Evaluation of the impact of the HLNatural, Inc. Tension Relief product on the reduction of symptoms in adults who suffer from mild to moderate tension headaches

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Sponsored by:
HLNatural, Inc.

Principal Investigator:
Soyona Rafatjah, MD

Version Number
Version 1.1

Day Month Year

July 17, 2019

Statement of Compliance

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- *U.S. Code of Federal Regulations applicable to clinical studies (45 CFR 46)*
- *ICH GCP E6*
- *Completion of Human Subjects Protection Training*
- *NIH Clinical Terms of Award*

Refer to:

https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/45-cfr-46/index.html
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator:

Signed: _____ Date: _____

Name

Project Manager:

Signed: _____ Date: _____

Name

Sponsor:

Signed: _____ Date: _____

Name

Statistician

Signed: _____ Date: _____

Name

Title: Evaluation of the impact of the HLNatural Tension Relief product on the reduction of symptoms in adults who suffer from mild to moderate tension headaches.

Population: The study will consist of at least 200 participants who self-identify as satisfying the inclusion criteria. The geography of participant enrollment will be spread across the United States.

Number of Sites: This is a single (virtual) site study.

Study Type **Single site, prospective, one arm observational study of Minimal Risk.**

Study Duration: The duration of the study is expected to be 6 months depending on the speed of enrollment.

Participant Duration: The duration of participation for each participant is expected to be 60 days.

Objectives: The purpose of this study is to demonstrate whether this herbal remedy will reduce the severity of symptoms of tension headache. This trial will gather data on performance of the product. These data will be used to describe the performance currently, and potentially to design a two-arm trial in the future.

Primary Endpoints:

- The primary endpoint is reduction in tension headache severity. There is no control group for the primary analysis.

Secondary Endpoints:

- The time to other intervention will be analyzed.
- A longitudinal analysis will be performed for patients who report on more than one incident of tension headache.
- Comparison against the participant's normal behavior.
- Net Promoter Score.
- Adverse events will be summarized.
- An additional data presentation will consist of results from both Treatment and Control in similar studies appearing in the literature. There will be no formal statistical comparison of results from this study and historical studies.

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1 KEY ROLES

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2 Background Information and Scientific Rationale

2.1 Background Information

The primary hypothesis of the present study is that supplementation with the Tension Relief test product will reduce the severity of symptoms of a tension headache.

A tension headache is generally a diffuse, mild to moderate pain in your head that's often described as a dull, aching head pain that feels like a tight band around your head. They can be episodic or chronic in nature. They are the most common type of primary headaches and affects approximately 80% of the population. Because of its high prevalence, the socio-economic consequences of tension type headache are significant as they are associated with increased depression, anxiety, insomnia and overall decrease in quality of life. [4] In one population study, persons with episodic tension type headache reported a mean of nine lost work days and five reduced-effectiveness days, while persons with chronic tension type headache reported a mean of 27 lost work days and 20 reduced-effectiveness days.[17] The burden is particularly high for the minority who has substantial and complicating co-morbidities. [18]

The two main therapeutic avenues of tension type headache are acute and prophylactic treatment. Simple or combined analgesics are the mainstay of acute treatment. Prophylactic treatment is needed in case of attacks that are frequent and/or difficult to treat. [4]

All efforts to develop nonsteroidal anti-inflammatory drugs (NSAIDs) which are devoid of gastrointestinal and cardiovascular system effects are still far from achieving a breakthrough. In order to avoid medications but still receive treatment for pain, there has been some existing research completed, demonstrating effective all natural solutions, such as sublingual feverfew/ginger as a first-line abortive treatment for a population of migraineurs who frequently experience mild headache prior to the onset of moderate to severe headache. [11, 3]

Consequently, HLNatural was formed to create an all-natural, herbal remedy product that is designed to avoid unnecessary synthetics, sweeteners, and preservatives found in over the counter remedies today while still providing safe and effective relief. Tension Relief test product is a plant-based remedy formulated with herbal and mineral ingredients with reported potential to reduce symptoms of a tension headache. The products combine ingredients previously reported as potentially beneficial into an easy-to-consume capsule designed for intake up to three times per day. The test product is 1) Magnesium Glycinate, 2) Boswellia (40% Boswellic Acid), 3) White Willow Bark (15% Salicin), 4) Skullcap, 5) Feverfew, 6) a vegetarian capsule made of cellulose and water, and 7) Rice Hull Concentrate. Below, the 7 ingredients of the test product are listed. All ingredients are Generally Recognized as Safe (GRAS) by the FDA.

Tension Relief

Active Ingredients: Magnesium (as Magnesium glycinate), Boswellia (40% Boswellic acids), White Willow Bark (15%Salicin), Skullcap, Feverfew.

Inactive Ingredients: Vegetarian capsule (vegetable cellulose, water), Rice Hull Concentrate.

The ingredients in the Tension Relief test product have been included because they are potentially beneficial in promoting both head and body comfort. The justifications for their inclusion are briefly described here:

Magnesium is an important mineral in the body that acts as a cofactor to many physiological processes, and it is estimated that the majority of Americans do not get enough from the diet. Scientific investigation has confirmed that Magnesium improves cognition, promotes comfort, while also increasing calmness and energy. For example, in a clinical study of 78 people magnesium supplementation resulted in both significantly increased head comfort, but also increased brain energy. [16]

Boswellia is also known as guggle or frankincense. Boswellia has had mounting scientific research which confirms its use for a number of pain-relieving conditions. This is mainly due to its confirmed activity of promoting cytokine balance and comfort. Boswellia extracts have gained attention additionally because their mechanism of action is entirely different than that of the NSAIDs. The Boswellic acids inhibit the enzyme 5-LOX (5 lipoxygenase), thereby reducing inflammatory signaling molecules. Clinical trials have shown efficacy for promoting comfort and cytokine balance in different body systems. For example, one clinical study found Boswellia to promote long-lasting head comfort. Several other clinical studies found Boswellia to promote both joint comfort and cytokine balance. [6, 9, 11, 20]

White Willow Bark is included for its ability to promote both head and body comfort. Although White Willow Bark is famous as being a source of salicylates, from which salicylic acid and Aspirin are produced, its activity is thought to not be due to just this component. White Willow Bark extract also contains other phytochemicals, such as antioxidant flavonoids and bioactive tannins, which are thought to play a synergistic role in promoting cytokine balance and head and body comfort. For example, an extract of willow bark was found to inhibit cyclooxygenase (COX)-2 mediated prostaglandin release, but not directly affect COX-1 or COX-2 activity. Additionally, constituents other than salicin have been found to prevent prostaglandin and cytokine release. Several clinical studies have found White Willow Bark to have beneficial effects while being tolerated much better than Aspirin. For example, in a Cochrane systematic review of studies, White Willow Bark (standardized to 120-240 mg salicin) was found to significantly promote comfort in the short-term compared to placebo. [2, 15, 21, 22, 23, 24, 25]

Skullcap is an herb belonging to the herbal class of plants called “nervines”, or tonics for the central nervous system. Generally, nervines are known to promote feelings of calm and relax the body and mind. Skullcap has an herbal history for the use of a number of tension-related conditions, including tension felt in the head. Its inclusion in Tension Relief promotes feelings of calm, while also promoting comfort. For example, in a clinical study involving healthy volunteers (with a low amount of tension), Skullcap was found to significantly enhance global mood. [7, 26, 27]

Feverfew is a well-known herb used for head comfort. This plant which produces masses of cheery white daisies has long been used for promoting head comfort and cytokine balance. Clinical studies have shown Feverfew to not only promote head comfort, but also reduce sensitivity to light and noise, and improve quality of life in some people. [3, 10, 28, 29, 30]

2.2 Scientific Rationale

This test product was designed based on promising clinical research evaluating utilization of natural ingredients to safely impact the symptoms of tension headaches. While the evidence to support the use of these individual active ingredients is growing, well-designed human clinical trials showing benefit are necessary to demonstrate efficacy of the test product's unique formulation.

Thus, the present study will include at least 200 patients who suffer the symptoms of mild to moderate tension headaches and will observe the level of symptoms reduction in this population after consuming the test product.

2.2.1 Potential Risk

Minimal risk is foreseen for participants through their participation in the study. All the ingredients composing the test product are Generally Recognized as Safe (GRAS) by the FDA for daily consumption at their present concentrations.

The ingredients in the test product have shown to have some theoretical drug interactions which have been listed in the appendix. (*Appendix A)*

Potential side-effects have been observed in high doses which are significantly greater than the dose of the capsule as recommended in the instruction for use:

- Diarrhea
- Nausea
- Stomach Cramps
- Acid Reflux
- Skin Rashes
- GI Bleeding
- Headaches
- Liver Damage

This study is determined by Sponsor and Principal Investigator to be a Minimal Risk Study.

Minimal risk is defined by 45 U.S. Code of Federal Regulations (CFR) 46.102 (i) as follows:

"Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."

Refer to: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.102

2.2.2 Known Potential Benefits

As with all medications, over the counter and prescription remedies for tension headaches may have undesirable side effects. Additionally, these products are known to contain additives, dyes, fillers and other unnatural or synthetic ingredients that consumers are looking to avoid. As such, these consumers are seeking natural, plant-based alternatives for symptom relief. Research participants may benefit from the intervention by eliminating such unwanted side effects when treating their symptoms of pain and/or tension headache while achieving symptom relief. If the intervention is shown to be efficacious, this would provide a viable prevention option for others in the general population to decrease their need for drugs that contain undesired ingredients. Other benefits include detailed surveillance of symptoms and documentation of activities, routine medications and supplements that may provide participants and their regular physician or other healthcare provider with useful information for diagnosis and treatment of symptoms should they occur.

2.2.3 Minimization of Risks

Research participants will be carefully screened to meet enrollment criteria. Participants meeting exclusion criteria will not be enrolled. The study participant informed consent will be presented with clear description of the study requirements and opportunity to have questions answered before enrollment. Once an event occurs review of symptoms will be ascertained at 15 and 30 minutes for up to an hour. Reporting of adverse events will be reviewed routinely and in accordance with regulatory guidelines (21CFR, GCP) by the Principal Investigator. Participants with occurrence of worsening symptoms or adverse events should stop taking the test product and may seek medical attention and exit the study.

3 Study Objectives

Beyond the obvious physical symptoms, lifestyle impact related to tension headaches include decreased work productivity and lost work time [17, 18]. The purpose of the present study is to 1) evaluate the impact of the tension relief test product on the symptoms of tension headaches and functional status in adult men and women who suffer from mild to moderate tension headaches by using the 10-point Mankoski scale [19] and 2) the

subjective experience of these participants related to general health, symptoms of tension headaches, and personal experience with the products.

This will be evaluated based on the primary and secondary endpoints. These endpoints, the analysis populations, and their respective measures are described below. Further details on the methods for measuring the outcomes can be found in the Study Outcome Measures and Analysis Plan sections.

Primary Endpoint:
The primary endpoint is reduction in tension headache severity. Patients will be asked to rate headache on the 10-point Mankoski scale at 4 time points: prior to taking the product, 15 minutes after taking the product, 30 minutes after taking the product and 1 hour after taking the product. The improvement in symptoms from baseline will be evaluated on a pairwise basis separately for each time point. P-values will be computed for the improvement.

There is no control group for the primary analysis.

