Amy Gelfand, MD

Clinical Research Protocol

MELATONIN FOR ADOLESCENT MIGRAINE PREVENTION STUDY
THE MAP STUDY

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Sponsor:	Amy Gelfand, MD 1825 4th Street 5th Floor, 5A San Francisco, CA 94158
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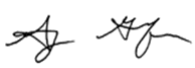

March 21, 2017

PI or Sponsor Signature *Date*

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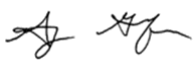
PROTOCOL AGREEMENT

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 required authorities with complete and 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: **MAP.1.0**

Protocol Title:
Melatonin for Adolescent Migraine Prevention Study. The MAP Study

Protocol Date: March 21, 2017



March 21, 2017

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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
IRB	Institutional Review Board
PedMIDAS	Pediatric Migraine Disability Assessment
IRB	Institutional Review Board
PI	Principal Investigator
SAE	Serious Adverse Experience
SAP	Statistical Analysis Plan
UCSF	University of California, San Francisco
UCLA	University of California, Los Angeles
US	United States

PROTOCOL SYNOPSIS

TITLE	Melatonin for Adolescent Migraine Prevention Study. The MAP Study
SPONSOR	Amy Gelfand, MD
FUNDING ORGANIZATION	1. Gelfand KL2 Grant Salary Support 2. Irene Perstein Award 3. UCSF Weill Institute for the Neurosciences Award
NUMBER OF SITES	2
RATIONALE	Safe, effective, and well-tolerated treatments are needed to reduce the frequency of migraine attacks in children and adolescents. Melatonin is a natural supplement that has an excellent safety profile and has been used to improve sleep in pediatrics. Melatonin 3 mg orally nightly has also been shown in a randomized, placebo-controlled trial to be superior to placebo for migraine prevention in adults. Given the excellent safety and tolerability of melatonin and its demonstrated efficacy for migraine prevention in adults, we propose to study melatonin for migraine prevention in adolescents.
STUDY DESIGN	This is a randomized, multi-site double-blind placebo-controlled trial of melatonin 3 mg vs. 6 mg vs. placebo orally nightly for migraine prevention in adolescents. We will use a "remote trial" design, wherein after the initial in-person enrollment visit all study procedures will be done from the comfort of the participant's own home. We intend to enroll approximately 210 participants over 24-30 months at two sites: UCLA and UCSF.
PRIMARY OBJECTIVE	1. To compare the number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between melatonin (combined 6mg + 3mg) vs. placebo.

SECONDARY OBJECTIVES	1. To compare the number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between melatonin 3 mg vs. placebo. 2. To compare the number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between melatonin 6 mg vs. placebo. 3. To compare the number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between melatonin 3 mg vs. 6 mg. 4. To compare the mean headache days in 5th-8th randomized phase in melatonin (combined) vs. placebo , (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using t-tests). 5. To compare the mean acute medication use days in 5th-8th randomized phase in melatonin (combined) vs. placebo, (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using t-tests). 6. To compare the mean PedMIDAS score (continuous) in 5th-8th randomized phase in melatonin (combined) vs. placebo, (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using t-tests). 7. To compare the number of ≥50% responder rate in 5th-8th randomized phase in melatonin (combined) vs. placebo (Chi-square or Fisher's exact (if needed), (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using Chi-square (or Fisher's exact)).
NUMBER OF SUBJECTS	Approximately 210 subjects
SUBJECT SELECTION CRITERIA	1. Age 10-17—inclusive 2. Weight ≥40 kg, so as not to require mg/kg based dosing 3. Meets International Classification of Headache Disorders III beta[1] criteria for migraine in children/adolescents (international standard diagnostic criteria for research) 4. Lives in the state of California- to allow shipping of study medication from our pharmacy 5. Has at least one parent who speaks English—in order to ensure good communication with study team by phone 6. Has daily access to a smartphone in order to provide daily headache diary data 7. A Parent/Guardian consents and the adolescent is cognitively capable of giving assent to participate 8. Either not on a migraine preventive medication, or if on one the dose has been stable for at least 4 weeks prior to enrollment, or are willing to wait to start the study until they

	have reached a stable dose for 4 weeks 9. Willing to not use OTC melatonin or change migraine preventives during the trial 10. Has ≥1 headache day per week, or 4-28 days of headache in a 28-day period 11. Episodic headaches have been present for a minimum of 6 months—This lowers the likelihood of a secondary cause of headaches Exclusion Criteria: 1. Continuous headache 2. History of seizures/epilepsy 3. Pregnant/lactating 4. Concomitant opioid or barbiturate overuse, wherein overuse is defined as ≥4 days per month of barbiturate containing compounds, ≥10 days per month of opioid containing compounds as these may impact sleepiness scales 5. If in the investigator's opinion there is a medical or psychiatric concern that makes them think the participant should not participate 6. Inability to swallow pills after teaching and practice 7. History of nocturnal asthma, as evidenced by a having a diagnosis of asthma and symptoms that manifest as nighttime awakening due to cough, wheeze, and/or shortness of breath Randomization Criteria: 1. Had 4-28 migraine/migrainous days in the 28-day period of weeks 5-8 of single-blind placebo treatment phase, but not continuous headache. 2. At least 80% compliance with headache diary (i.e. at least 23 headache diary days) during weeks 5-8 of single-blind placebo treatment phase.
TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	3 mg or 6 mg melatonin orally nightly for the 8 active weeks of study treatment.
CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION	Comparable placebo taken orally nightly for the 8 active weeks of study treatment.

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Subjects will be in the study for 16 weeks 1) 8-week single-blind placebo treatment-phase 2) 8-week double-blind randomized treatment phase. The total duration of the study is expected to be 24-30 months.
CONCOMMITANT MEDICATIONS	Allowed: All medications are allowed, except specified below, as long as the dose is stable for 4 weeks prior to enrollment. Prohibited: Overuse of opioid and barbiturate medications, wherein medication overuse is defined as ≥4 days per month of barbiturate containing compounds and/or ≥10 days per month of opioid containing compounds
EFFICACY EVALUATIONS	• Headache diary • PedMIDAS score (PedMIDAS is a validated score for measuring headache related disability in adolescents) • Cleveland Adolescent Sleepiness Questionnaire score, (a validated instrument for measuring excessive daytime sleepiness in 11-17 year olds)
PRIMARY ENDPOINT	• Number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between melatonin (combined 6mg + 3mg) vs. placebo. We will control for baseline migraine/migrainous day frequency in the 5-8th week of the single-blind treatment phase and use an ANCOVA analysis.
SECONDARY ENDPOINTS	• Number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between melatonin 3 mg vs. placebo. • Number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between melatonin 6 mg vs. placebo. • Number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between melatonin 3 mg vs. 6 mg. • Mean headache days in 5th-8th randomized phase in melatonin (combined) vs. placebo , (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using t-tests). • Mean acute medication use days in 5th-8th randomized phase in melatonin (combined) vs. placebo, (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using t-tests). • Mean PedMIDAS score (continuous) in 5th-8th randomized phase in melatonin (combined) vs. placebo, (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using t-tests). • ≥50% responder rate in 5th-8th randomized phase in melatonin (combined) vs. placebo (Chi-square or Fisher's exact (if needed),

