Evaluation of the impact of the HLNatural, Inc. Immune Support Product in Reducing the Length of Cold Symptoms in Adults Suffering from the Common Cold

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July, 17th 2019

Evaluation of the impact of the HLNatural, Inc. Immune Support Product in Reducing the Length of Cold Symptoms in Adults Suffering from the Common Cold

Sponsored by:
HLNatural, Inc.

Principal Investigator:
Soyona Rafatjah, MD

Version Number
Version 1.1

Day Month Year
July, 17th 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:

http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm#46.
http://www.fda.gov/cder/guidance/959fnl.pdf
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html
http://cme.cancer.gov/c01/

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, Inc. Immunity product in reducing the length of cold symptoms in adults suffering from the common cold

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 90 days from the day of study start date.

Objectives: The purpose of this study is to demonstrate whether or not this test product will reduce the duration of cold symptoms. This trial will gather data on performance of the test product. These data will be used to describe the performance currently, and potentially to design a two-arm trial in the future.

<u>Primary Endpoints</u>:

- The primary endpoint will be time to freedom from cold symptoms, with the clock starting at the onset of the cold. The primary analysis will be a Kaplan-Meier analysis of time to absence of all symptoms, based on the participants' self-report. There is no control group for the primary analysis.

<u>Secondary Endpoints:</u>

- Secondary endpoints involve the duration and severity of the separate cold symptoms.
- 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 daily supplementation with the Immune Support test product will reduce the time to freedom from cold symptoms.

The common cold is a viral infection most commonly caused by the Rhinovirus; however, it can be caused by a number of other virus families as well. Cold viruses are transmitted via airborne and fomite routes and has a seasonal distribution in the autumn and winter; although it can occur at any time of the year. It is the most common infectious disease in the US and industrialized countries. Symptoms resulting from the common cold include nasal stuffing, sneezing, sore throat and coughing. These symptoms are a result of the cytokines, especially interleukin-8 (IL-8), released In response to infection with rhinovirus. IL-8 has been shown to cause up-regulation of adhesion molecule receptors on neutrophils and can cause neutrophil degranulation in addition to chemotaxis of eosinophils, T-lymphocytes, and basophils. Thus, cytokine elaboration, especially IL-8, plays an important role in the influx of polymorphonuclear cells (PMN) into nasal secretions and development of these symptoms of the common cold. Studies of volunteers inoculated with rhinovirus also demonstrated that symptoms during infection correlated with an increase in the concentration of IL-8 in nasal secretions. [38]

While implications on physical health are significant, the economic consequences of the common cold are also vast; direct costs associated with the cold amount to $17 billion in the United States through more than 500 million viruses. Additionally, its microeconomic impact on workplace productivity is also prevalent. The United States population misses up to 26 million days of work due to the common cold, a cause of lost productivity. [10, 26, 31]

Every year, tens of millions of dollars are spent trying to help prevent the common cold. While the common cold has associated medications that can help ease the symptoms, there has been no

therapy to treat the viral infections comprehensively. Particular drug classes, such alpha agonists (phenylephrine) and nonsteroidal anti-inflammatory drugs (NSAIDs), have helped improve symptoms in conjunction with common cold onset. However, several side effects are known for these as well as other over-the-counter products. NSAIDs have been shown to have effects on many organ systems in the body. The side-effects include dyspepsia, peptic ulcer disease, bleeding, modest worsening of hypertension, edema, myocardial infarction, and many others. [39] While oral alpha-agonists (phenylephrine) have shown to cause anxiety, dizziness, headache, insomnia, nervousness, restlessness.[40] Additionally, antibiotics are not recommended as colds are viral, not bacterial. [10, 31]

HLNatural, Inc. was formed to create an herbal product that is designed to avoid side effects as well as unnecessary synthetics, sweeteners, and preservatives found in over the counter remedies today. As such, HILMA created a line of products containing high-quality, well-researched ingredients creating a unique product unlike anything else on the market. This Immune Support Product is formulated with ingredients with demonstrated potential to reduce duration and symptoms associated with the common cold. The products combine ingredients previously reported as potentially beneficial into an easy to consume powder drink-mix designed for intake twice a day. The ingredients in the test product are 1) Echinacea 2) Ivy Extract, 3) Camu Camu, 4) Ginger, 5) Turmeric, 6) Zinc, 7) Monk Fruit Extract, 8) Natural Flavor, 9) Guar Gum, 10) Citric Acid. Listed below are the 6 active ingredients of the test product. All ingredients are Generally Recognized as Safe (GRAS) by the FDA.