Secondary Endpoints:

- The time to other intervention will be analyzed.
- A longitudinal analysis will be performed for patients who report on more than one incident of headache.
- Comparison against the participant's normal behavior.
- Net Promoter Score.
- Adverse events will be summarized.
- An additional data presentation will consist of results from both Treatment and Control in similar studies appearing in the literature. There will be no formal statistical comparison of results from this study and historical studies.

4 Study Design

The present study will be a prospective, one arm observational study. Patients will begin taking the capsules at the onset of headache symptoms. Onset is defined as the time the participant takes the test product for relief of symptoms. When the participant decides to take the test product, they will report symptoms in the headache diary immediately before to taking the product and rate their symptoms on a 10-point Mankoski scale. After consuming the product, the participant will complete a Mankoski scale at 15 minutes, 30 minutes and 1 hour after taking the product. If needed the participant will be allowed to take alternative medication (alternative treatment) after an hour after taking the product. If alternative medication is taken, the participant will record this in their headache diary.

Study enrollment and management will be de-centralized, where participants do not visit an investigator or a clinic for clinical assessment. The participants will participate in the study at home.

All data collected from during this study will be reported by the patient via eCRFs, eDiary, and other electronic data entries. If a visit is required, it will be conducted via remote contact by telephone.

4.1 Test Product

Below are descriptions of the test products and their ingredients.

Tension Relief Product

Description: Combining Boswellia, Magnesium, Feverfew, Skullcap and White Willow Bark for multi-faceted effective, yet health-building head comfort. This formula is designed to promote comfort of the head and body in the short-term.

Active Ingredients: Magnesium (as Magnesium glycinate), Boswellia (40% Boswellic acids), White Willow Bark (15%Salicin), Skullcap, Feverfew.

Inactive Ingredients: Vegetarian capsule (vegetable cellulose, water) Rice Hull Concentrate.

4.2 Required Behavior

During the 1 hour after taking the test product, no medication or supplementation (including all CBD products) other than the test product should be taken. Once the 1-hour report has been submitted the patient may take other medications.

Patients are asked to limit the consumption of alcohol beverages to less than or equal to two drinks per day and to abstain from the use of cannabis for the duration of the study.

4.3 Participation Period

Participants are expected to participate in the study for 60 days after study start. The product may be used after each onset of tension headache, but not more often than three times per day. Patients will be discontinued from the study 60 days after study start or after three recorded headache episodes. Study start is defined as the day the participant received the test product and completed the receipt of test product form.

4.4 Data Collection

All data in the present study will be self-reported by the participant and collected via their online portal (Hawthorne Effect Study Visit Management System (HE VMS)). Participants will be asked to take the test product according to the instructions for use, complete study surveys and respond to study reminders during the course of the study. The instructions for use and study forms can be found in the appendix. (*Appendices B, D, E, F, G*)

5 Study Population

5.1 Selection of the study Population

The study population will consist of at least 200 adult patients who suffer from symptoms of tension headaches and who have completed the self-enrollment form and who meet the inclusion-exclusion criterion. The participants will otherwise be in good health.

The target sample size for this study is initially 200 participants, with a desired sample of 97 treated participants. This is described in detail in the Statistical Considerations section.

At such time as 180 participants have been enrolled, the available data will be analyzed using a constant hazard model to determine if it seems realistic that the desired number of 97 treated patients will be met by the end of follow-up. If the expected number of treated patients is less than 97, the target sample size will be increased as needed, considering both the desire for 97 treated participants and the timelines of the trial sponsor. The actual outcomes of treated participants will not be considered in this analysis, merely whether or not enrolled participants have reported starting using the test product.

Enrollment will be stopped once 200 patients have been enrolled, no further patients will be offered a place in the trial once the target sample size criteria has been met. All patients who have already been offered places, but who have not yet consented, will be allowed to participate as long as they have signed the study consent within 15 days and the total number of participants does not exceed 125% of the target (either 200 or the recomputed target if recomputation has been performed).

In order to ensure an age and sex distribution that is reasonably representative of the US population, enrollment may be stopped early in some age and sex groups.

Target population for this study are candidates who suffer from mild to moderate tension headaches.

Participants will be enrolled from across the United States. No participants will be enrolled outside of the United States. It is expected that the geographical distribution of the participants enrolled in the study will correlate with the geographical distribution of the general population across the United States.

Participants will be recruited via digital advertisements and social media.

After clicking on an advertisement, potential participants will then be directed to a website where they will complete a screening questionnaire (See *Appendix C*). The screening questionnaire will automatically qualify or disqualify them for study participation. If the participant qualifies, they will be provided an informed consent. Upon completion of the informed consent they will be deemed enrolled in the study.

5.2 Inclusion/Exclusion Criteria

Prior to being enrolled, participants will fill out a screening questionnaire. The screening questionnaire will automatically qualify or disqualify them for study participation. The full screening questionnaire can be found in the Appendix. (*Appendix C*)

Inclusion Criteria:

Adult candidates who are in overall good health and who suffer from mild to moderate tension headaches.

Participants will be deemed to be in good health if they do not report any of the existing medical conditions asked about in the screening questionnaire.

Exclusion Criteria:

- Those who have been diagnosed with migraine headaches.
- Those who score between 36-40 or 66-78 on screening questionnaire.
- Is < 18 years of age
- Women that are pregnant or breastfeeding.
- Alcohol consumption more than 10 drinks per week.
- Chronic renal disease
- Chronic liver disease
- Allergy to any of the following: Aspirin or any other product including Salicylates, Boswellia, Feverfew, Skullcap, White Willow Bark, Rice Hull, or Vegetable Cellulose.
- Unable to swallow pills.
- Unwilling to try test product for relief of pain and tension headache symptoms.
- Participants who are currently taking any anticoagulation medications daily. (Aspirin, Warfarin, Heparin etc.)

6 Study Evaluation

6.1 Study Procedures

- Potential participants will review information about the study and complete a screening form.
- During the screening process, the potential participant will be asked questions regarding their symptoms and medical history to ensure that they meet the requirements to participate in this study. Potential participants will also be asked questions to ensure that they do not meet any of the exclusion criteria and meet all of the inclusion criteria.
- After successful screening (participant does not meet any exclusion criteria), participants will review and sign study informed consent.
- Upon verification of signed informed consent, participant will be enrolled into the study.
- At time of enrollment, participant will be given access to the HIPAA compliant study portal.
    - The study portal provides access to study information, signed informed consent form, instructions for product use, frequently asked questions, study surveys, headache diary, and data collection tools.
- Participant shall complete baseline assessments upon access to the portal.
    - Baseline assessment will include questions regarding the participants' demographics, medications and detailed information regarding their headaches including treatment.
- To ensure that baseline assessments are completed before test product is used by the participant, study materials and study welcome package will be shipped to the participant once the clinical study manager/clinical ops coordinator confirms that the baseline assessment has been completed.
- The welcome package will include an information sheet that will outline instructions for their participation in the trial, the test product, and paper forms of the documents (paper form of study documents will be provided for real time data collection, in the event that the participant cannot log into the study portal to input data).
- Once the participant receives the test product, the participant will log into the study portal to acknowledge the receipt of the test product.
- Study start date will be the reported date of receipt of test product.
- Participant will be sent weekly email reminders that remind them of their participation in the study.
- At the onset of the headache, the participant will start a Headache Diary and complete a 10-point Mankoski pain scale.
    - Onset is defined as the time the participant takes the test product for relief of symptoms.
- After completing the surveys, the participant will take test product. The participant will take 2 capsules with 6-8 oz. of water per headache episode. With a max of 6 pills per day. (If participant takes 6 pills in 1 day this will be defined as 3 headache episodes and the patient will be exited from the study).
- After taking the test product, the participant will complete a Mankoski pain scale at 15 minutes, 30 minutes, and 1 hour after taking the test product.
- Once the participant's symptoms resolve, the participant will complete the headache diary.
- If the participant takes any other medication outside of the test product, the participant will record this on the headache diary.
- After taking the test product, the participant will be instructed to fill out an Adverse Event form for any side-effects experienced.
- After the first headache episode, the participant will be asked to complete the same process for another 2 headache episodes; however, these are not required.
- If the participant completes the required assessments for a total of 3 headache episodes, they will be prompted, by email, to exit the study.

- If the participant only completes the required assessments for the required 1 headache episode, the participant will be prompted, by email, to complete the study exit form and will be exited from the study on day 60 (60 days from the day of receipt of the test product).
- The sponsor nor Hawthorne Effect Inc. will not make any attempt to collect any unused product.
- Upon receipt of study exit survey and review of completed study forms, participant will receive an Amazon gift card of $25 via email.

6.2 Study Schedule of activities

Assessments	Screening	Consent	Before Receipt of Test Product	Product Received	Event 1	15 Minutes After Event Start	30 Minutes After Event Start	60 Minutes After Event Start
Study Window								
Screening Survey	X							
Consent		X						
Baseline Survey			X					
Demographics			X					
Medications & Supplements			X					
Acknowledgement of receipt of test product				X				
Headache Diary					X			X
10-point Mankoski Scale					X	X	X	X
Test Product Consumed					X			
AE Assessment					X	X	X	X
Study Exit Survey								

Assessments	**Event 2**	**15 Minutes After Event Start**	**30 Minutes After Event Start**	**60 Minutes After Event Start**	**Event 3**	**15 Minutes After Event Start**	**30 Minutes After Event Start**	**60 Minutes After Event Start**	**Study Exit**
Study Window									
Screening Survey									
Consent									
Baseline Survey									
Demographics									
Medications & Supplements									
Acknowledgement of receipt of test product									
Headache Diary	X			X	X			X	
10-point Mankoski Scale	X	X	X	X	X	X	X	X	
Test Product Consumed	X				X				
AE Assessment	X	X	X	X	X	X	X	X	X
Study Exit Survey									X

6.3 Participant Enrollment and Follow-Up

Patients suffering from mild to moderate tension headache symptoms will complete a cloud-based, HIPAA-secured screening survey to determine eligibility. All eligibility criteria must be met for participants to be approved for enrollment in the study. Participants will be provided informed consent and the opportunity to ask questions related to the study procedures, risks and benefits, and rights related to participation in the study. Participants who sign the study informed consent will be prospectively enrolled in the study and provided a link to a patient portal, which provides study resources. Participants will take the study formula at the onset of symptoms and provide information related to pain and tension headache symptoms during the follow-up period. A remote study coordinator may prompt participants to provide study information to ensure that the study forms are completed. Efforts will be taken to ensure minimal withdrawals and loss to follow-up.

6.4 Adverse Event and Safety Monitoring

Adverse Events (AEs) are defined as any untoward medical occurrences described by the study participant. All AEs will be self-reported and documented on the platform. The AEs will be reviewed by the study team including the remote trial coordinator and study principal investigator and reported according to the IRB requirements. Participants who experience adverse events will be advised to stop taking the test product and seek medical attention.

In the event that a participant experiences an adverse event, the clinical study manager or clinical ops coordinator will notify both the PI and Sponsor. The Sponsor will take appropriate action according to their standard operating procedures for any adverse events that warrant action by the Sponsor.

6.4.1 Anticipated Adverse Events

Anticipated Adverse Events are complications that are known to be associated with the test product (in high doses exceeding recommended use):

- Diarrhea
- Nausea
- Stomach Cramps
- Acid Reflux
- Skin Rashes
- GI Bleeding
- Headaches
- Liver Damage

6.4.2 Adverse Event Relationship

Each reported AE will be assessed by the Investigator for relatedness, severity and causality.