	(followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using Chi-square (or Fisher's exact)). *(We will control for the baseline level of these outcomes in all of these analyses).*
OTHER EVALUATIONS	***Safety outcomes:*** 1. Proportion with adverse events between groups a. Proportion with serious adverse events between groups b. Proportion of adverse events thought to be related to the study treatment 2. Mean Sleepiness score in 5th-8th randomized phase in melatonin (combined) vs. placebo, (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using t-tests). ***Trial design assessment outcome:*** 1. Proportion of participants on melatonin who correctly guessed they were on it (just playing chance, 66% should guess melatonin) 2. Proportion of participants on melatonin who guessed their dose correctly (by chance 50% 3 mg, 50% 6 mg). 3. Proportion of participants on placebo who correctly guessed they were on placebo (by chance, 33% should guess this) 4. The same three above but with investigators guessing.
SAFETY EVALUATIONS	Incidence of adverse events
PLANNED INTERIM ANALYSES	**DATA SAFETY MONITORING PLAN** The study only includes children without serious medical illness to reduce the risk of any possible side effects. In addition, melatonin has been studied in children and found to be generally safe and well tolerated. Participants or their family member can report an adverse event via phone, and serious adverse events will immediately be reported to the PI. The PI will promptly judge each AE's impact on the risk/benefit ratio of the study as well as the risk/benefit ratio for each participant as they are reported, so that these ratios will be continuously reassessed throughout the study period. Causality will be determined by the PI for all AEs reported and all AEs will be carefully documented (including AEs determined to be unrelated or only possibly related to the study supplement). AEs will be sent to the DSMB for review at the midpoint and end of study. In the case of an AE occurring that necessitates breaking the blind, the subjects will be discontinued from the study and the data collected before discontinuation will be analyzed as "intent to treat". We have a

	procedure in place to break the study blind at any time. Any serious adverse events will be communicated to the IRB, in accordance with their guidelines. All serious and non-serious adverse events will be collected in an adverse event reporting form and reported to the DSMB as required. This information will be summarized and published in the final study publication. Once the study data are analyzed following the end of the study, participants will be sent information about the results and notified of their treatment group assignment (melatonin 3 mg, 6 mg or placebo). They will be encouraged to discuss with their personal physician the possibility of continuing the supplement.
STATISTICS **Primary Analysis Plan**	Primary outcome: Number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between melatonin (combined 6 mg+3mg) vs. placebo. We will control for baseline migraine/migrainous day frequency in the 5-8th week of the single-blind treatment phase and use an ANCOVA analysis.
Rationale for Number of Subjects	*Power calculation*: To detect a difference of 1.1 migraine/migrainous days (SD 1.8) between groups, as was seen in the adolescent topiramate migraine prevention trial that led to FDA-approval of that agent in 12-17 year-olds[8], we need outcome data on 42 participants/arm. We anticipate that 25% of enrolled participants will be screened out by the single-blind placebo run-in process, and that 85% of those who randomize will complete the trial. Therefore we will enroll 70 per arm, or *n*=210 total.

1 BACKGROUND

Migraine affects 6.3% of adolescents (5.0% of boys, 7.7% of girls) [2]. In addition to causing significant suffering, migraine causes children and adolescents to miss school and can negatively impact school performance[3]. Currently, only one migraine preventive is FDA-approved in adolescents—topiramate—an anti-epileptic medication that has the potential for significant side effects such as cognitive slowing and increased suicidality in adolescents. Safe, effective, and well-tolerated treatments are needed to reduce the frequency of migraine attacks in this young age group. Melatonin is a natural supplement that has an excellent safety profile and has been used to improve sleep in pediatrics[4]. Melatonin 3 mg has also been shown in a randomized, placebo-controlled trial to be superior to placebo for migraine prevention in adults [5]. Given the excellent safety and tolerability of melatonin and its demonstrated efficacy for migraine prevention in adults, we propose to study melatonin for migraine prevention in adolescents.

Observational studies support a role for melatonin in the treatment of migraine. Adults with migraine have lower melatonin levels on migraine days compared to non-headache days and those with chronic migraine have lower melatonin levels than those with episodic migraine [6, 7]. Nocturnal melatonin levels are lower in women with migraine with aura whose attacks occur around menses compared to control women.

There is also experimental evidence supporting a therapeutic role for melatonin in migraine prevention, though with some conflicting data. In a double-blind, randomized, placebo-controlled, 3-arm trial with approximately 65 participants per arm, the efficacy of 3 mg of immediate release melatonin was superior to placebo and comparable to amitriptyline 25 mg nightly. The observed reduction in headache frequency at three months was: 2.7 in those treated with melatonin, 2.2 for amitriptyline (p=0.19), and 1.2 for placebo (p=0.009). The tolerability of melatonin was comparable to placebo and better than amitriptyline [5]. In contrast, in a smaller randomized, double-blind cross-over design study of 46 subjects, 2 mg of sustained release melatonin was not different from placebo for migraine prevention after 8 weeks of treatment [8]. Mean baseline migraine attack frequency (SD) was 4.2±1.2; during the placebo phase it was 2.9±1.4 vs. 2.8±1.6 during the melatonin treatment phase, p=0.75. Three participants (7%) had daytime tiredness and dizziness during melatonin treatment.

There are a number of possible reasons for the disparate findings between the two above trials, including differences in melatonin dose (3 mg vs. 2 mg) and formulation (immediate release vs. sustained release), trial design (parallel-group vs. crossover), treatment duration (3 months vs. 8 weeks), difference of outcome measures (headache days vs. migraine attacks) and possible under-powering in the smaller study. Crucially, the placebo response in the Peres and colleagues study was in-line with modern, adequately powered placebo-controlled migraine preventive studies, while the Alstadhaug and colleagues study placebo response was high. Additional randomized placebo-controlled trials are needed to clarify the role of melatonin in migraine prevention.

Uncontrolled studies have generally supported a therapeutic role for melatonin in migraine. In a pilot study of adult patients with migraine or tension-type headache, melatonin 4 mg appeared to be an effective dose for migraine prevention. Forty-nine

patients were enrolled, of whom 37 had migraine, and 41 completed the 6-month treatment phase. Headache frequency, and Headache Impact Test scores were statistically significantly lower in the migraine group at 6-months of treatment compared to baseline [9].

Uncontrolled work in pediatrics also suggests melatonin may be useful in the treatment of pediatric and adolescent migraine. In one study, 60 pediatric and adolescent participants were treated with up to 6 mg melatonin nightly (formulation unspecified). At three months, mean(SD) migraine attack frequency decreased from 15.6±7.6 to 7.1±4.4 per month[10]. In a smaller open-label pediatric study, 14 migraineurs were treated with 3 mg melatonin nightly. Ten (71%) had a ≥50% improvement in headache frequency at 3 months[11]. Melatonin was well tolerated in these pediatric studies: in the study where children received up to 6 mg of melatonin, 7(12%) had daytime sleepiness vs. 1(7%) in the smaller study where they received 3 mg[10, 11].

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

Studies of melatonin in adults with migraine:

In adults, melatonin levels are lower on migraine attack days compared to headache-free days.[3] In a 2013 study by Peres *et al.*, melatonin given at a dose of 3 mg orally nightly was shown to be effective for prevention of episodic migraine in adults in a three-month long double-blind randomized placebo-controlled trial[4]. An earlier study of melatonin for migraine prevention in adults was negative, but it was underpowered, had used a lower melatonin dose of 2 mg instead of 3 mg nightly, and a prolonged release formulation instead of the immediate release formulation used in the 2013 study[7].

Studies of melatonin in children with migraine:

Open label studies of melatonin in children and adolescents suggest it is beneficial for migraine prevention.[5, 6] In an open-label neurology clinic-based study of 60 children with migraine (ages 5-15 years), the participants were treated with 0.3mg/kg melatonin (max 6 mg) orally nightly for three months. Headache frequency dropped from 15.6(±7.6) days per month to 7.1(±4.4), $p < 0.001$. A ≥50% reduction in headache frequency was seen in 70% of the participants (95% CI 58-82%). There was also a statistically significant improvement in headache severity, duration, and disability (as measured by PedMIDAS score), as well as a decrease in analgesic use after treatment with melatonin.

In a smaller open-label study of 22 children recruited from a pediatric headache clinic in Rome, 14 of the children had migraine and 8 had tension-type headache. The age range was 6-16 years (mean 12.2±2.6) and they were treated with melatonin 3 mg orally nightly for three months. Twenty-one completed the study, 13 of whom had migraine. Ten of these 13 migraineurs experienced a ≥50% decrease in headache frequency[5]. In addition, of twelve children with post-traumatic headaches treated with melatonin 3-10 mg nightly, headaches improved in nine (75%)[8].

Safety of melatonin in children and in migraine:

Melatonin is a safe and well-tolerated sleep aid, even for children[5, 9-25]. We are aware of no serious adverse events ever reported from melatonin supplementation in neurodevelopmentally normal children. While a small trial of six children with multiple neurologic disabilities raised concern when four developed more frequent seizures on melatonin[26], subsequent research involving larger numbers of children with neurodevelopmental disabilities demonstrated excellent safety[9, 12, 20, 22, 24, 27]. In fact melatonin treatment has been associated with *reduced* seizure frequency in children and adults with intractable epilepsy[14, 19, 28].