Immune Support

Active Ingredients: Echinacea Fresh, Ivy Extract, Camu Camu, Ginger, Turmeric, Zinc

Inactive Ingredients: Natural Flavor, Guar Gum, Monk Fruit Sweetener, Citric Acid

Supplement Facts

Serving Size 1 Sachet (5.4g)
Servings per Container 3

	Amount Per Serving	% Daily Value
Calories	5	
Total Carbohydrate	1 g	<1% *
Total Sugars	<1 g	†
Vitamin C (as Camu-camu (Fruit) Powder & Ascorbic Acid)	500 mg	833%
Zinc (as Zinc Gluconate)	15 mg	100%
Organic Turmeric Powder (Rhizome)	500 mg	†
Echinacea purpurea Extract (Aerial)	400 mg	†
Organic Ginger Powder (Root)	250 mg	†
English Ivy Extract (Leaf)	25 mg	†

*Percent Daily Values are based on a 2,000 calorie diet.
† Daily Value Not Established

OTHER INGREDIENTS: Natural Flavor, Guar Gum, Monk Fruit Extract, Citric Acid

The ingredients in the Immune Support Product have been included because of previously demonstrated benefits in supporting the immune system and reducing duration and symptoms of colds. The justifications for their inclusion are briefly described here:

Echinacea has shown to be clinically effective for supporting the immune system. Through preclinical and clinical studies, Echinacea has been shown to have multiple supportive effects on the immune system, such as stimulating macrophages and other cells of the innate immune system. Several clinical studies have also shown that Echinacea supports healthy immune function while reducing duration of colds. In one clinical study, Echinacea improved immune function in healthy people experiencing fatigue. The improvement in immune function in this study correlated with a higher measure of wellness. [4, 11, 12, 16, 17, 25, 27, 37]

Ivy Extract is a traditional European herb that has been used for centuries for supporting the respiratory system. Numerous preclinical and clinical studies have been conducted on Ivy Leaf Extract, which have substantiated its safe use for soothing cough, thought due to its expectorant and antispasmodic activity. In a review of 18 clinical trials, Ivy Extract was shown to be well established in supporting respiratory health. [3, 13, 32]

Camu Camu The Vitamin C in Immune Support is from a whole food source, called Camu Camu, a fruit from the Amazon with one of the highest Vitamin C contents in the world. Vitamin C is an important supportive nutrient in this formula for supporting the immune system. Additionally, Vitamin C acts as a cofactor for a number of enzymes and metabolic reactions in the body responsible for maintaining health and wellness. The Vitamin C from Camu Camu is also combined with naturally occurring bioflavonoids from its whole food source, providing a more full-spectrum

antioxidant support. In two controlled trials, showed that regularly administered vitamin C shortened the duration of colds, indicating a biological effect. They found a statistically significant dose-response, for the duration of common cold symptoms. [2, 8, 14, 19, 30, 41]

Ginger is a spice with a long history of traditional use for symptoms of a cold, including digestive discomfort, cough, and aches and pains. Clinical research shows that Ginger supports health through its benefits to the immune and respiratory systems, as well as promoting normal cytokine balance. [21, 24, 28, 29, 33]

Turmeric is a spice with a long history of traditional use for symptoms of a cold. Clinical and preclinical studies have shown it to support the immune & respiratory systems and support normal cytokine balance. Turmeric is used traditionally for wide uses, and as the research builds it shows that it is indeed capable of supporting multiple body systems, substantiating the tonic effect of this herb in maintaining overall health and vitality. [1, 15, 36]

Zinc is an essential mineral important for numerous physiological processes, notably, healthy immune response. Zinc has also been found to support immune health through a number of preclinical and clinical studies. In one study involving 100 people, zinc supplementation resulted in significant immune support. In another trial, supplementation with a zinc lozenge showed a significant decrease in the duration of cold symptoms. [6, 7, 9, 19, 20, 22, 34, 35]

2.2.Scientific Rationale

The test product formulation is based on the most promising clinical research on natural ingredients to safely impact the immune system and reduce duration of the common cold. 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.