6.4.3 Serious Adverse Events

A Serious Adverse Event is an Adverse Event that leads to death or to serious deterioration in the health of the participant that either resulted in a life-threatening illness or injury, or a permanent impairment of a body structure or body function.

6.5 Lost to Follow-Up

If a patient fails to provide event information via the study/patient portal 30 days after the start of the trial, the remote coordinator will attempt to contact the participant to ascertain whether or not the participant has had a headache episode or not and if the participant wishes to and/or should continue in the study.

Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's study record.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study and the study exit form will be completed.

6.6 Test Product Packaging/Handling/Storage/Accountability

- The three-episode supply of test product will be packaged and labeled with ingredients and a study ID number.
- Participants will receive guidance on how to report receipt, store, and use the test product.
- Hawthorne Effect Inc. will support storage and shipment of test product, documentation of test product assignment, and completion of test product accountability.

6.7 Study Management

This study uses a decentralized clinical trial format to foster inclusivity, diversity and accessibility for a broad study population and to ensure efficiencies for enrollment and study data collection. The study will be managed using an end to end virtual clinical trial platform called Hawthorne Effect Study Visit Management Platform which is designed to

make patient participation in clinical trials more accessible and as least burdensome as possible. The Hawthorne Effect platform (www.hawthorne-effect.com) is GCP/ICH/21CFR and HIPAA compliant. Hawthorne Effect uses a network of specialty vetted and trained healthcare professionals, or HEROs who are study investigators, screeners and conduct personalized patient visits for screening and follow-up. For this trial, the Hawthorne Effect study visits will be virtual, and the platform will be used to collect patient reported outcomes and to track screening, enrollment and study compliance.

7 Statistical Considerations

7.1 Study Outcomes Measures

Analysis populations:

The *intent to treat* (ITT) population consists of all participants who are consented, report the onset of a headache, and have taken the study medication at least once. The primary analysis will be in the ITT population.

Primary Endpoint:

The primary endpoint is reduction in headache severity. Patients will be asked to rate headache on the 10-point Mankoski scale at 4 time points: prior to taking the product, 15 minutes after taking the product, 30 minutes after taking the product, and 1 hour after taking the product. The improvement in symptoms from baseline will be evaluated on a pairwise basis separately for each time point. P-values will be computed for the improvement.

There is no control group for the primary analysis.

Secondary Endpoints:

- Time to intervention (taking any product other than the study medication) will be analyzed as a time dependent variable, with the clock starting when the test product is taken.
- A longitudinal analysis will be performed for patients who report on more than one incident of headache.
- Net Promoter Score.
- Comparison against normal behavior will use the paired sample *t*-test.
- An additional data presentation will consist of results from both Treatment and Control

in similar studies appearing in the literature. There will be no formal statistical comparison of results from this study and historical studies.

Secondary endpoints will be gathered on the subjective experience of these participants related to general health, personal experience with the product. The secondary endpoints will be self-reported by the participant on their online portal. There will be a questionnaire related to general health and the subjective experience of the participant administered at baseline and at study exit.

The purpose of the secondary analyses is to investigate the association between various baseline and other measurements and outcomes. These secondary analyses are considered hypothesis generating, and the descriptions are somewhat informal. The trial data may suggest secondary analyses not described here.

7.2 Sample Size Considerations

Based on information from a variety of studies, a highly pessimistic assumption is that there would be a mean improvement of 2 points on the Mankoski scale with a standard deviation of 5 points. Based on these assumptions, a sample size of 68 patients would result in a 90% power to detect an improvement using the paired-sample *t*-test. We also assume that 50% of the patients will experience headaches during the 60-day period; the other patients would furnish no useful data. The final sample size of 200 patients has been chosen to allow for various contingencies, including uncertainties in the assumptions and about compliance in this self-reported trial. If data from multiple headaches per patient are useful, the power to detect an improvement would increase.

It should be emphasized that these assumptions are for sample size purposes only. Trial analysis will use the data as collected.

As discussed above, the number 200 may be increased based on observed data concerning the number of participants with heartburn/indigestion. The actual outcomes of treated participants will not be considered in this analysis, merely whether or not enrolled participants have reported starting using the test product. The method of reevaluating the sample size will be described in the Statistical Analysis Plan.

7.3 Analysis Plan

Separate tables will be presented showing the changes from baseline for tension headache severity and functional status at each time point. The changes will be evaluated by the paired-sample t-test. An appropriate nonparametric analysis will also be reported.

Secondary endpoints will be gathered on the subjective experience of these participants related to general health, functional status, personal experience with the products. The secondary endpoints will be self-reported by the participant on their online portal. There will be a questionnaire related to general health, functional status, and the subjective experience of the participant administered at baseline and at study exit.

The purpose of the secondary analyses is to investigate the association between various baseline and other measurements and outcome variables. These secondary analyses are considered hypothesis generating, and the descriptions are somewhat informal. The trial data may suggest secondary analyses not described here.

General statistical methods:

Data will be analyzed using standard statistical methods, as further specified in a statistical analysis plan (SAP), which will be prepared in detail later.

- Data analysis will largely consist of summary statistics and graphs. The only formal group comparisons will be in covariate analyses.
- For continuous variables data presentation will consist of means, confidence intervals computed using the t-statistic, medians, and interquartile ranges. Group comparisons will use t-tests or ANOVA.
- For discrete variables confidence intervals will use the exact intervals, where available. Group comparisons will use Fisher's exact test, with the Monte Carlo version used where computationally necessary.
- For time to event variables analysis will use the Kaplan-Meier algorithm, and group comparisons will use the log-rank or proportional hazards methods, depending on the data type.
- Visual analog scale values will be treated as continuous variables. Frequency counts will also be provided for scales with 10 or fewer distinct response levels.
- Covariate analyses will investigate the relation between baseline and outcome variables, using methods appropriate to the data types involved. Age, gender, and baseline medications will be included in these analyses where appropriate data are available.
- Present intention is that the analysis will be performed in R, and the precise form of algorithms will be the default of R. Kaplan-Meier, log-rank, and proportional hazards algorithms will be the defaults of the survival package. [13]
- The exact items to be compared depend on what is reported in each historical control study. When possible, the items will include symptom relief at each time measured, including within-patient p-values, and time to the lowest level on a 4-point scale and to

the lowest 2 levels on a 10-point scale. as well as reported baseline characteristics. When two-arm studies are compared, both arms will be reported in this comparison. Specific studies to be considered will be identified prior to the analysis of actual trial data.

8 Informed Consent Process

The study protocol and informed consent will be reviewed approved by Advarra Institutional Review Board, prior to study start.

Study candidates will learn about the study via digital advertisements. If interested in learning more, they will be referred to a website “landing page” that will provide detailed information about the study. They may opt to complete a screening survey ascertaining study eligibility through patient reported outcomes. If successfully completed (no exclusion criteria are selected), candidate will be invited to review the study consent form tutorial which includes the opportunity to ask questions related to the study from the Principal Investigator or delegated authority of the investigator. Candidate will be provided with contact information to reach investigator or study manager as desired.

Candidate may sign the informed consent via electronic signature as provided by Hawthorne Effect. The study manager will verify candidate signature prior to enrollment as a study participant.

9 Subject Confidentiality

All participants’ data and personal information will be kept confidential. Only those involved with the study will have access to participant information. The data will be stored by Hawthorne Effect on a HIPAA compliant platform. The platform, which the data is stored on, will require a personalized username and password to gain access.

10 Publication

Prior to the first patient enrolled, study will be registered on clinicaltrials.gov and submit the results for advertisement and promotion purposes.

11 Limitations

The study described in this protocol has some limitations. There is no concurrent control, as seems appropriate for the first study on this combination product. The study relies solely on patients' subjective information and self-reporting; there is no medical review of symptoms, and no independent check on patient compliance. Some patient groups are not studied, including those under 18 years of age and pregnant women.

12 Bibliography

1. 15 Pain Scales (And How to Find The Best Pain Scale For You). (2018, January 05). Retrieved from https://paindoctor.com/pain-scales/
2. Beer, A., & Wegener, T. (2008). Willow bark extract (Salicis cortex) for gonarthrosis and coxarthrosis – Results of a cohort study with a control group. Phytomedicine, 15(11), 907-913. doi:10.1016/j.phymed.2008.07.010
3. Cady, R. K., Goldstein, J., Nett, R., Mitchell, R., Beach, M., & Browning, R. (2011). A Double-Blind Placebo-Controlled Pilot Study of Sublingual Feverfew and Ginger (LipiGesicTMM) in the Treatment of Migraine. Headache: The Journal of Head and Face Pain, 51(7), 1078-1086. doi:10.1111/j.1526-4610.2011.01910.x
4. Ertsey, C., Magyar, M., Gyüre, T., Balogh, E., & Bozsik, G. (2019). [Tension type headache and its treatment possibilities]. Ideggyogy Sz, 13-21. doi:10.18071/https://doi.org/10.18071/isz.72.0013
5. Friedman, L. M., Furberg, C., DeMets, D. L., Reboussin, D., & Granger, C. B. (2015). Fundamentals of clinical trials. Cham: Springer.
6. Kimmatkar, N., Thawani, V., Hingorani, L., & Khiyani, R. (2003). Efficacy and tolerability of Boswellia serrata extract in treatment of osteoarthritis of knee – A randomized double-blind placebo-controlled trial. Phytomedicine, 10(1), 3-7. doi:10.1078/094471103321648593
7. Kubala, J., MS, RD. (2019, April 30). Skullcap: Benefits, Side Effects, and Dosage. Retrieved from https://www.healthline.com/nutrition/skullcap
8. McMahon, G. (2019). Comparison of a Numeric and a Descriptive Pain Scale in the Occupational Medicine Setting. Retrieved from https://scholarworks.sjsu.edu/etd_doctoral/98/
9. Riva A1, Allegrini P, Franceschi F, Togni S, Giacomelli L, Eggenhoffner R. A novel boswellic acids delivery form (Casperome®) in the management of musculoskeletal disorders: a review. Eur Rev Med Pharmacol Sci. 2017 Nov;21(22):5258-5263. doi: 10.26355/eurrev_201711_13849.
10. Pareek, A., Suthar, M., Rathore, G., & Bansal, V. (2011). Feverfew (Tanacetum parthenium L.): A systematic review. Pharmacognosy Reviews, 5(9), 103. doi:10.4103/0973-7847.79105
11. Prabhavathi, K., Chandra, U. S., Soanker, R., & Rani, P. (2014). A randomized, double blind, placebo controlled, cross over study to evaluate the analgesic activity of Boswellia serrata in healthy volunteers using mechanical pain model. Indian Journal of Pharmacology, 46(5), 475-479. doi:10.4103/0253-7613.140570