In the study of 22 children with headache treated with 3 mg melatonin nightly—there was just one child with an adverse event—excessive daytime sleepiness that caused them to discontinue the medication[5]. In the larger study of 60 children, who were given 0.3mg/kg for migraine prevention, serious side effects were not seen. The side effects seen were: 12% tiredness (excessive daytime sleepiness 5%), 7% vomiting, 3% mild hypotension, and 2% constipation[6]. In the Peres *et al.* positive adult melatonin study, the tolerability of melatonin was not different from placebo. In the Alstadhaug *et al*. crossover study of melatonin 2 mg orally nightly for migraine prevention in adults, the number of participants experiencing adverse events was higher in the placebo phase than in the melatonin phase.

Melatonin at a dose of 3 mg[12, 24]or higher[20, 21, 23, 24]has been used safely with excellent tolerability in several randomized pediatric trials. In a systematic review article of melatonin use for children with ADHD, children ranged from 6-14 years and were treated with 3-6 mg melatonin nightly—there were no serious adverse events and generally adverse events were similar to placebo; of note one child was reported to have severe migraine[29]. In another study, children treated with melatonin for between 1-4.6 years (mean 3.1 years) at a mean dose of 2.7 mg (range 0.3-10 mg) nightly had normal sleep quality, mental health scores, and pubertal development[30]. Melatonin has even been given safely to neonates for its analgesic[15], anti-inflammatory[16, 17], and anti-oxidant[18] properties. Furthermore, there is evidence melatonin might be neuroprotective after perinatal hypoxic-ischemic injury[31].

At UCSF we conducted a pilot remote RCT of melatonin 3 mg vs. placebo in 12-17 year olds (IRB #14-14251.) We are still completing analysis on that study, however there were no serious adverse events and only one participant (out of 26 randomized participants) stopped study medication due to daytime tiredness (they were in the melatonin group).

2 STUDY RATIONALE

Safe, effective, and well-tolerated treatments are needed to reduce the frequency of migraine attacks in this young age group. Melatonin is a natural supplement that has an excellent safety profile and has been used to improve sleep in pediatrics. Melatonin has also been shown in a randomized, placebo-controlled trial to be superior to placebo for migraine prevention in adults. Given the excellent safety and tolerability of melatonin and its demonstrated efficacy for migraine prevention in adults, we propose to study melatonin for migraine prevention in adolescents.

2.1 Risk / Benefit Assessment

The most significant potential benefits are a potential reduction in migraine/migrainous headache days and reduction in associated disability. As the placebo response rate in pediatric migraine trials is generally high, both participants randomized to melatonin and those randomized to placebo may experience the benefit of a decreased number of migraine/migrainous headache days. Other potential benefits include decreased headache severity and duration, and decreased need to take acute headache medications. Participants also may find it easier to fall asleep at bedtime. Also, most of the study can be completed from home.

These benefits outweigh the relatively minor potential risks that have been reported with the proposed melatonin dosages in developmentally normal pediatric patients—essentially sleepiness or drowsiness during the day.

Participants may not take over the counter melatonin during the study, or 4 weeks prior to enrollment. They may; however, be on a different migraine preventive medication as long as the dose has been stable for 4 weeks prior to enrollment—hence they have access to other effective migraine preventive treatments during the study. They are also allowed to use acute migraine treatments as long as there is no concomitant opioid or barbiturate overuse.

3 STUDY OBJECTIVES

3.1 Primary Objective

To compare the number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between melatonin (combined 6 mg+3mg) vs. placebo. We will control for baseline migraine/migrainous day frequency in the 5-8th week of the single-blind treatment phase and use an ANCOVA analysis.

3.2 Secondary Objectives

1. To compare the number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between **melatonin 3 mg vs. placebo.**
2. To compare the number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between **melatonin 6 mg vs. placebo.**
3. To compare the number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between **melatonin 3 mg vs. 6 mg.**
4. To compare the mean headache days in 5th-8th randomized phase in melatonin (combined) vs. placebo, (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using t-tests).
5. To compare the mean acute medication use days in 5th-8th randomized phase in melatonin (combined) vs. placebo, (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using t-tests).
6. To compare the mean PedMIDAS score (continuous) in 5th-8th randomized phase in melatonin (combined) vs. placebo, (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using t-tests).
7. To compare the number of ≥50% responder rate in 5th-8th randomized phase in melatonin (combined) vs. placebo (Chi-square or Fisher's exact (if needed),

(followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using Chi-square (or Fisher's exact)).

4 STUDY DESIGN

4.1 Study Overview

Randomized, multi-site double-blind placebo-controlled trial of melatonin 3 mg vs. 6 mg vs. placebo. Randomization will be 1:1:1 in blocks of 6 by site. We will use a "remote trial" design, wherein after the initial in-person enrollment visit all study procedures will be done from the comfort of the participant's own home.

We intend to enroll approximately 210 participants over 24-30 months at two sites: UCLA and UCSF. The duration of participation for each participant will be 4 months:

1) 8-week single-blind placebo treatment-phase

2) 8-week randomized treatment phase

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

1. Mean migraine/migrainous days in weeks 5-8 of randomized treatment phase in melatonin treated participants vs. placebo.

5.2 Secondary Efficacy Endpoints

1. Mean migraine/migrainous days in weeks 5-8 of randomized treatment phase in melatonin 6 mg vs. placebo.
2. Mean migraine/migrainous days in weeks 5-8 of randomized treatment phase in melatonin 3 mg vs. placebo.
3. Mean migraine/migrainous days in weeks 5-8 of randomized treatment phase in melatonin 6 mg vs. melatonin 3 mg.
4. Change in mean migraine/migrainous days from weeks 5-8 of single-blind treatment phase to weeks 5-8 of randomized treatment phase for each group.
5. Mean PedMIDAS (headache related disability score) in weeks 5-8 of randomized treatment phase in melatonin treated group vs placebo, and in each of the three pair-wise group comparisons.
6. Mean CASQ score in weeks 5-8 of randomized treatment phase in melatonin treated group vs. placebo, and in each of the three pair-wise group comparisons.
7. Number of days acute medication is used in weeks 5-8 of randomized treatment phase in melatonin treated group vs. placebo, and in each of the three pair-wise group comparisons.
8. Number of headache days in weeks 5-8 of randomized treatment phase in melatonin treated group vs. placebo, and in each of the three pair-wise group comparisons.

5.3 **Safety Evaluations**

1. Incidence of adverse events

6 SUBJECT SELECTION

6.1 Study Population

Subjects with a diagnosis of migraine who meet the inclusion and exclusion criteria will be eligible for participation in this study.

6.2 Inclusion Criteria

1. Age 10-17—inclusive
2. Weight ≥40 kg, so as not to require mg/kg based dosing
3. Meets International Classification of Headache Disorders III beta[1] criteria for migraine in children/adolescents (international standard diagnostic criteria for research)
4. Lives in the state of California- to allow shipping of study medication from our pharmacy
5. Has at least one parent who speaks English—in order to ensure good communication with study team by phone
6. Has daily access to a smartphone in order to provide daily headache diary data
7. A Parent/Guardian consents and the adolescent is cognitively capable of giving assent to participate
8. Either not on a migraine preventive medication, or if on one the dose has been stable for at least 4 weeks prior to enrollment, or are willing to wait to start the study until they have reached a stable dose for 4 weeks
9. Willing to not use OTC melatonin or change migraine preventives during the trial
10. Has ≥1 headache day per week, or 4-28 days of headache in a 28-day period
    Episodic headaches have been present for a minimum of 6 months—This lowers the likelihood of a secondary cause of headaches

6.3 Exclusion Criteria

1. Continuous headache
2. History of seizures/epilepsy
3. Pregnant/lactating
4. Concomitant opioid or barbiturate overuse, wherein overuse is defined as ≥4 days per month of barbiturate containing compounds, ≥10 days per month of opioid containing compounds as these may impact sleepiness scales
5. If in the investigator's opinion there is a medical or psychiatric concern that makes them think the participant should not participate
6. Inability to swallow pills after teaching and practice
   History of nocturnal asthma, as evidenced by a having a diagnosis of asthma and symptoms that manifest as nighttime awakening due to cough, wheeze, and/or shortness of breath

Randomization Criteria:

1. Had 4-28 migraine/migrainous days in the 28-day period of weeks 5-8 of single-blind placebo treatment phase, but not continuous headache.

2. At least 80% compliance with headache diary (i.e. at least 23 headache diary days) during weeks 5-8 of single-blind placebo treatment phase.