The present study will include at least 200 adult participants in the general population who are seeking herbal remedies to reduce the duration of their common cold symptoms.

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.

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:

- epigastric pain
- nausea
- vomiting
- loss of appetite
- abdominal cramps
- diarrhea
- headaches

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

Over-the-counter and prescription remedies aimed toward relieving the symptoms of the common cold may have known undesirable side effects Study participants may benefit from the test product by eliminating unwanted exposure to undesirable ingredients and side effects of other-the-counter drugs when treating a common cold, while still achieving symptom relief and reducing the duration of their cold.

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 will be provided. Once an event occurs, review of symptoms will be

ascertained daily until symptoms have resolved or for 18 days. 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 will be advised to stop the product and may seek medical attention and exit the study.

3.Study Objectives

The purpose of the present study is to evaluate 1) the impact of the Immune Support test product on the duration of symptoms of the common cold in adult participants and 2) the subjective experience of these participants related to general health, common cold symptoms, and personal experience with the product. [13, 18, 29, 32]

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 will be time to freedom from cold symptoms, with the clock starting at the onset of the cold. Where the onset is defined as the point in time when the participant experiences 2 or more cold symptoms. The primary analysis will be a Kaplan-Meier analysis of time to absence of all symptoms, based on the participants' self-report. There is no control group for the primary analysis. [5]

Secondary Endpoint:

- Secondary endpoints involve the duration and severity of the separate cold symptoms.
- 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 single site, prospective, single arm observational study of minimal risk consisting of at least 200 participants who suffer from cold symptoms. The participants must meet additional inclusion/exclusion criteria (see Inclusion/Exclusion Criteria). Participants will begin taking the powder drink-mix at the onset of their cold symptoms. Onset is defined as the point in time the participant experiences 2 or more cold symptoms (cough, hoarseness, muscle ache, nasal drainage,

nasal congestion, scratchy throat, sore throat, sneezing, or an oral temperature greater than 37.7 °C (99.9 °F)). When the participant experiences 2 or more symptoms, they will report symptoms in the cold start form. If they meet the criteria for a cold, they will start completing the daily cold symptom diary prior to taking the test product. After consuming the product, the participant will complete the cold symptom diary daily until all symptoms resolve. Since none of the ingredients in the test product have been seen to provide relief from fever or pain, the participant will be allowed to take a pain reliever and fever reducer (e.g. ibuprofen or acetaminophen). If medication is taken, the participant will record this in their symptom diary.

Study enrollment and management will be decentralized, 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 participant 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

Overview:

Participants in this study will consume the test product twice a day (4-6 hours apart) at the onset of cold symptoms. The participant will mix one packet of the test product in 6-8 ounces of water. The test product will be delivered to the participants' residence in a single shipment consisting of an18-day supply (36 packets) of the test product. The study participant will mix the contents of the packet into 6-8 oz. of hot water and drink twice a day during the duration of the cold.

Below is the description of the test product and its ingredients.

Test Product

Description: Combining whole food sourced Vitamin C, Echinacea, Ivy Extract, Zinc, Ginger and Turmeric. This formula is designed to support the immune system while reducing the duration of cold.

Active Ingredients: Echinacea, Ivy Extract, Camu Camu (Vitamin C), Ginger, Turmeric, Zinc.

Inactive Ingredients: Natural Flavor, Guar Gum, Monk Fruit Sweetener, Citric Acid.

4.2.Required Behavior

If the participant is prescribed antibiotics or any other medications for any reason, they should report this prescription and they will be withdrawn from the trial as of the prescription date.