12. Taylor, F. R. (2018, November 17). Tension-type headache in adults: Pathophysiology, clinical features, and diagnosis. Retrieved from https://www.uptodate.com/contents/tension-type-headache-in-adults-pathophysiology-clinical-features-and-diagnosis
13. The R Project for Statistical Computing. (n.d.). Retrieved from https://www.R-project.org/.
14. Vitamin C. (2017, October 18). Retrieved from https://www.mayoclinic.org/drugs-supplements-vitamin-c/art-20363932
15. Willow Bark Uses, Benefits & Dosage. (n.d.). Retrieved from https://www.drugs.com/npp/willow-bark.html
16. Wu, B. (n.d.). Magnesium glycinate: Uses, benefits, and side effects (A. Carter PharmD, Ed.). Retrieved from https://www.medicalnewstoday.com/articles/315372.php
17. Schwartz, BS., Stewart, WF., Simon, D., Lipton, RB. (1998). Epidemiology of tension-type headache. JAMA, 279(5):381-3. DOI:10.1001/jama.279.5.381
18. Jensen, R., Stovner, LJ. (2008). Epidemiology and comorbidity of headache. The Lancet Neurology, 7(4):354-61. Doi:10.1016/S1474-4422(08)70062-0.
19. Douglas, ME., Randleman, ML., DeLane, AM., Palmer, GA. (2014). Determining pain scale preference in veteran population experiencing chronic pain. Pain Management Nursing, 15(3):625-31.doi:10.1016/j.pmn.2013.06.003
20. Majeed M1,2,3, Majeed S2, Narayanan NK3, Nagabhushanam K3. A pilot, randomized, double-blind, placebo-controlled trial to assess the safety and efficacy of a novel Boswellia serrata extract in the management of osteoarthritis of the knee. Phytother Res. 2019 Mar 6. doi: 10.1002/ptr.6338. [Epub ahead of print]
21. Nahrstedt A, Schmidt M, Jäggi R, Metz J, Khayyal MT. Willow bark extract: the contribution of polyphenols to the overall effect. Wien Med Wochenschr. 2007;157(13-14):348-51
22. Fiebich BL1, Chrubasik S. Effects of an ethanolic salix extract on the release of selected inflammatory mediators in vitro. Phytomedicine. 2004 Feb;11(2-3):135-8.
23. Chrubasik S, Eisenberg E, Balan E, et al. Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. Am J Med 2000;109:9-14.
24. Gagnier JJ1, Oltean H, van Tulder MW, Berman BM, Bombardier C, Robbins CB. Herbal Medicine for Low Back Pain: A Cochrane Spine (Phila Pa 1976). 2016 Jan;41(2):116-33. Review.
25. Oltean H1, Robbins C, van Tulder MW, Berman BM, Bombardier C, Gagnier JJ. Herbal medicine for low-back pain. Cochrane Database Syst Rev. 2014 Dec 23;(12):CD004504
26. Skullcap monograph. Engles, G. Herbalgram. The American Botanical Council. Issue 83, pg 1-2
27. Brock C, Whitehouse J, Tewfik I, Towell T. American skullcap (Scutellaria lateriflora): a randomised, double-blind placebo-controlled crossover study of its effects on mood in healthy volunteers. Phytother Res 2014;28(5):692-8
28. Johnson ES, Kadam NP, Hylands DM, Hylands PJ. Efficacy of feverfew as prophylactic treatment of migraine. Br Med J (Clin Res Ed) 1985;291:569-73.
29. Randomised double-blind placebo-controlled trial of feverfew in migraine prevention. Murphy JJ, Heptinstall S, Mitchell JR. Lancet. 1988 Jul 23;2(8604):189-92.

30. Palevitch D, Earon G, Carasso R. Feverfew (tanacetum parthenium) as a prophylactic treatment for migraine- a double-blind, placebo-controlled study. Phytotherapy Res 1997;11:508-11.

13 Supplement and Appendix

13.1 Appendices

13.1.1 Appendix A Drug interactions

Drug Interactions for Tension Product

BOSWELLIA

There are no Serious Drug Interactions known for Boswellia. There are some theoretical Moderate Interactions, where Boswellia may interact in the metabolism of certain drugs (which utilize the same enzymes it inhibits). See Below for List.

CYTOCHROME P450 1A2 (CYP1A2) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

In vitro evidence shows that boswellia inhibits cytochrome P450 1A2 (CYP1A2) (21178). Theoretically, use of boswellia with drugs that are metabolized by CYP1A2 might increase drug levels and increase the potential for adverse events. Some drugs metabolized by CYP1A2 include clozapine (Clozaril), cyclobenzaprine (Flexeril), fluvoxamine (Luvox), haloperidol (Haldol), imipramine (Tofranil), mexiletine (Mexitil), olanzapine (Zyprexa), pentazocine (Talwin), propranolol (Inderal), tacrine (Cognex), zileuton (Zyflo), zolmitriptan (Zomig), and others.

CYTOCHROME P450 2C19 (CYP2C19) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

In vitro evidence shows that boswellia inhibits cytochrome P450 2C19 (CYP2C19) (21178). Theoretically, use of boswellia with drugs that are metabolized by CYP2C19 might increase drug levels and increase the potential for adverse events. Some drugs metabolized by CYP2C19 include amitriptyline (Elavil), carisoprodol (Soma), citalopram (Celexa), diazepam (Valium), lansoprazole (Prevacid), omeprazole (Prilosec), phenytoin (Dilantin), warfarin (Coumadin), and many others.

CYTOCHROME P450 2C9 (CYP2C9) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

In vitro evidence shows that boswellia inhibits cytochrome P450 2C9 (CYP2C9) (21178). Theoretically, use of boswellia with drugs that are metabolized by CYP2C9 might increase drug levels and increase the potential for adverse events. Some drugs metabolized by CYP2C9 include celecoxib (Celebrex), diclofenac (Voltaren), fluvastatin (Lescol), glipizide (Glucotrol), ibuprofen (Advil, Motrin), irbesartan (Avapro), losartan (Cozaar), phenytoin (Dilantin), piroxicam (Feldene), tamoxifen (Nolvadex), tolbutamide (Tolinase), torsemide (Demadex), and warfarin (Coumadin).

CYTOCHROME P450 2D6 (CYP2D6) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

In vitro evidence shows that boswellia inhibits cytochrome P450 2D6 (CYP2D6) (21178). Theoretically, use of boswellia with drugs that are metabolized by CYP2D6 might increase drug levels and increase the potential for adverse events. Some drugs metabolized by CYP2D6 include amitriptyline (Elavil), codeine, desipramine (Norpramin), flecainide (Tambocor), haloperidol (Haldol), imipramine (Tofranil), metoprolol (Lopressor, Toprol XL), ondansetron (Zofran), paroxetine (Paxil), risperidone (Risperdal), tramadol (Ultram), venlafaxine (Effexor), and others.

CYTOCHROME P450 3A4 (CYP3A4) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

In vitro evidence shows that boswellia inhibits cytochrome P450 3A4 (CYP3A4) (21178). Theoretically, use of boswellia with drugs that are metabolized by CYP3A4 might increase drug levels and increase the potential for adverse events. Some drugs metabolized by CYP3A4 include amitriptyline (Elavil), amiodarone (Cordarone), citalopram (Celexa), felodipine (Plendil), lansoprazole (Prevacid), ondansetron (Zofran), prednisone (Deltasone, Orasone), sertraline (Zoloft), and many others.

IMMUNOSUPPRESSANTS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**

In vitro studies show that boswellia has immunostimulant properties (21179,21180). Theoretically, boswellia might decrease the effectiveness of immunosuppressive drugs. Immunosuppressant drugs include azathioprine (Imuran), basiliximab (Simulect), cyclosporine (Neoral, Sandimmune), daclizumab (Zenapax), muromonab-CD3 (OKT3, Orthoclone OKT3), mycophenolate (CellCept), tacrolimus (FK506, Prograf), sirolimus (Rapamune), prednisone

(Deltasone, Orasone), and other corticosteroids (glucocorticoids).

Interactions with Herbs & Supplements
None known.

MAGNESIUM

There are no Serious Drug Interactions known for Magnesium. There are some anecdotal moderate interactions with various drugs, including antibiotics, antacids, and others.

13.1.1.1 AMINOGLYCOSIDE ANTIBIOTICS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**

Use of an aminoglycoside antibiotic and magnesium concurrently can lead to neuromuscular weakness and possible paralysis. Both agents reduce presynaptic acetylcholine release, which can lead to neuromuscular blockade. This is most likely to occur with high doses of magnesium given intravenously (13362). The aminoglycosides include amikacin (Amikin), gentamicin (Garamycin), kanamycin (Kantrex), streptomycin, and tobramycin (Nebcin).

13.1.1.2 ANTACIDS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

Use of antacids may reduce the laxative effect of magnesium oxide. A retrospective analysis shows that use of H2 receptor antagonists (H2RA) or proton pump inhibitors (PPI) is associated with a higher dose of magnesium oxide needed to attain a therapeutic laxative effect (90033). This may be due to the fact that, under acidic conditions, magnesium oxide is converted to magnesium chloride then magnesium bicarbonate, which promotes the osmotic laxative effect. Antacids, which reduce the acidity of the stomach, may reduce the conversion of magnesium oxide to the active bicarbonate salt.

Some antacids include calcium carbonate (Tums, others), dihydroxyaluminum sodium carbonate (Rolaids, others), magaldrate (Riopan), magnesium sulfate (Bilagog), aluminum hydroxide (Amphojel), and others.

13.1.1.3 ANTICOAGULANT/ANTIPLATELET DRUGS

Interaction Rating = **Minor** Be watchful with this combination.
Severity = Moderate • Occurrence = Unlikely • Level of Evidence = **B**

In vitro evidence suggests that magnesium sulfate inhibits platelet aggregation at concentrations as low as 0.5-1.0 mM (20304,20305). Some preliminary clinical evidence suggests that infusion of magnesium sulfate increases bleeding time by 48% and reduces platelet activity (20306). However, other clinical research seems to show that magnesium does not affect platelet aggregation, although inhibition of platelet-dependent thrombosis (PDT) can occur (60759). Theoretically, concomitant use of magnesium with anticoagulants or antiplatelets could increase the risk of bleeding.

Some of these drugs include aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, indomethacin (Indocin), ticlopidine (Ticlid), warfarin (Coumadin), and others.

13.1.1.4 BISPHOSPHONATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **B**

Cations, including magnesium, can decrease bisphosphonate absorption. Advise patients to separate doses of magnesium and these drugs by at least 2 hours (13363). The bisphosphonates include alendronate (Fosamax), etidronate (Didronel), tiludronate (Skelid), and risedronate (Actonel).

13.1.1.5 CALCIUM CHANNEL BLOCKERS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**

Magnesium inhibits calcium entry into smooth muscle cells and may therefore have additive effects with calcium channel blockers. Severe hypotension and neuromuscular blockades may occur when nifedipine is used with intravenous magnesium (3046,20264,20265,20266), although some contradictory evidence suggests that concurrent use of magnesium plus nifedipine does not increase the risk of neuromuscular weakness (60831). High doses of magnesium could theoretically have additive effects with other calcium channel blockers. These drugs include nifedipine (Adalat, Procardia), nicardipine (Cardene), isradipine (DynaCirc), amlodipine (Norvasc), and others.

13.1.1.6 DIGOXIN

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **B**

Clinical evidence suggests that treatment with oral magnesium hydroxide or magnesium trisilicate reduces absorption of digoxin from the intestines (198,20268,20270). This may reduce the blood levels of digoxin and decrease its therapeutic effects.