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new preventive therapies.

7.1 Allowed Medications and Treatments:

As stated in the exclusionary criteria above, subjects can use their usual acute headache medications as long as there is not medication overuse (defined above). All other medications are acceptable.

7.2 Prohibited Medications and Treatments:

Overuse of acute headache medications, wherein medication overuse is defined as ≥4 days per month of barbiturate containing compounds and/or ≥10 days per month of opioid containing compounds.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

Randomization: 1:1:1 to melatonin 3 mg: 6 mg: placebo. Randomization will be done in blocks of 6 by site. A computer-generated scheme will be used to generate the randomization.

8.2 Blinding

Due to the objectives of the study, the identity of test and control treatments will not be known to investigators, research staff, or patients. The two melatonin doses and the placebo will be indistinguishable in terms of color, appearance, taste, and smell.

During the study, the blind may be broken **only** in emergencies when knowledge of the patient's treatment group is necessary for clinical patient management.

The study blind will be broken on completion of the clinical study and after the study database has been locked.

8.3 Formulation of Test and Control Products

8.3.1 Formulation of Test Product

The drug product is a commercial melatonin 3 mg tablet that is lawfully marketed in the U.S. by Nature's Bounty. The commercial label is attached to this application. For the purpose of blinding, Safeway Pharmacy will over-encapsulate the tablets using a microcrystalline cellulose filler. We will not make any other changes of any kind to the finished marketed Nature's Bounty melatonin product. We do not think that overencapsulating this melatonin product will effect absorption and we have discussed this with the study pharmacist. While it is possible that absorption will be somewhat slower than with the under the tongue method, we do not think this is problematic as we

do not think speed of absorption of melatonin will have a role in its efficacy as a migraine preventive.

Those assigned to placebo will take 1 placebo capsule nightly. Those assigned to melatonin 3 mg will take one capsule nightly (will contain 1 x 3 mg tablet). Those assigned to melatonin 6 mg will take 1 capsule nightly (will contain 2 x 3 mg tablets).

	Study Drug	**Placebo**
Active Ingredient, mg/mL	3.36mg melatonin (as per labdoor.com analysis—attached)	N/A
Other ingredient, mg/mL	Mannitol, Crospovidone, Vegetable Stearic Acid, Natural Cherry Flavor, Beet Juice Color, Malic Acid, Sucralose, Vegetable Magnesium Stearate, Microcrystalline cellulose	Microcrystalline cellulose

8.3.2 Formulation of Control Product

Safeway Pharmacy will make matching placebos capsules using the same gelatin capsules and microcrystalline cellulose filler. They will be visually indistinguishable from the over-encapsulated Nature's Bounty melatonin product.

8.3.3 Packaging and Labeling

Preparations (both active and placebo) will be packaged in white HDPE (high density polyethylene plastic) vials topped with cotton balls.

8.4 Supply of Study Drug at the Site

8.4.1 Dosage/Dosage Regimen

Participants will take the study drug (either 3 mg melatonin, 6 mg melatonin or placebo) at night one hour before bedtime (approximately 21:00 hours).

8.4.2 Dispensing

A medication bottle will be given to participants at the enrollment visit for the single blind placebo phase. For those eligible to continue to the 8-week double blind phase, the pharmacy will ship the final study drug bottle to the participant's home.

8.4.3 Administration Instructions

Participants will take the study drug (either 3 mg melatonin, 6 mg melatonin or placebo) orally at night one hour before bedtime (approximately 21:00 hours).

8.4.4 Storage

Pharmacy storage – the pharmacy is capable of monitoring temperature ranges via digital USB data loggers that can track humidity, temperature, and dew point. These reports can be regularly downloaded, printed for record, and monitored for consistency.

Storage at participants' homes—Study drug should be stored at the participants' homes at room temperature, 15 to 30ºC (59 to 86ºF). High humidity and high temperatures should be avoided.

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 PI will verify these documents throughout the course of the study. In the daily headache diary, participants will also self-report whether they took the study drug that evening. Staff will be able to monitor this real time.

8.6 Measures of Treatment Compliance

Subjects will be asked to complete a daily headache diary and will be asked whether they took the study medication that evening. The diaries will be monitored by study staff. Also, a manual pill count will be performed after each phase of the study.

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/guardian. Assent from the participant must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at 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, gender, race) will be recorded at screening.

9.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent respiratory history, and information regarding underlying diseases will be recorded at screening.

9.1.4 Physical Examination

A physical examination will be performed by either an investigator or a sub-investigator at the screening visit.

9.1.5 Vital Signs

Body temperature, blood pressure, and pulse will be performed after resting for 5 minutes.

9.1.6 Adverse Events

Information regarding occurrence of adverse events will be captured throughout 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).

9.2 Clinical Laboratory Measurements

9.2.1 Pregnancy Test

A urine pregnancy test will be obtained from female subjects who are of childbearing age and have had their first menstrual period, prior to their participation in the study.

10 EVALUATIONS BY VISIT

10.1 Visit 1 (Screening and Enrollment, Day 1)

We will do a one-time enrollment visit at either UCSF or UCLA.

Consent/assent: At the start of an enrollment visit, potential subjects and their parent/guardian will be told about the study by a study investigator and/or study coordinator and will be provided with an informed consent document to review. For 12-17 year-olds, the informed consent document is addressed to the adolescent and is to be signed by both the adolescent and their parent/guardian. For 10-11 year-olds, the parent will sign the consent form and the participant will be provided with a simplified assent document. For this group the participant's assent will be documented by a study team member. Participants and parents/guardians will be given the opportunity to ask questions and have them answered to their satisfaction before deciding whether to participate. Consent and HIPPA can be signed with paper/pen or via DocuSign.

Enrollment visit data:

The enrollment visit data will be entered directly into the study database during the enrollment visit. Demographic and logistical information will be collected including name, age, sex, race/ethnicity, shipping address, participant smartphone number, parent smartphone number, and best times for follow-up calls. A pediatric headache neurologist will review the headache history to ensure the participant meets ICHD criteria for migraine with or without aura and will review the current medication list and past medical history. We will measure weight, blood pressure, pulse, and respiratory rate. There will be a general medical examination and a neurologic examination. Girls who have had their first period will undergo a urine pregnancy test. Baseline assessment of the PedMIDAS score and CASQ score will be assessed. Participants will be taught how to use the headache diary on their smartphone. They will be given the study medication for the single-blind placebo treatment phase and instructed to take study medication 1 hour before bedtime**.**

10.2 8-week single-blind placebo treatment phase (Weeks 1-8):

Participants will take the study medication nightly and complete a headache diary nightly. A text message will be sent from the study database each evening to remind them to do

these two tasks, and to provide a link to their headache diary. If they do not complete the headache diary, a reminder text will be sent the next morning. If they do not complete the headache diary for three days in a row, a study staff member will call to check in and remind them to do it and answer any questions. There will be a scheduled check in call at the four-week mark and again at the 8-week mark. If they provide headache diary data on ≥80% of days in each 28-day period, they will receive a $5 gift card each month. Once they have completed the 8-weeks of placebo treatment, they will return their study medication in a self-addressed envelope via FedEx.

10.3 Assessment of randomization eligibility (Day 57):

If the participant meets randomization criteria, the study pharmacy (Safeway) will be notified by study staff and the study pharmacy will review the randomization scheme to assign treatment and will enter this data into the study database. The study medication will be shipped to the participant's shipping address via FedEx.

Study staff will track the shipment via FedEx's tracking number on their website. Once the package shows as delivered, study staff will enter this information into the study database and a text message will be sent to the parent's smartphone asking them to confirm receipt of the study medication. The date the parent confirms receipt of the study medication will be day 1 of the randomized treatment phase.

10.4 8-week randomized treatment phase (Weeks 9-16):

Participants will take the study medication nightly and complete a headache diary nightly. A text message will be sent from the study database each evening at 9:00 PM to remind them to do these two tasks, and to provide a link to their headache diary. If they do not complete the headache diary, a reminder text will be sent the next morning. If they do not complete the headache diary for three days in a row, a study staff member will call to check in and remind them to do it and answer any questions. There will be a scheduled check in call at the four-week mark and again at the 8-week mark. If they provide headache diary data on ≥80% of days in each 28-day period, they will receive a $5 gift card each month. Once they have completed the 8-weeks of treatment, they will return their study medication in a self-addressed envelope via FedEx.

