each attack.

Migraine attacks should be separated by at least 24 hours' headache freedom in between.

Participants will be provided with the Good Day sleep chocolate product and told their randomly assigned dose (either 1mg or 4mg for under 40kg, and either 2mg or 8mg for greater than or equal to 40kg). They will be given three bottles:

- Bottle 1 is labeled **Attack #1** and will have their exact dose (as described above)
- Bottle 2 is labeled **Attack #2** will have their exact dose (as described above)
- Bottle 3 is labeled **Extra** and will have either 4 or 8 pieces so they can have enough extra pieces if they drop or lose some of the pieces from bottle 1 or 2, as well as so they can use some if they want to treat another attack (they have been instructed to only use the dose they are assigned to)

Chocolate melatonin supplies will be given to the parents for all young children who, in the opinion of the investigator, may need additional supervision. If a child were to eat all of the chocolate melatonin pieces at once, this would still be considered a safe amount, as neonates have been safely given 10mg/kg IV melatonin[3].

They will also be given a paper headache diary (either in person or shipped). They will be instructed to treat as early as possible in an attack, i.e. ideally while the pain is still mild, however they will still be permitted to treat even if the pain has reached the moderate or severe levels. Participants will be asked to treat attacks that occur at home (or attacks that are not yet treated when they reach home), or that occur at another location where they can stay for at least 8 hours if needed, so as to ensure driving after dosing will not be necessary (for older teens), and that headache diaries will be available, and participants can sleep after dosing if desired.

Participants will record baseline pain intensity (and other migraine symptom intensity) at time zero, i.e. right before they dose the melatonin. They will be asked not to take other acute medications for two hours, and to record pain intensity (and other symptom intensity) at 30, 60, 90 min and the two-hour time marks. If they fall asleep, parents/caretakers will be instructed **not** to wake them for data collection, as sleep may be a mechanism by which melatonin helps acute

migraine. They will resume data collection as soon as they first awaken. They will be asked to collect data also at 4 hours and 24 hrs, and to record any acute medication used between 2-24 hours. They will also be asked to record their impressions about the treatment's efficacy, side effects, and whether or not they slept after dosing and if so for how long.

Study staff will contact participants until they complete the study to remind them about when to treat an acute attack and to answer any questions. Participants may be sent 'retention' packages (small office supplies, pens, or other small items) to remind them about the study. At the completion of the study, participants will be asked to mail back the headache diary in a pre-paid FedEx envelope. A $5 gift card will be given to participants once they mail back the diary.

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered a pharmaceutical product and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current protocol or of greater severity or frequency than expected based on the information in the protocol.

The study team will collect AE information in the headache diary data. Adverse events will be recorded in the patient CRF. Adverse events will be described by severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in

Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Drug

The relationship of an AE to the study drug should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.
Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization

- a persistent or significant disability/incapacity
- a congenital anomaly/birth defect

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF CHR Guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

11.3 Medical Monitoring

Dr. Amy Gelfand should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (415) 860-2202
Pager: (415) 443-2089

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the subject's parent/guardian, or the investigator think that it is not in the subject's best interest to continue.

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator team until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should tell the study site.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

12.3 Withdrawal of Subjects from the Study

A subject may be discontinued from study treatment at any time if the subject, the subject's parent/guardian, or the investigator think that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

12.4 Replacement of Subjects

Subjects who withdraw from the study treatment will not be replaced.

Subjects who withdraw from the study will not be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

Failure to meet inclusion/exclusion criteria

Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The investigator will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by the Investigator. A copy of the form will be filed in the site's regulatory binder.

14 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a Statistical Analysis Plan (SAP) will be written describing analyses that will be performed.

Data Sets Analyzed

All eligible patients who are randomized into the study and receive at least one dose of the study drug (the Safety Population) will be included in the safety analysis.

14.1 Demographic and Baseline Characteristics

The following demographic variables at screening will be summarized by dose level: sex, age, and weight.

14.2 Analysis of Primary Endpoint

We will use generalized estimating equations (GEE) to compare mean change from baseline to 2-hour time-points in high-dose vs. low-dose, controlling for repeated measures.

14.3 Analysis of Secondary Endpoints

Safety and tolerability data will be summarized by treatment group.

Adverse event rates will be coded by body system and MedDra classification term. Adverse events will be tabulated by treatment group and will include the number of patients for whom the event occurred, the rate of occurrence, and the severity and relationship to study drug.

14.4 Interim Analysis

There is no planned interim analysis.

14.5 Sample Size and Randomization

Participants will be randomized based on weight (over or under 40kg). Randomization will be in blocks of 4. Nineteen participants per arm will be randomized in each of the four treatment arms.

19 @ < 40 kg, given 1 mg at each of 2 attacks
19 @ < 40 kg given 4 mg at each of 2 attacks
19 @ ≥40 kg given 2 mg at each of 2 attacks
19 @ ≥40 kg given 8 mg at each of 2 attacks

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

Data will be entered by the participant (headache diary) and by study staff (demographics, pill counts etc.). Subjects will not be identified by name in the study database, but by subject number. The study team will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

Every effort will be made to keep participant data secure, though there is some risk of loss of privacy. The main privacy loss risk would be that it could be revealed than a child or adolescent has migraine and is taking a treatment for it. While sometimes migraine is stigmatized as being "just a headache" and the sufferer can be seen as a "complainer", by being part of a medical research study on migraine treatment that might give legitimacy to the condition and thereby the sufferer.

15.2 Data Management Procedures

The data will be entered into a validated REDCap database. The study team will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

15.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the IRB and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued.

15.6 Monitoring

Monitoring visits will be conducted by the investigator according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

15.7 Subject Confidentiality

In order to maintain subject confidentiality, only a subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without

written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Any amendment to the protocol will be written by the investigator. Protocol amendments cannot be implemented without prior written IRB approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the UCSF IRB prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB in accordance with the standard operating procedures and policies of the IRB, and the Investigator will keep the IRB informed as to the progress of the study. The Investigator will obtain assurance of IRB compliance with regulations.

Any documents that the IRB may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB. The IRB's written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB's unconditional approval statement will be implemented by the Investigator prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The consent form generated by the Investigator must be approved by the IRB. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations.

A properly executed, written, informed consent will be obtained from each subject's parent/guardian prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. Assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

16.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual agreement among the study investigators. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

16.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.

10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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