13.1.1.7 GABAPENTIN (Neurontin)

Interaction Rating = **Minor** Be watchful with this combination.
Severity = Mild • Occurrence = Unlikely • Level of Evidence = **B**

Clinical research shows that giving magnesium oxide orally along with gabapentin decreases gabapentin maximum concentration by 33%, time to maximum concentration by 36%, and area under the curve by 43% (90032). Advise patients to take these gabapentin at least 2 hours before, or 4 to 6 hours after, magnesium supplements.

13.1.1.8 POTASSIUM-SPARING DIURETICS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **D**

Potassium-sparing diuretics also have magnesium-sparing properties, which can counteract the magnesium losses associated with loop and thiazide diuretics (9613,9614,9622). Theoretically, increased magnesium levels could result from concomitant use of potassium-sparing diuretics and magnesium supplements. The potassium-sparing diuretics include amiloride (Midamor), triamterene (Dyrenium), and spironolactone (Aldactone).

13.1.1.9 QUINOLONE ANTIBIOTICS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **D**

Magnesium can form insoluble complexes with quinolones and decrease their absorption (3046). Advise patients to take these drugs at least 2 hours before, or 4 to 6 hours after, magnesium supplements. Quinolones (fluoroquinolones) include ciprofloxacin (Cipro), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), and others.

13.1.1.10 SEVELAMER (Renagel, Renvela)

Interaction Rating = **Minor** Be watchful with this combination.
Severity = Mild • Occurrence = Possible • Level of Evidence = **B**

Clinical research shows that taking sevelamer may increase serum magnesium levels. In patients on hemodialysis, sevelamer use was associated with a 0.28 mg/dL increase in serum magnesium. The mechanism of this interaction remains unclear (96486). Advise patients to talk to their healthcare provider before taking magnesium supplements if they are taking sevelamer.

13.1.1.11 SKELETAL MUSCLE RELAXANTS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **A**

Parenteral magnesium shortens the time to onset of skeletal muscle relaxants by about 1 minute and prolongs the duration of action by about 2 minutes. This is thought to occur because magnesium potentiates the effects of skeletal muscle relaxants by decreasing acetylcholine release from motor nerve terminals (3046,97492). A clinical study found that low-dose rocuronium (0.45 mg/kg), when given after administration of magnesium 30 mg/kg over 10 minutes, undergoes an accelerated onset of effect, which matches the onset of effect seen with a full-dose rocuronium regimen (0.6 mg/kg) (96485). Along with rocuronium (Zemuron), skeletal muscle relaxants include atracurium (Tracrium), cisatracurium (Nimbex), mivacurium (Mivacron), rapacuronium (Raplon), pancuronium (Pavulon), vecuronium (Norcuron), and others.

13.1.1.12 SULFONYLUREAS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Mild • Occurrence = Probable • Level of Evidence = **B**

Clinical research suggests that concomitant administration of magnesium hydroxide and non-micronized glibenclamide increases the absorption of glibenclamide, leading to a 35-fold increase in maximum insulin response compared to treatment with non-micronized glibenclamide alone (20307). Similarly, concomitant administration of magnesium hydroxide and glipizide increases the absorption of glipizide and enhances the maximal glucose decrease by 35% compared to glipizide alone (20308). This effect relates to the ability of magnesium-based antacids to elevate gastrointestinal pH, leading to increased solubility and enhanced absorption of sulfonylureas (22364). Due to this interaction, concomitant use of sulfonylureas and magnesium-based antacids may theoretically increase the risk of hypoglycemia in some patients. Other sulfonylurea agents include carbutamide, acetohexamide, chlorpropamide, tolbutamide, gliclazide, glibornuride, glyclopyramide, and glimepiride.

13.1.1.13 TETRACYCLINE ANTIBIOTICS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **D**

Magnesium can form insoluble complexes with tetracyclines in the gut and decrease their absorption and antibacterial activity (12586). Advise patients to take these drugs at least 2 hours before, or 4 to 6 hours after, magnesium supplements. Tetracyclines include demeclocycline (Declomycin), doxycycline (Vibramycin), minocycline (Minocin), and tetracycline (Achromycin, Sumycin).

Interactions with Herbs & Supplements

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: In vitro evidence suggests that magnesium sulfate inhibits platelet aggregation at concentrations as low as 0.5-1.0 mM (20304,20305). Some preliminary clinical evidence suggests that infusion of magnesium sulfate increases bleeding time by 48% and reduces platelet activity (20306). However, other clinical research seems to show that magnesium does not affect platelet aggregation, although inhibition of platelet-dependent thrombosis (PDT) can occur (60759). Theoretically, concomitant use of magnesium with other herbs and supplements that affect platelet aggregation might increase the risk of bleeding. Some other herbs and supplements that affect platelet aggregation include angelica, clove, danshen, garlic, ginger, glucosamine, Panax ginseng, and others.

BORON: Boron supplements can reduce urinary excretion of magnesium and increase serum levels in women (940,9529,9623). In young women, age 18 to 25 years, the effect appears to be greater in sedentary than athletic women (940). In postmenopausal women, the effect is more marked in women with low dietary magnesium intake (9623). The clinical significance of these effects, and whether they occur in men, is not known.

CALCIUM: Calcium supplements can decrease the absorption of dietary magnesium, but only at very high, supra-therapeutic doses (2600 mg daily). However, in people with adequate magnesium stores, calcium doesn't have any clinically significant effect on long-term

magnesium balance. Advise patients at high risk for magnesium deficiency to take calcium supplements at bedtime, instead of with meals, to avoid inhibiting dietary magnesium absorption (4623,7555,11159). Magnesium does not seem to affect calcium absorption (12587).

VITAMIN D: One intestinal route of magnesium absorption is thought to be vitamin D dependent (9634). Various forms of vitamin D, including ergocalciferol, 25-hydroxyergocalciferol, 25-hydroxycholecalciferol (calcifediol), and 1,25-dihydroxycholecalciferol (calcitriol) increase magnesium absorption; especially when taken in high doses (9634,9635,9636,9637). This effect has been used to treat hypomagnesemia in people with malabsorption syndromes (9516,9635,9636).

ZINC: Supplementation with high doses of zinc, 142 mg daily, appears to decrease magnesium absorption and magnesium balance in healthy adult males (9624). Also, moderately high dietary zinc intake, 53 mg daily, seems to increase magnesium excretion without affecting copper metabolism in postmenopausal women. This might adversely affect bone health. Zinc may compete with magnesium for ion exchange transport in the intestine (12424). More research on the clinical importance of these observations is needed.

WHITE WILLOW BARK

There is one Serious Drug Interactions known for White Willow Bark, of which it is anecdotal. Just like aspirin, White Willow Bark might increase the risk of bleeding, and so the concomitant use of anticoagulants and antiplatelet drugs should be avoided.

13.1.1.14 ACETAZOLAMIDE

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

Willow bark contains salicin, a plant salicylate. Human case reports suggest a combination of acetazolamide and salicylate increase unbound plasma levels of acetazolamide, as well as adverse effects related to acetazolamide (86481). Theoretically, willow bark might result in additive adverse effects associated with acetazolamide.

13.1.1.15 ANTICOAGULANT/ANTIPLATELET DRUGS

Interaction Rating = **Major** Do not take this combination.
Severity = High • Occurrence = Probable • Level of Evidence = **D**

Concomitant use theoretically might increase the risk of bleeding due to decreased platelet aggregation. Willow bark has antiplatelet effects, but less so than aspirin (12810). Avoid concomitant use with other anticoagulant and antiplatelet drugs. Some of these drugs include aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, ticlopidine (Ticlid), warfarin (Coumadin), and others.

13.1.1.16 ASPIRIN

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **D**

Willow bark contains salicin, a plant salicylate. Theoretically, willow bark might have an additive effect with other salicylate-containing drugs such as aspirin (12808).

13.1.1.17 CHOLINE MAGNESIUM TRISALICYLATE (Trilisate)

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **D**

Willow bark contains salicin, a plant salicylate. Theoretically, willow bark might have an additive effect with other salicylate-containing drugs such as choline magnesium trisalicylate (12808).

13.1.1.18 SALSALATE (Disalcid)

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Probable • Level of Evidence = **D**

Willow bark contains salicin, a plant salicylate. Theoretically, willow bark might have an additive effect with other salicylate-containing drugs such as salsalate (12808).

Interactions with Herbs & Supplements

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Concomitant use of herbs that have antiplatelet/anticoagulant effects could theoretically increase the risk of bleeding in some people (12810). These herbs include clove, danshen, garlic, ginger, ginkgo, ginseng, meadowsweet, red clover, and others.

SALICYLATE-CONTAINING HERBS: Theoretically, concomitant use may potentiate salicylate effects and adverse effects (12808). Salicylate-containing herbs include aspen bark, black haw, poplar, and meadowsweet.

FEVERFEW

There are no Serious Drug Interactions known for Feverfew. There are some anecdotal interactions of moderate concern, such as anticoagulant drugs, and also drugs that utilize enzymes that Feverfew may inhibit.

13.1.1.19 ANTICOAGULANT/ANTIPLATELET DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**

Some evidence suggests that feverfew may inhibit platelet aggregation. However, this has not been demonstrated in humans (6935,6936,6942,6943,6944,6945,6951). Theoretically, feverfew might have additive effects and increase the risk of bleeding when used with these drugs.

13.1.1.20 CYTOCHROME P450 1A2 (CYP1A2) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

There's preliminary evidence that feverfew might inhibit cytochrome P450 1A2 (CYP1A2) (12479). So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP1A2 in patients taking feverfew. Some drugs metabolized by CYP1A2 include amitriptyline (Elavil), haloperidol (Haldol), ondansetron (Zofran), propranolol (Inderal), theophylline (Theo-Dur, others), verapamil (Calan, Isoptin, others), and others. Use feverfew cautiously or avoid in patients taking these drugs.

13.1.1.21 CYTOCHROME P450 2C19 (CYP2C19) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

There's preliminary evidence that feverfew might inhibit cytochrome P450 2C19 (CYP2C19) (12479). So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP2C19 in patients taking feverfew. Some drugs metabolized by CYP2C19 include proton pump inhibitors including omeprazole (Prilosec), lansoprazole (Prevacid), and pantoprazole (Protonix); diazepam (Valium); carisoprodol (Soma); nelfinavir (Viracept); and others.

13.1.1.22 CYTOCHROME P450 2C8 (CYP2C8) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

There's preliminary evidence that feverfew might inhibit cytochrome P450 2C8 (CYP2C8) (12479). So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP2C8 in patients taking feverfew. Some drugs metabolized by CYP2C8 include amiodarone (Cardarone), paclitaxel (Taxol); nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac (Cataflam, Voltaren) and ibuprofen (Motrin); rosiglitazone (Avandia); and others.

13.1.1.23 CYTOCHROME P450 2C9 (CYP2C9) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

There's preliminary evidence that feverfew might inhibit cytochrome P450 2C9 (CYP2C9) (12479). So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP2C9 in patients taking feverfew. Some drugs metabolized by CYP2C9 include nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac (Cataflam, Voltaren), ibuprofen (Motrin), meloxicam (Mobic), and piroxicam (Feldene); celecoxib (Celebrex); amitriptyline (Elavil); warfarin (Coumadin); glipizide (Glucotrol); losartan (Cozaar); and others. Use feverfew cautiously or avoid in patients taking these drugs.