10.5 Study completion (Day 113):

At the end of the 8-week randomized treatment phase there will be a study completion phone visit. We will again assess the PedMIDAS and CASQ scores. We will query for adverse events, and will solicit participant and parent feedback on the study design. We will remind participants to mail back the study medication bottle using the self-addressed FedEx envelope, and once this is received we will perform both a manual pill count and compare to the self-report count in their 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 or of greater severity or frequency than expected.

The study team will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), 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:

2. death
3. a life-threatening adverse experience
4. inpatient hospitalization or prolongation of existing hospitalization
5. a persistent or significant disability/incapacity
6. 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 IRB Guidelines. The collection period for all SAEs will begin after informed consent is obtained, after study drug is administered for at least one dose, and will end after procedures for the final study visit have been completed.

All serious and non-serious adverse events will be collected in an adverse event reporting form. This information will be supplied to the Data Safety Monitoring Board (DSMB) and all adverse event information will be summarized and published in the final study publication.

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 and DSMB per UCSF IRB guidelines.

During the study, safety will be monitored by a 3-member Data Safety Monitoring Board (DSMB) which will be led by a pediatric headache specialist. The DSMB will review all study procedures before the initiation of the study. They will have the full and final authority to stop the study for any safety concern at any point. They will also review study data at the midpoint of the study, and at any subsequent interval that they recommend. Interim reports to the DSMB will be blinded to treatment status, though the DSMB may request unblinded information from the investigators at any time for any reason. Reports to the DSMB will be prepared by a UCSF Dept of Epidemiology and Biostatistics faculty member who is not otherwise involved in the study and who will not communicate with the study investigators regarding any aspect of the DSMB reports.

Serious and unexpected adverse events associated with the use of the study drug or procedures will be reported to the IRB and DSMB with subsequent follow-up submission of a detailed written report in accordance with the respective policies and procedures of the IRB. http://irb.ucsf.edu/adverse-event

Written IND Safety Reports will be submitted to the FDA as soon as possible and, in no event, later than 15 calendar days following the investigator-sponsor's receipt of the respective adverse event information.

The FDA will be notified by telephone or facsimile transmission of a human adverse event that is fatal or life-threatening no later than 7 calendar days after receiving the respective human adverse event information, followed by the subsequent submission of a written IND Safety Report

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 or investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Positive pregnancy test (females)
- If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should be encouraged to complete all remaining scheduled visits and procedures.

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

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

If the study (in part or in entirety) is discontinued for any reason, the UCSF sponsor-investigator will notify all other investigators, sub-investigators and study staff within FDA guidelines. Since melatonin at 3mg and at 6mg can be stopped without weaning, there will be no further data collected to ensure subject safety. If part of the study is discontinued, subjects will be reconsented with an updated consent as soon as it is approved by the IRB. All parts of the study that have been discontinued will be ended within FDA guidelines.

12.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject or the investigator, thinks 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.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

12.3 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 and in the Investigator's files.

14 STATISTICAL METHODS AND CONSIDERATIONS

14.1 Data Sets Analyzed

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

Dr. Gelfand will analyze the data using STATA. As a UCSF KL2 Scholar, she will have assistance from the UCSF Dept. of Epidemiology and Biostatistics faculty and CTSI consulting services as needed for statistical issues.

14.2 Demographic and Baseline Characteristics

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

14.3 Analysis of Primary Endpoint

Primary outcome: Number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between melatonin (combined 6 mg+3mg) vs. placebo. We will control for baseline migraine/migrainous day frequency in the 5-8th week of the single-blind treatment phase and use an ANCOVA analysis.

Definition of migraine/migrainous day:

1) Patient had a moderate or severe headache and took a migraine-specific medication (triptan or ergot)
2) Patient had a moderate or severe headache; headache lasted for at least 2 hours, and
    a. At least one of the following was present (throbbing quality, movement sensitivity, or unilateral/bilateral location) AND
    b. At least one of the following was also present (photophobia, phonophobia, nausea or vomiting)

14.4 Analysis of Secondary Endpoints

Secondary outcome measures will include ≥50% responder rates, tolerability (as measured by CASQ scores), and need for use of acute headache medications. Safety and tolerability data will be summarized by treatment group. Adverse event rates will be coded by body system. 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.

Secondary outcomes:

(We will control for the baseline level of these outcomes in all of these analyses)

Effectiveness secondary outcomes:

1. Number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between **melatonin 3 mg vs. placebo.**

2. Number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between **melatonin 6 mg vs. placebo.**
3. Number of migraine/migrainous days in the 5th-8th weeks of randomized treatment between **melatonin 3 mg vs. 6 mg.**
4. Mean headache days in 5th-8th randomized phase in melatonin (combined) vs. placebo, (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using t-tests).
5. Mean acute medication use days in 5th-8th randomized phase in melatonin (combined) vs. placebo, (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using t-tests).
6. Mean PedMIDAS score (continuous) in 5th-8th randomized phase in melatonin (combined) vs. placebo, (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using t-tests).
7. ≥50% responder rate in 5th-8th randomized phase in melatonin (combined) vs. placebo (Chi-square or Fisher's exact (if needed), (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using Chi-square (or Fisher's exact)).

Safety outcomes:

1. Proportion with adverse events between groups
    a. Proportion with serious adverse events between groups
    b. Proportion of adverse events thought to be related to the study treatment
2. Mean Sleepiness score in 5th-8th randomized phase in melatonin (combined) vs. placebo, (followed by melatonin 3 mg vs. placebo, melatonin 6 mg vs. placebo, and melatonin 3 mg vs. melatonin 6 mg using t-tests).

Trial design assessment outcome:

1. Proportion of participants on melatonin who correctly guessed they were on it (just playing chance, 66% should guess melatonin)
2. Proportion of participants on melatonin who guessed their dose correctly (by chance 50% 3 mg, 50% 6 mg).
3. Proportion of participants on placebo who correctly guessed they were on placebo (by chance, 33% should guess this)
4. The same three above but with investigators guessing.

14.5 Interim Analysis

We are not currently planning an interim analysis.

14.6 Sample Size and Randomization

To detect a difference of 1.1 migraine/migrainous days (SD 1.8) between groups, as was seen in the adolescent topiramate migraine prevention trial that led to FDA-approval of that agent in 12-17 year-olds, we need outcome data on 42 participants/arm. We anticipate that 25% of enrolled participants will be screened out by the single-blind placebo run-in process, and that 85% of those who randomize will complete the trial. Therefore we will enroll 70 per arm, or *n*=210 total.

15 DATA COLLECTION, RETENTION AND MONITORING

15.1 Data Collection Instruments

The UCSF and UCLA Investigators will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change. A copy of the CRF will remain at the site at the completion of the study.

The UCSF and UCLA Investigators are responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study will be reviewed and verified for completeness and accuracy by each site's Investigators.

After recruitment begins, a monthly call or teleconference between the study team will occur to update each site on the status of the study. A shared, de-identified, password-protected spreadsheet will keep a record of each site's enrollment numbers, screen fails, Serious and other Adverse Events. Email and pager numbers will be shared from each site in order to communicate in the event of an emergency. Annually, the UCSF study team will travel to UCLA to perform a detailed data and safety review.

15.2 Data Management Procedures

The data will be entered into a validated, HIPAA compliant database. The Data Management group 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. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

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.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Investigators must make study data accessible to the IRB/IEC, 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, Bill of Rights, Assent Form and copies of all source documentation related to that subject. The Investigators 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 will be conducted by the PI and study staff. Additionally, we will request an annual review of the data to be conducted by the UCSF Quality Improvement Unit within the UCSF Human Research Protection Program.

http://irb.ucsf.edu/routine-site-visits-and-directed-investigations

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.

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 or on a password protected computer. 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 UCSF sponsor-investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval and FDA notification if applicable, 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.

The Sponsor will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change to a Phase 2 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of Phase 2 clinical protocol changes requiring the submission of a Protocol Amendment include:

- Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
- Any significant change in the design of the protocol (such as the addition or deletion of a control group).
- The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor the safety of the investigational drug.

16.2 Institutional Review Boards and Independent Ethics Committees

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

Any documents that the IRB/IEC 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/IEC. The IRB/IECs 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/IECs unconditional approval statement will be transmitted 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/IEC 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/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC 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 Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the IRB/IEC. The consent form generated by the Investigator must be approved by the IRB/IEC. 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. The Investigator keep an IRB/IEC-approved copy of the Informed Consent Form for the study file.

A properly executed, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects (or their parent/guardian/legal representative) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, 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 subjects or the parent/guardian/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 the PI. 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 IRB, 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 IRB 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 as required.
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 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.

17.0 REFERENCES:

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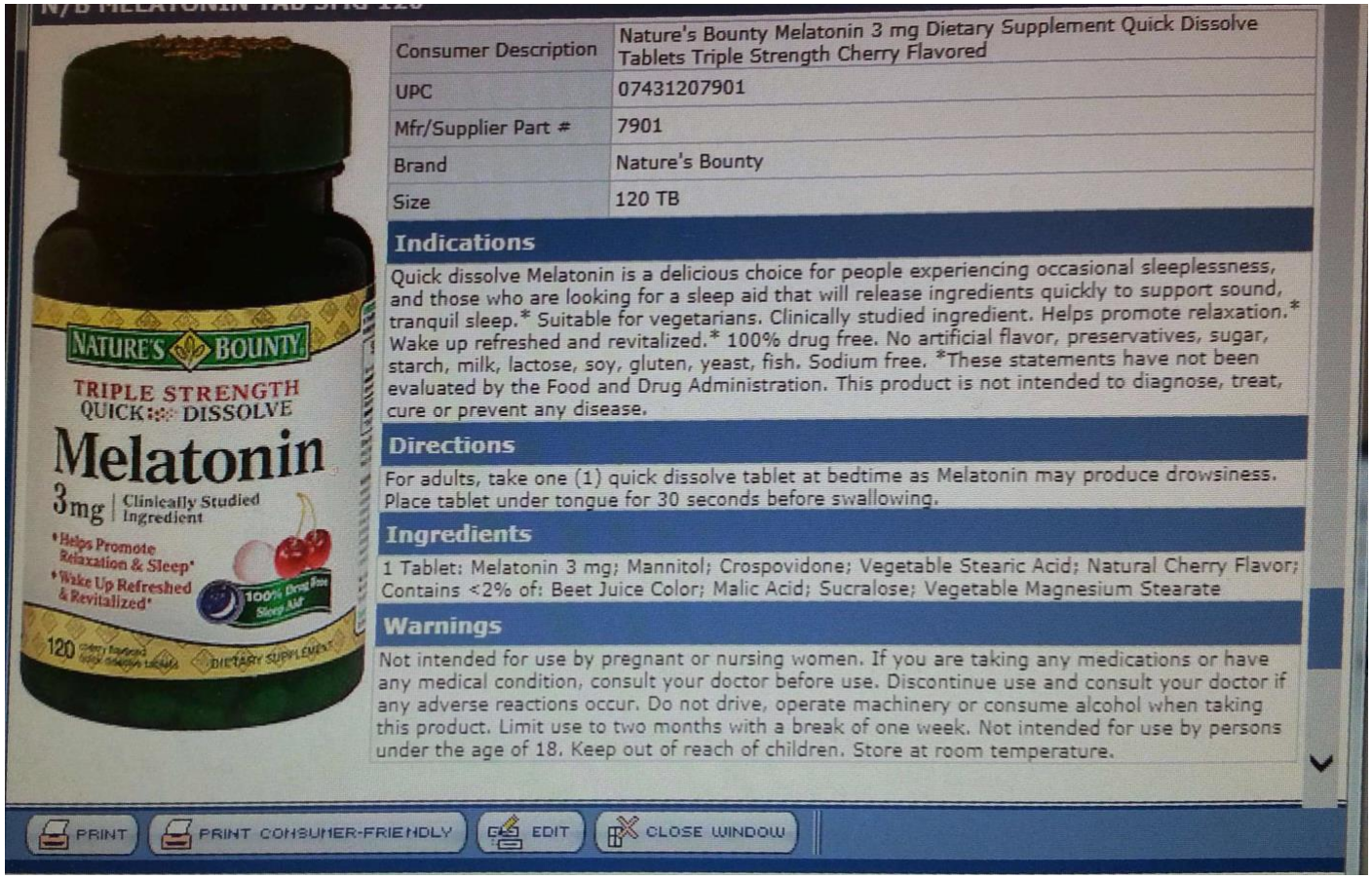
APPENDIX 1. SCHEDULE OF STUDY VISITS

	VISIT 1 (Enrollment, Day 1)[a]	VISIT 2 PHONE CALL (After 4 weeks on placebo)[a]	VISIT 3 PHONE CALL (After 8 weeks on placebo)[a]	VISIT 4 PHONE CALL (After 4 weeks in active phase)[a]	VISIT 5 PHONE CALL (After 4 weeks in active phase)[a]
Informed Consent	**X**				
Medical History	**X**				
Complete Physical Exam	**X**				
Height	**X**				
Weight	**X**				
Vital Signs	**X**				
Pregnancy Test (Urine)	**X**				
Randomization			**X**		
Dispensing or Administration of Study Drug	**X**		**X**		
Counting of Returned Study Drug			**X**		**X**
Initiate Subject Diary	**X**				
Subject Diary Review		**X**	**X**	**X**	**X**
Concomitant Medication Review	**X**	**X**	**X**	**X**	**X**
Adverse Experiences		**X**	**X**	**X**	**X**

[a] ±3 business

APPENDIX 2. Nature's Bounty Melatonin 3mg Label



APPENDIX 3. Safeway Compounding Pharmacy

Safeway Compounding Pharmacy

PCAB ACCREDITED Compounding Pharmacy A SERVICE OF ACHC

Phone: 408-227-1098
Toll Free: 844-448-2291
Fax: 408-227-1206
www.SafewayCompounding.com

NABP NATIONAL ASSOCIATION OF BOARDS OF PHARMACY

Safeway Compounding Pharmacy is a state-of-the-art fully licensed and PCAB Accredited compounding facility. We bill most major insurance companies and ship free of charge.

We are honored to be among the few compounding pharmacies in the nation who have achieved PCAB Accreditation® as it further sets us apart from other compounding pharmacies. Currently less than 3% of compounding pharmacies in the nation have earned this status.

What is PCAB Accreditation?
PCAB Accreditation® is a system of national standards created by industry experts designed to continually monitor and improve quality through standardized process control. Our new status ensures we have undergone the profession's most rigorous review and inspection measures.

Please call us. We will be happy to help you with your compounding needs.