13.1.1.24 CYTOCHROME P450 2D6 (CYPD6) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

There's preliminary evidence that feverfew might inhibit cytochrome P450 2D6 (CYP2D6) (12479). So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP2D6 in patients taking feverfew. Some drugs metabolized by CYP2D6 include tricyclic antidepressants such as imipramine (Tofranil) and amitriptyline (Elavil); antipsychotics such as haloperidol (Haldol), risperidone (Risperdal), and chlorpromazine (Thorazine); beta-blockers such as propranolol (Inderal), metoprolol (Lopressor, Toprol XL), and carvedilol (Coreg); tamoxifen (Nolvadex); and others.

13.1.1.25 CYTOCHROME P450 3A4 (CYP3A4) SUBSTRATES

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

There's preliminary evidence that feverfew might inhibit cytochrome P450 3A4 (CYP3A4) enzyme (12479,19361). So far, this interaction has not been reported in humans. However, watch for an increase in the levels of drugs metabolized by CYP3A4 in patients taking feverfew. Some drugs metabolized by CYP3A4 include lovastatin (Mevacor), ketoconazole (Nizoral), itraconazole (Sporanox), fexofenadine (Allegra), triazolam (Halcion), and numerous others. Use feverfew cautiously or avoid in patients taking these drugs.

Interactions with Herbs & Supplements

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Some evidence suggests that feverfew may inhibit platelet aggregation. However, this has not been demonstrated in humans (6935,6936,6942,6943,6944,6945,6951). Theoretically, concomitant use of feverfew and herbs that affect platelet aggregation could increase the risk of bleeding in some people. Some of these herbs include angelica, clove, danshen, garlic, ginger, ginkgo, Panax ginseng, horse chestnut, red clover, turmeric, and others.

SKULLCAP

There are no Serious Drug Interactions known for Skullcap. There is one moderate interaction of anecdotal evidence that Skullcap may cause sedation, so there should be caution as there may be additive effects of the use with CNS deressants.

13.1.1.26 CNS DEPRESSANTS

Interaction Rating = **Moderate** Be cautious with this combination.
Severity = High • Occurrence = Possible • Level of Evidence = **D**

Animal research and clinical evidence suggests that skullcap might cause sedation and cognitive impairment (12216,74008). Theoretically, concomitant use of skullcap and drugs with sedative and anesthetic properties may cause additive therapeutic and adverse effects. Some CNS depressants are benzodiazepines, pentobarbital (Nembutal), phenobarbital (Luminal), secobarbital (Seconal), thiopental (Pentothal), fentanyl (Duragesic, Sublimaze), morphine, propofol (Diprivan), and others.

Interactions with Herbs & Supplements

HERBS AND SUPPLEMENTS WITH SEDATIVE PROPERTIES: Skullcap might cause sedation and cognitive impairment (12216,74008). Theoretically, concomitant use of skullcap with herbs that have sedative properties might enhance the therapeutic and adverse effects. Some of these supplements include 5-HTP, calamus, California poppy, catnip, hops, Jamaican dogwood, kava, St. John's wort, valerian, yerba mansa, and others.

13.1.2 Appendix B Instructions for Use

This Tension Relief for support with head and body comfort, combining Boswellia, Magnesium, Feverfew, Skullcap and White Willow Bark for multi-faceted effective, yet health-building head comfort. This formula is designed to promote comfort of the head and body in the short-term, but also help build long-term health.

Daily Dosage:
2 capsules contain

Directions: Take 2 capsules with 6-8 oz. of water, up to three times daily for relief of your headache symptoms

***These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.**

13.1.3Appendix C Screening Form

Screening

1. Are you at least 18 years old? (DOB?)
2. Do you suffer from headaches (**Y**/N)?
3. Have you ever been diagnosed with any chronic liver disease? (Y/N)
4. Have you ever been diagnosed with any chronic Renal disease? (Y/N)
5. Are you pregnant or breastfeeding? (Y/N)
6. Have you ever been diagnosed by a physician with any type of headaches by a physician? (Y/N)
   □ Cluster □ Tension □ Migraine □ Exertional □ Other: _____□ None of the above

7. Do you have any allergies to any of the following? (Y/N)
   a. Boswellia
   b. Feverfew
   c. Skullcap
   d. White Willow Bark
   e. Vegetable Cellulose
   f. Rice Hull
8. Do you have more than 10 alcoholic beverages per week? (Y/N)
9. Are you able to swallow pills? (Y/N)
10. Are you willing to try the test product for relief of your symptoms? (Y/N)
11. Are you currently taking any anticoagulation, blood-thinning, medication daily (aspirin, warfarin, etc.)? (Y/N)

Headache questionnaire:

HIT-6™
(VERSION 1.1)

HEADACHE IMPACT TEST™

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.

	Never	Rarely	Sometimes	Very Often	Always
1 When you have headaches, how often is the pain severe?					
2 How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?	Never	Rarely	Sometimes	Very Often	Always
3 When you have a headache, how often do you wish you could lie down?	Never	Rarely	Sometimes	Very Often	Always
4 In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?	Never	Rarely	Sometimes	Very Often	Always
5 In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?	Never	Rarely	Sometimes	Very Often	Always
6 In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?	Never	Rarely	Sometimes	Very Often	Always
	COLUMN 1 (6 points each)	+ COLUMN 2 (8 points each)	+ COLUMN 3 (10 points each)	+ COLUMN 4 (11 points each)	+ COLUMN 5 (13 points each)

To score, add points for answers in each column. Total Score

Please share your HIT-6 results with your doctor.

Higher scores indicate greater impact on your life.

Score range is 36-78.

HEADACHE IMPACT TEST™
What Does Your Score Mean?

If You Scored 60 or More
Your headaches are having a very severe impact on your life. You may be experiencing disabling pain and other symptoms that are more severe than those of other headache sufferers. Don't let your headaches stop you from enjoying the important things in your life, like family, work, school or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 56 – 59
Your headaches are having a substantial impact on your life. As a result you may be experiencing severe pain and other symptoms, causing you to miss some time from family, work, school, or social activities.

Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 50 – 55
Your headaches seem to be having some impact on your life. Your headaches should not make you miss time from family, work, school, or social activities.

Make sure you discuss your HIT-6 results and your headaches at your next appointment with your doctor.

If You Scored 49 or Less
Your headaches seem to be having little to no impact on your life at this time. We encourage you to take HIT-6 monthly to continue to track how your headaches affect your life.

If Your Score on HIT-6 is 50 or Higher
You should share the results with your doctor. Headaches that are disrupting your life could be migraine.

Take HIT-6 with you when you visit your doctor because research shows that when doctors understand exactly how badly headaches affect the lives of their patients, they are much more likely to provide a successful treatment program, which may include medication.

HIT is also available on the Internet at www.headachetest.com.

The Internet version allows you to print out a personal report of your results as well as a special detailed version for your d octor.

Don't forget to take HIT-6 again or try the Internet version to continue to monitor your progress.

About HIT
The Headache Impact Test (HIT) is a tool used to measure the impact headaches have on your ability to function on the job, at school, at home and in social situations. Your score shows you the effect that headaches have on normal daily life and your ability to function. HIT was developed by an international team of headache experts from neurology and primary care medicine in collaboration with the psychometricians who developed the SF-36 ® health assessment tool.

HIT is not intended to offer medical advice regarding medical diagnosis or treatment. You should talk to your healthcare provider for advice specific to your situation.

13.1.4Appendix D Baseline Form

Baseline

Please answer the following questions to the best of your abilities.

1. Demographics
    a. Race/Ethnicity (Black or African American, White, Asian, American Indian or Alaska Native, Native Hawaiian or another pacific islander, other: ____, do not want to share)
    b. Sex (M, F, or Do not want to share)
2. On average how often do you have headaches? (A few times a year, once a month, A few times a month, once a week, 2-3 times a week, Everyday)
3. How do your headaches typically begin? (Gradually, suddenly or Varies)
4. How long does it usually take for your headache to reach maximum intensity? (0-30 min, 31 min- 1 hour, +1 hour)
5. How long do your Headaches usually last without medication? (30 min-1hour, 1-2 hour, >2 hours, does not resolve)
6. On average how bad are your headaches without medication? (1-10)
7. What do your headaches usually feel like? (pressure, stabbing, throbbing, Tight band, burning, dull ache)
8. Do any of the following bring on or trigger your headaches (check all that apply)?
    a. Food
    b. Caffeine (too much/too little)
    c. Hunger/skipping meals
    d. Fatigue
    e. Stress
    f. Alcohol/wine
    g. Too much/too little sleep
    h. Menstruation
    i. Physical activity
    j. Prolonged computer work
    k. Bright light/sun
    l. Loud sounds
    m. Other: _____
    n. None of the above
9. Do you experience any of the following symptoms before your headache begins (check all that apply)?
    a. Mood/Personality Changes
    b. Changes in appetite
    c. Neck pain
    d. Fatigue

e. Other: _____
f. No, I do not experience any of these symptoms

10. Do you experience any of these symptoms during your Headache (check all that apply)?
    a. Nausea/upset stomach
    b. Bright lights/sun bothers you
    c. Strong smells/odors bother you
    d. Dizziness/lightheadedness/vertigo
    e. Numbness or tingling
    f. Increased sensitivity of the scalp/hair/ears
    g. Eye tears
    h. Difficulty concentrating
    i. Runny or stuffy nose
    j. Mood changes/irritability
    k. Other: _____
    l. None of the above
11. During a headache, what makes you feel the most comfortable (Check all that apply)?
    a. Lying down/sleeping'
    b. Keeping physically active
    c. Massage your head
    d. Cold pack on your head/neck
    e. Being in a dark quiet room
    f. Pacing back-and-forth
    g. Tying something around your head
    h. Hot pack on your head/neck
    i. Other: _____
    j. Nothing makes you feel comfortable
12. Effect of headaches on your ability to function:
    a. During Milder headaches
        i. I am able to function normally
        ii. My ability to function is slightly decreased
        iii. My ability to function is severely decreased
        iv. I am totally bedridden
    b. During Moderate Headaches
        i. I am able to function normally
        ii. My ability to function is slightly decreased
        iii. My ability to function is severely decreased
        iv. I am totally bedridden
13. Do you take medications to treat your headache? (yes/no)
    a. If yes, what medication do you use to treat your headaches? (free response)
    b. On average how bad are your headaches with medication? (1-10)
    c. When you have a headache how long do you wait before taking medication?
        i. Right away
        ii. Within an hour
        iii. 1-2 hours

iv. >2 hours

d. How long do your headaches usually last with medication? (30 min-1hour, 1-2 hour, >2 hours, does not resolve)

14. How many hours of work/school/leisure time do you miss a month because of your headaches? (Free response)

13.1.5Appendix E Headache Diary

Headache Diary

Please complete the following items during your second headache event. We encourage you to complete the forms online in real time. However, if you cannot log into your patient portal at the time of your symptoms please complete these forms and log into your patient portal as soon as possible and complete the online forms.

Reminder: Do not take any other medications or supplements within the first hour of taking the test product.

Date of Onset: _____ Time of Onset: _____

Trigger (Check all that apply): □ Food □ Caffeine (too much/little) □ Hunger/Skipping meals □ Fatigue □ Stress □ Alcohol □ Too much/little sleep □ Menstruation □ Physical Activity □ Prolonged Computer Work □ Bright Light/Sun □ Loud Sounds □Other: _____ □None of the above □ I do not know

Type/Description of pain: □ Pressure-Like □ Stabbing □ Throbbing □ Tight band around your head □ burning □ dull ache □ Other: _____

Location: □ One-Sided □ Two-Sided □ Other: _____

Other Symptoms (write none if you have no other symptoms): _____

Time test product taken: _____

Please complete the following Pain Scales at 15, 30, and 60 minutes after taking the test product.