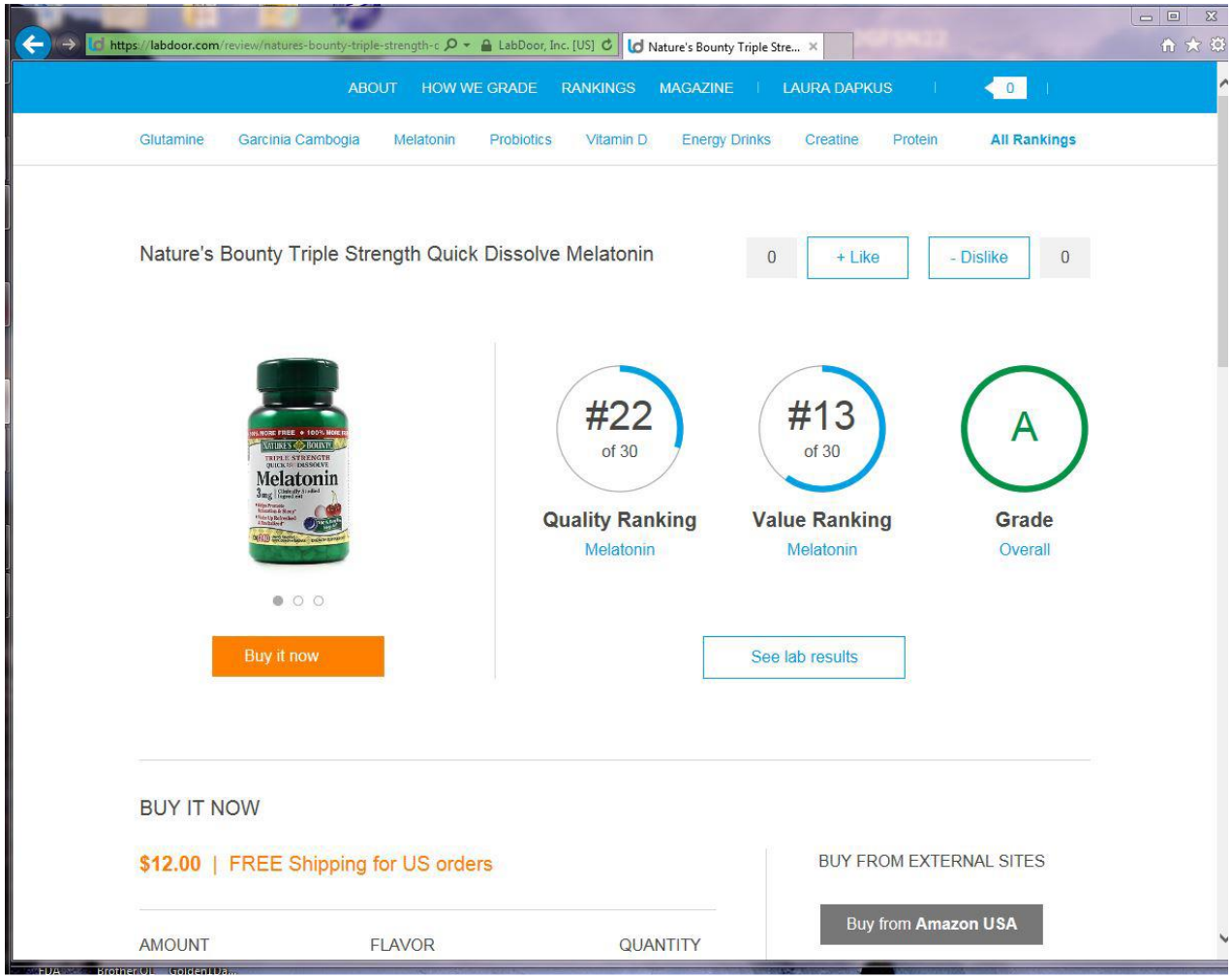
Phone: 408-227-1098
Toll Free: 844-448-2291
Fax: 408-227-1206
Email: Compounding@Safeway.com

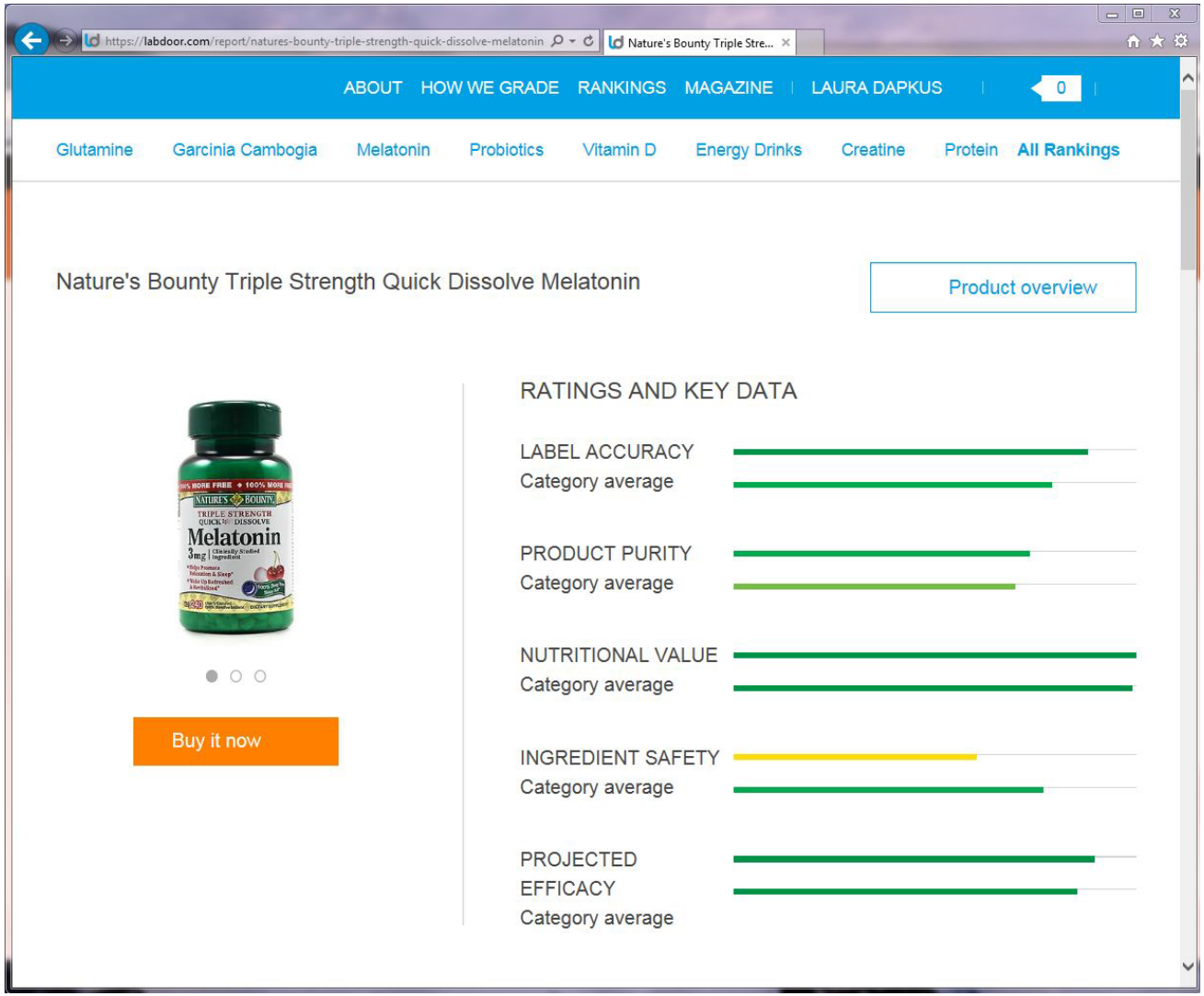
Monday - Friday 8 - 5 PST

NOTE: While we do not offer any walk-in services, new prescriptions can be dropped off by your patients at their local Safeway Pharmacy, or called/faxed by their provider