Pain Scale at Onset (immediately before taking the test product)

Please rate your pain prior to taking the test product. Circle your answer

0 - Pain Free

1 - Very minor annoyance - occasional minor twinges. No medication needed.

2 - Minor Annoyance - occasional strong twinges. No medication needed.

3 - Annoying enough to be distracting. Mild painkillers take care of it (Aspirin, Ibuprofen).

4 - Can be ignored if you are really involved in your work, but still distracting. Mild painkillers remove pain for 3-4 hours.

5 - Can't be ignored for more than 30 minutes. Mild painkillers ameliorate pain for 3-4 hours.

6 - Can't be ignored for any length of time, but you can still go to work and participate in social activities. Stronger painkillers (Codeine, narcotics) reduce pain for 3-4 hours.

7 - Makes it difficult to concentrate, interferes with sleep. You can still function with effort. Stronger painkillers are only partially effective.

8 - Physical activity severely limited. You can read and converse with effort. Nausea and dizziness set in as factors of pain.

9 - Unable to speak. Crying out or moaning uncontrollably - near delirium.

10 - Unconscious. Pain makes you pass out.

Pain Scale at 15 minutes

Please rate your pain 15 minutes after taking the test product. Circle your answer.

0 - Pain Free

1 - Very minor annoyance - occasional minor twinges. No medication needed.

2 - Minor Annoyance - occasional strong twinges. No medication needed.

3 - Annoying enough to be distracting. Mild painkillers take care of it (Aspirin, Ibuprofen).

4 - Can be ignored if you are really involved in your work, but still distracting. Mild painkillers remove pain for 3-4 hours.

5 - Can't be ignored for more than 30 minutes. Mild painkillers ameliorate pain for 3-4 hours.

6 - Can't be ignored for any length of time, but you can still go to work and participate in social activities. Stronger painkillers (Codeine, narcotics) reduce pain for 3-4 hours.

7 - Makes it difficult to concentrate, interferes with sleep. You can still function with effort. Stronger painkillers are only partially effective.

8 - Physical activity severely limited. You can read and converse with effort. Nausea and dizziness set in as factors of pain.

9 - Unable to speak. Crying out or moaning uncontrollably - near delirium.

10 - Unconscious. Pain makes you pass out.

Pain Scale at 30 minutes

Please rate your pain 30 minutes after taking the test product. Circle your answer.

0 - Pain Free

1 - Very minor annoyance - occasional minor twinges. No medication needed.

2 - Minor Annoyance - occasional strong twinges. No medication needed.

3 - Annoying enough to be distracting. Mild painkillers take care of it (Aspirin, Ibuprofen).

4 - Can be ignored if you are really involved in your work, but still distracting. Mild painkillers remove pain for 3-4 hours.

5 - Can't be ignored for more than 30 minutes. Mild painkillers ameliorate pain for 3-4 hours.

6 - Can't be ignored for any length of time, but you can still go to work and participate in social activities. Stronger painkillers (Codeine, narcotics) reduce pain for 3-4 hours.

7 - Makes it difficult to concentrate, interferes with sleep. You can still function with effort. Stronger painkillers are only partially effective.

8 - Physical activity severely limited. You can read and converse with effort. Nausea and dizziness set in as factors of pain.

9 - Unable to speak. Crying out or moaning uncontrollably - near delirium.

10 - Unconscious. Pain makes you pass out.

Pain Scale at 1 hour

Please rate your pain 1 hour after taking the test product. Circle your answer.

0 - Pain Free

1 - Very minor annoyance - occasional minor twinges. No medication needed.

2 - Minor Annoyance - occasional strong twinges. No medication needed.

3 - Annoying enough to be distracting. Mild painkillers take care of it (Aspirin, Ibuprofen).

4 - Can be ignored if you are really involved in your work, but still distracting. Mild painkillers remove pain for 3-4 hours.

5 - Can't be ignored for more than 30 minutes. Mild painkillers ameliorate pain for 3-4 hours.

6 - Can't be ignored for any length of time, but you can still go to work and participate in social activities. Stronger painkillers (Codeine, narcotics) reduce pain for 3-4 hours.

7 - Makes it difficult to concentrate, interferes with sleep. You can still function with effort. Stronger painkillers are only partially effective.

8 - Physical activity severely limited. You can read and converse with effort. Nausea and dizziness set in as factors of pain.

9 - Unable to speak. Crying out or moaning uncontrollably - near delirium.

10 - Unconscious. Pain makes you pass out.

After your headache resolved please complete any of the following questions if applicable.

Did your symptoms resolve completely with the test product? Yes No If yes, time of complete symptom resolution: _____

Did you need to take another medication: Yes No

Medication #1: _____ Dose: _____ Time: _____

Medication #2: _____ Dose: _____ Time: _____

Medication #3: _____ Dose: _____ Time: _____

Did your symptoms resolve completely with taking your medication? Yes No

After taking medication, time of complete resolution of symptoms: _____

Did you experience any side effects after taking the test product? (Y/N) If yes, **Please fill out the Adverse Event form.**

13.1.6Appendix F Study Exit Form

Study Exit

1. Please rate your overall experience with the test product.

0	1	2	3	4	5	6	7	8	9	10
Poor					Neutral					Excellent

1a. Why? (free response)

2. Do you feel that the test product helped with your headaches?

0	1	2	3	4	5	6	7	8	9	10
Not at all					Neutral					definitely

3. How likely are you to recommend the test product to your friends or family members?

0	1	2	3	4	5	6	7	8	9	10
Not Likely					Neutral					Extremely Likely

4. Do you feel that the test product helped your body cope with occasional tension and occasional head discomfort?

0	1	2	3	4	5	6	7	8	9	10
Not at all					Neutral					definitely

5. Is there anything else that you like to let us know about your experience with the product (taste, smell, consistency, or other)? (y/n) → (free response)

6. Did the test product help prevent you from having to take any other medication for your symptoms? (y/n)

13.1.7Appendix G Adverse Event Form

Tension AE document

1. Did you experience any side effects after taking the test product? Y/N
    a. If so, did you experience any of the following
        - itching, rash, hives, throat/lip/tongue swelling, wheezing
        - low blood pressure, fainting, chest pain, shortness of breath, palpitations, irregular heart beat
        - severe, persistent nausea, vomiting, diarrhea, or abdominal pain
        - difficulty urinating, decreased urination
        - fatigue, appetite loss, yellowing skin/eyes, itching, dark urine
        - severe joint/muscle pain
        - slurred speech, one-sided weakness of face, arm, leg, vision
        - abnormal bleeding from nose or gums
        - blood in urine, stool, vomit,
        - marked mood, cognitive, or behavioral changes, thoughts of suicide
        - Other:
2. Please give a description of the event
3. How soon after taking the test product did you experience the side effect?
4. What did you do to alleviate the side effect?
5. Did you have to go to the hospital or see a doctor for this side effect?
    a. Please describe any diagnosis or treatment that they provided.
    b. If you were seen in the hospital, please upload any discharge paperwork or other documents from the hospital.

13.1.8Appendix H Test Product Insert

Welcome to the Tension Headache Relief Trial!

We appreciate you taking the time to participate in this trial. As you may already know, the aim of this study is to measure the impact the test product has on your headache symptoms. Please take the time to read the following information below to become acquainted with the trial instructions.

Instructions upon Study Product Receipt:

1. Please log onto the study portal and acknowledge the receipt by completing the 'Start Form'
2. Enclosed in the study bag, please find a 3-episode supply of the tension relief test product.
3. You will take the test product the next time you have a headache and need to take something to relieve the discomfort.

Instructions Once Product Intake Begins:

1. The next time you have a headache and feel the need to take the test product, you will FIRST start the headache diary (paper forms included in this package).
    - You will complete the date of the episode, the time the episode began, what triggered the headache, type/description of the pain, its location, and record other symptoms (if applicable).
    - **REMINDER: DO NOT TAKE ANY OTHER MEDICATION/SUPPLEMENT DURING THE HOUR AFTER TAKE THE TEST PRODUCT.**
2. Next, you will complete the Pain Scale at Onset page.
3. Take the test product (2 capsules with 6-8 oz of water) and record the time you take the product.
4. Complete the pain scale again at 15, 30, and 60 minutes after taking the test product.
5. After your headache resolves, you will complete the headache diary.
    - Record whether or not your symptoms completely went away with the study product, if so, record the approximate time your symptoms resolved.
    - Record whether or not you needed to take alternative medication to help with the pain/discomfort (remember you are only allowed to take alternative medication 1 hour after from taking test product).
    - Record the name, dose, and time you took the alternative medication.
    - Record whether or not your symptoms completely went away with the alternative medication you took and the approximate time this occurred.
6. If at any point after taking the test product you experience any side effects from the test product, please log into the study portal and complete an Adverse Event form.

7. After the first headache episode, you will be asked to complete the same process for another 2 headache episodes; although we encourage you to complete these steps for another 2 episodes, they are not required.
8. If you complete the required assessments for a total of 3 headache episodes, you will be prompted, by email, to exit the study and complete the study exit form.
9. If you only complete the required assessments for the required 1 headache episode, you will be prompted, by email, to complete the study exit form on day 60 (60 days from the day of receipt of the test product).
10. Upon receipt of study exit survey and review of completed study forms, participant will receive an Amazon gift card of $25 via email

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Thank you again for participating in this trial!

If you have any questions, please contact:
Jerome Tonog, Clinical Study Manager
Jerome.tonog@hawthorne-effect.com

13.1.9Appendix I Informed consent form

RESEARCH PARTICIPANT
INFORMED CONSENT FORM & HIPAA AUTHORIZATION

Sponsor / Study Title:	**HLNatural, Inc. / "Evaluation of the impact of the HLNatural Tension Relief product on the reduction of symptoms in adults who suffer from mild to moderate tension headaches"**
Principal Investigator: (Study Doctor)	**«PiFullName»**
Telephone:	**«IcfPhoneNumber»**
Address:	**«PiLocations»**

Experimental Subjects Bill of Rights

The rights below are the rights of every person who is asked to be in a research study. As an experimental subject I have the following rights:

1. To be told what the study is trying to find out.
2. To be told what will happen to me and whether any of the procedures, drugs, or devices is different from what would be used in standard practice.
3. To be told about the frequent and/or important risks, side effects, or discomforts of the things that will happen to me for research purposes.
4. To be told if I can expect any benefit from participating, and, if so, what the benefit might be.
5. To be told of the other choices I have and how they may be better or worse than being in the study.
6. To be allowed to ask any questions concerning the study both before agreeing to be involved and during the course of the study.
7. To be told what sort of medical treatment is available if any complications arise.
8. To refuse to participate at all or to change my mind about participation after the study is started. This decision will not affect my right to receive the care I would receive if I were not in the study.
9. To receive a copy of the signed and dated consent form.
10. To be free of pressure when considering whether I wish to agree to be in the study.

WELCOME

Introduction

You are invited to participate in a research study that examines a new investigational product for potential tension headache relief. The test product contains all-natural ingredients which have been combined and placed into a capsule. The test product is to be taken when you begin to have symptoms of a tension headache. All participants will receive the test product as part of their participation in the study.