FREE SHIPPING ON ALL PRESCRIPTIONS

APPENDIX 4. Labdoor Safety Review

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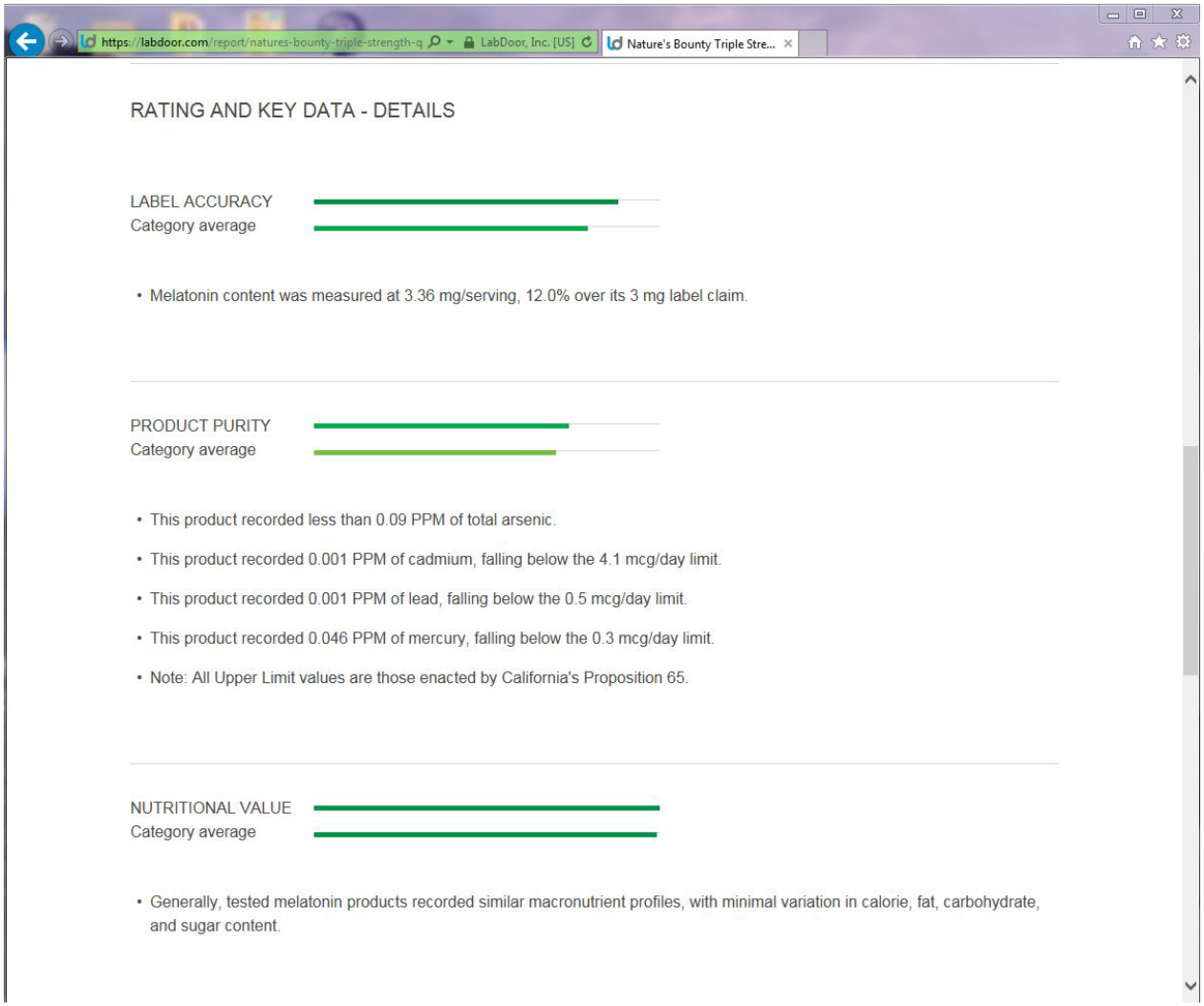
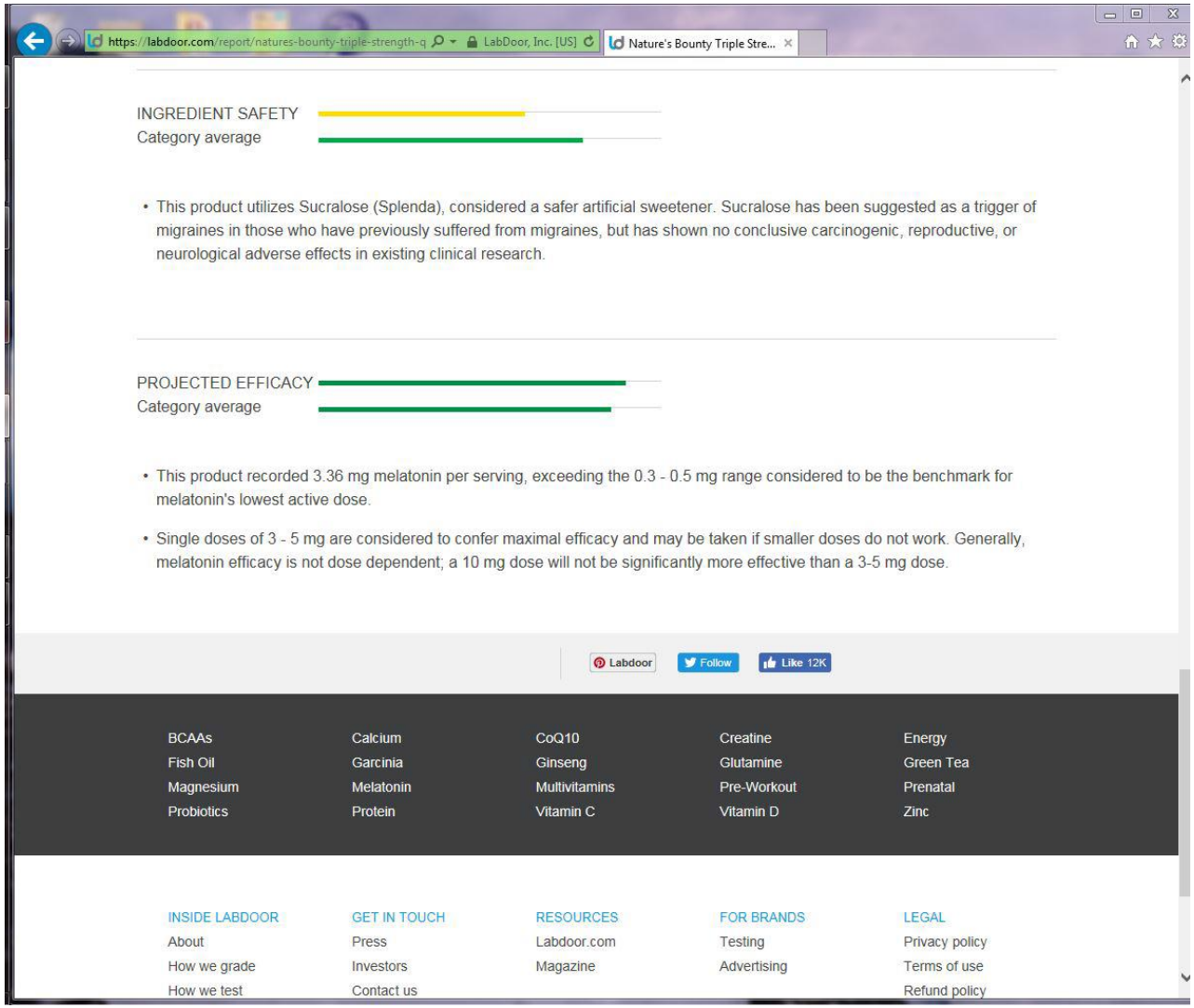
Nature's Bounty Triple Stre...
ABOUT
HOW WE GRADE
RANKINGS
MAGAZINE
LAURA DAPKUS
0
Glutamine
Garcinia Cambogia
Melatonin
Probiotics
Vitamin D
Energy Drinks
Creatine
Protein
All Rankings
Nature's Bounty Triple Strength Quick Dissolve Melatonin
Product overview
Melatonin
Buy it now
RATINGS AND KEY DATA
LABEL ACCURACY
Category average
PRODUCT PURITY
Category average
NUTRITIONAL VALUE
Category average
INGREDIENT SAFETY
Category average
PROJECTED EFFICACY
Category average


https://labdoor.com/report/natures-bounty-triple-strength-q
LabDoor, Inc. [US]
Nature's Bounty Triple Stre...
RATING AND KEY DATA - DETAILS
LABEL ACCURACY
Category average
• Melatonin content was measured at 3.36 mg/serving, 12.0% over its 3 mg label claim.
PRODUCT PURITY
Category average
• This product recorded less than 0.09 PPM of total arsenic.
• This product recorded 0.001 PPM of cadmium, falling below the 4.1 mcg/day limit.
• This product recorded 0.001 PPM of lead, falling below the 0.5 mcg/day limit.
• This product recorded 0.046 PPM of mercury, falling below the 0.3 mcg/day limit.
• Note: All Upper Limit values are those enacted by California's Proposition 65.
NUTRITIONAL VALUE
Category average
• Generally, tested melatonin products recorded similar macronutrient profiles, with minimal variation in calorie, fat, carbohydrate, and sugar content.


https://labdoor.com/report/natures-bounty-triple-strength-q
LabDoor, Inc. [US]
Nature's Bounty Triple Stre...
INGREDIENT SAFETY
Category average
• This product utilizes Sucralose (Splenda), considered a safer artificial sweetener. Sucralose has been suggested as a trigger of migraines in those who have previously suffered from migraines, but has shown no conclusive carcinogenic, reproductive, or neurological adverse effects in existing clinical research.
PROJECTED EFFICACY
Category average
• This product recorded 3.36 mg melatonin per serving, exceeding the 0.3 - 0.5 mg range considered to be the benchmark for melatonin's lowest active dose.
• Single doses of 3 - 5 mg are considered to confer maximal efficacy and may be taken if smaller doses do not work. Generally, melatonin efficacy is not dose dependent; a 10 mg dose will not be significantly more effective than a 3-5 mg dose.
Labdoor
Follow
Like 12K
BCAAs
Calcium
CoQ10
Creatine
Energy
Fish Oil
Garcinia
Ginseng
Glutamine
Green Tea
Magnesium
Melatonin
Multivitamins
Pre-Workout
Prenatal
Probiotics
Protein
Vitamin C
Vitamin D
Zinc
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