An investigational product is one that is not approved by the United States Food and Drug Administration (FDA).

A company called HLNatural, Inc. is sponsoring (paying for) this research study.

Participation in this study is voluntary. Before you decide to participate, please read this form carefully and ask the study staff for further information or clarification as necessary. Ask as many questions as required to fully understand what your participation will involve. Please do not sign and date this form unless you are fully satisfied with the answers you have received.

This form is called an *informed consent form* and it contains information regarding the purpose of the study, participation requirements, potential risks, potential benefits, and how your protected health information (PHI) will be managed.

Please take as much time as you need to review the material and make an informed decision.

ABOUT THE STUDY

Background

A tension headache is generally a mild to moderate pain in your head that's often described as a dull, aching head pain that feels like a tight band around your head. They can be episodic or chronic in nature. They are the most common type of primary headaches and affect approximately 80% of the population. Because of their high prevalence, the socio-economic consequences of tension type headaches are significant as they are associated with increased depression, anxiety, insomnia and overall decrease in quality of life.

Today, headache sufferers routinely take acetaminophen (for example, Tylenol) or a non-steroidal pain reliever (for example, Advil) for symptom relief. The side effects of these common over-the-counter products can potentially lead to gastrointestinal and cardiovascular system effects.

Who can participate?

Anyone who is at least 18 years of age who is in overall good health and suffers from mild to moderate tension headaches. All potential participants in the study must meet the rules of the study. These are called the inclusion-exclusion criteria. You will be asked to complete a few screening questions before you can be enrolled in the study. If you meet all the criteria, you may choose to participate in the study.

About 200 participants will be in this study.

What is the purpose of the study?

The purpose of the study is to evaluate the impact of the test product on the symptoms of tension headaches in adult men and women who suffer from mild to moderate tension headaches.

How long is the study?

The duration of participation for each participant is expected to be the shorter of two outcomes: 1) 60 days after your start date (the day you receive and report receipt of test product) or 2) after you complete the protocol assessments for 3 headache episodes.

Can I withdraw from the study?

Your participation in the study is voluntary. You may choose not to participate without penalty or loss of benefits. You are free to withdraw your consent at any time for any reason without prejudice. If you decide to participate, you may change your mind at any time throughout the study without any penalty or loss of benefits. If you withdraw from the study, any data collected from you prior to your withdrawal may be used for study purposes; however, no data will be collected after your withdrawal. You will not be asked to return the product.

The study doctor or the sponsor can stop your participation at any time, without your consent, for any reason.

What's in the test product capsule?

Active Ingredients: Magnesium (as Magnesium glycinate), Boswellia (40% Boswellic acids), White Willow Bark (15% Salicin), Skullcap, Feverfew
Inactive Ingredients: Vegetarian capsule (vegetable cellulose, water), Rice Hull Concentrate

The ingredients in the test product have been included because they are potentially beneficial in promoting both head and body comfort.

When will I take the test product?

You will be asked to take the test product at the onset of your tension headache. The onset is defined as the time you take the test product.

Instructions for taking the product are: take 2 capsules with 6-8 oz. of water per headache episode. The product may be used after each onset of tension headache, but not more often than three times per day.

What else will I be asked to do?

1. Complete the screening survey.
2. Sign and date the eConsent.
3. Complete a baseline survey that includes demographic information as well as information on what medication and supplements you currently take.
4. Receive test product, log into study portal, and complete test product receipt form. This will mark the start of your participation in this study.
5. 1st Tension Headache Event: start your Headache Diary, complete the 10-point Mankoski Scale (pain scale).
6. Take test product after completing the pain scale and first part of the headache diary.
7. Continue to fill out the pain scale at the following time points: 15 minutes, 30 minutes, and 60 minutes.
8. Write down any adverse or ill effects after taking the test product any time after taking the test product.
9. Complete the Headache Diary 60 minutes after taking the test product.
10. Repeat steps 5-9 for event 2 and event 3 (this is encouraged but not required).
11. Note any final adverse events (side effects) and complete the exit form.
12. During the 1 hour after taking the test product, no medication or supplementation (including all CBD products) other than the test product should be taken for relief of headache. Once the 1-hour report has been submitted, you may take other medications if required and record that behavior as part of your diary entry.
13. Participants are asked to limit the consumption of alcoholic beverages to less than or equal to two drinks per day, and to abstain from the use of cannabis for the duration of the study.

You will be exited from the study if you complete the required assessments for three headache episodes or 60 days after the study start date (the day you receive the test product). When you reach either of these milestones you will be prompted, by email, to exit the study.

Are there any potential risks?

Minimal risk is foreseen for participants through their participation in the study. All the ingredients composing the test product are Generally Recognized as Safe (GRAS) by the FDA for daily consumption at their present concentrations.

The potential risks seen with high doses (significantly higher than the dosage for the study) are:

- Diarrhea
- Nausea
- Stomach Cramps
- Acid Reflux
- Skin Rashes
- GI Bleeding
- Headaches
- Liver Damage

There are some potential drug interactions that have only been noted in animal trials or preliminary/pre-clinical trials.

Since the test product is investigational, there may be other risks that are unknown.

What are the potential benefits?

You may experience relief from your tension headache symptoms faster than otherwise experienced by taking the test product as directed. However, there is no guarantee that you will benefit from your participation in this study. Information learned from the study may help other people in the future.

New findings

Any new important information that is discovered during the study that may influence your willingness to continue participation in the study will be provided to you.

Alternatives

This research study is for research purposes only. The only alternative is to not participate in this study.

Compensation and Cost

If you complete the study, including all of the surveys and study forms, you will receive an Amazon gift card of $25.00 sent to your email, at the end of your participation in the study. You will not receive any other compensation.

There will be no charge to you for your participation in this study. The test product will be sent to each participant without any cost. Any leftover test product will not need to be returned.

Compensation for study related illness

If you experience an adverse health outcome as a result of participation in this research, you should seek immediate medical attention. As soon as possible after the incident, contact the study doctor or study staff at the phone number listed on the first page of this form.

If your adverse health outcome is found to result from the product provided to you as part of this study, the study sponsor will compensate you for related medical care as the law pertains. By signing and dating this document, you will not lose any of your legal rights or release anyone involved in the research from responsibility for mistakes.

To pay medical expenses, the sponsor will need to know some information about you like your name, date of birth, and Medicare Beneficiary Identifier (MBI). This is because the sponsor has to check to see if you receive Medicare and if you do, report the payment it makes to Medicare.

How will my information be protected?

The Health Insurance Portability and Accountability Act (HIPAA) describes how your Protected Health Information (PHI) may be used, disclosed and made accessible. You will be asked to logon to a secured internet site using a login code and a password. The platform (internet site) used for the data collection is HIPAA compliant, meaning your private information is protected by law.

In order to validate your identity, communicate with you, determine your eligibility, and send you the product, we will collect your name, address, phone number, email address, date of birth, and some medical records. Through the surveys, we will be collecting personal health information related to the study.

The information we collect will be kept confidential and will be used only for the purpose of this study. Only study staff who are involved in this study will have access to your PHI. All reports and communications released from this study will identify participants by an identification number only and will not contain identifying information. The overall results of the study may be published; however, the identity of participants will not be included.

Your right to access your PHI in the study records will be suspended during the study to keep from changing the study results. When the study is over, you can access your study health data.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You will be emailed a PDF copy of this signed and dated consent form. There may be risks of loss of privacy and confidentiality if the PDF copy of this consent form is viewed and/or stored on a personal electronic device (PED), especially if that PED is shared with other users or is lost, hacked, or subject to a search warrant or subpoena. Also, the PDF copy of the consent may not be able to be permanently removed from a PED.

Medical Release

By signing and dating this document, you authorize the study doctor, the research team, the FDA, Advarra Institutional Review Board, and/or other authorized members of HLNatural, Inc. and the Hawthorne Effect workforce to request, receive, use, and share all health information pertaining to your medical history, mental or physical condition, and treatment received for the duration of your participation in this research study.

Once your health data has been shared with authorized users, it may no longer be protected by federal privacy law and could possibly be used or disclosed in ways other than those listed here.

If you decide not to sign and date this form, you will not be able to take part in the study.

You understand that the research team and other authorized members of the Hawthorne Effect workforce may use and share your information to ensure that the research meets legal, institutional or accreditation requirements.

You understand that in all disclosures outside of Hawthorne Effect, you will not be identified by name, social security number, address, telephone number, or any other direct personal identifier unless disclosure of the direct identifier is required by law.

Your authorization to use and share your study records does not expire; however, in California and any other state that does require an expiration date, the authorization will expire 50 years after you sign and date this authorization document.

You understand that you may withdraw your permission for the use and disclosure of any of your protected information for research, but you must do so in writing to the study doctor at the address on the first page.

You understand that even if you withdraw your permission, the study doctor for the research study may still use your protected information that was already collected if that information is necessary to complete the study.

Your health information may still be used or shared after you withdraw your authorization if you should have an adverse event (a bad side effect) from being in the study.

If you withdraw your permission to use your protected health information for research, that means you will also be withdrawn from the research study, but standard medical care and any other benefits to which you are entitled will not be affected. You can also tell us you want to withdraw from the research study at any time without cancelling the authorization to use your data.

If you have other questions, you should ask the study doctor or anyone on the research team. In addition, you may contact the Institutional Review Board, which is concerned with protection of volunteers in research projects.

You will receive a signed and dated copy of this form for your records.

_____

Printed Name of Participant

_____ _____

Signature of Participant Date

Whom to contact about this study

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the Investigator at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact**:**

- By mail:
  Study Subject Adviser
  Advarra IRB
  6940 Columbia Gateway Drive, Suite 110
  Columbia, MD 21046
- or call **toll free**: 877-992-4724
- or by **email**: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: Pro00037556.

Closing Statement

I have read and understand the information in this informed consent form. My questions (if any) have been answered to my satisfaction and I do not have any further questions or doubts about partaking in this study. All written and oral communication regarding this study were in a language I fully comprehend. My decision to participate in this study is voluntary. I hereby consent to participate in this study under the conditions described above.

An electronic copy of the signed and dated consent form will be sent to you as an email attachment.

Be aware that electronic copies may not be readily removed from personal electronic devices. If the personal electronic device is shared with other users, lost, or hacked, the consent form may be revealed.

If you would like to request a paper copy of your consent as an alternative to the electronic copy, please inform study staff before signing and dating the consent.

AE	Adverse Event
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
DMID	Division of Microbiology and Infectious Diseases, NIAID, NIH, DHHS
DSMB	Data and Safety Monitoring Board
FWA	Federal-Wide Assurance
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent or Institutional Ethics Committee
IRB	Institutional Review Board
ISM	Independent Safety Monitor
JAMA	Journal of the American Medical Association
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NEJM	New England Journal of Medicine
NIAID	National Institute of Allergy and Infectious Diseases, NIH, DHHS
NIH	National Institutes of Health
OCRA	Office of Clinical Research Affairs, DMID, NIAID, NIH, DHHS
OHRP	Office for Human Research Protections
ORA	Office of Regulatory Affairs, DMID, NIAID, NIH, DHHS
PI	Principal Investigator
SAE	Serious Adverse Event
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
WHO	World Health Organization