Participants are asked not to ingest or take any other form of cold remedy (over-the-counter (NyQuil/Dayquil/Cough Syrup/Cough Drops/EmergenC/Airborne/Zarbee's or any similar cold-relief product or prescription drugs) during the 18-day study period. If taken during the study duration the participant will record this as part of their diary and will be exited from the study.

Because none of the active ingredients are aimed at pain relief or reducing fever, participants will be allowed to take pain relievers/fever reducers (Advil/Tylenol or their equivalent).

Participants are asked to limit the consumption of alcohol beverages to less than or equal to two drinks per day and avoid recreational drugs or use of cannabis during the study period.

4.3.Participation Period

Participants are expected to participate in the study for 18 days after the onset of the first cold. Onset is defined as the day that the participant experiences 2 or more cold symptoms. Participant will be exited once all symptoms have been resolved or at 18 days whichever is shorter. If no cold has started within 90 days of participant study start date (date the participant receives and records receipt of test product) participants will be exited from the study.

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.

The primary endpoint will be time to freedom from cold symptoms, with the clock starting at the onset of the cold. The primary analysis will be a Kaplan-Meier analysis of time to absence of all symptoms, based on the participants' self-report. There is no control group for the primary analysis.

Secondary endpoints involve evaluation of the duration and severity of the separate cold symptoms. 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.

5.Study Population

5.1.Selection of the study Population

The study population will consist of at least 200 participants 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 80 treated participants This sample size has been calculated to provide a reasonable estimate of the time to cold resolution, as further 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 80 treated participants will be met by the end of follow-up. If the expected number of treated participants is less than 80, the target sample size will be increased as needed, considering both the desire for 80 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 the target number of participants have been enrolled; no further participants will be offered a place in the trial once the target sample size criteria has been met. All participants 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 are in the general population who are seeking herbal remedies to reduce the duration of their common cold symptoms.

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. Ads will target those who are prone to getting the common cold; travelers, healthcare providers, teachers, daycare workers, etc.

After clicking on an advertisement, potential participants will then be directed to a website where they will complete a screening questionnaire (See Appendix). The screening questionnaire will

automatically qualify or disqualify them for study participation. If the participant qualifies, she 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.

Inclusion Criteria:

Adult candidates in the general population who are in good health and are seeking herbal remedies to reduce the duration of their common cold symptoms when they should arise. Participants will be deemed to be in good health if they do not report any of the medical conditions asked about in the screening questionnaire.

Exclusion Criteria:

- Age < 18 years old
- Unwilling to try the test product during their first cold experience in the trial
- Has any of the following medical conditions:
    - Allergy to any of the following ingredients: Echinacea, Ivy Extract, Camu Camu, Vitamin C, Ginger, Turmeric, Zinc or a known allergy to Guar Gum, Monk Fruit, Citric Acid, Natural Flavors.
    - Alcohol consumption more than 10 drinks per week
    - Chronic renal disease
    - Chronic liver disease
    - Known autoimmune or immunodeficiency disorders
    - Pregnant or breastfeeding

6.Study Evaluation

6.1.Study Procedures

- Candidates will review information about the study and complete a screening form.
- During the screening process, the participant will be asked questions regarding their symptoms and medical history to ensure that they meet the requirements to participate in this study. The potential participant 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, symptom 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, detailed information regarding previous colds, 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 operations 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, disposable thermometer, 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 date of acknowledgement of receipt of test product.
- Participant will be sent weekly email reminders that remind them of their participation in the study. Once the participant indicates they are experiencing a cold. The participant will be reminded by email daily to complete their symptom diary.
- At the onset of their cold symptoms, the participant will complete the cold start form.
    - Onset is defined as the point in time the participant experiences 2 or more cold symptoms (cough, hoarseness, muscle ache, nasal drainage, scratchy throat, sore throat, sneezing, oral temperature greater than 37.7°C (99.9 °F)).
    - If fever is a symptom that the participant experiences, they will use the provided disposable thermometer to take their temperature and record it in the diary.
- If the participant meets all the criteria for a cold, they will start their symptom diary prior to taking the test product.
- After completing the surveys, the participant will take the test product. The participant will mix 1 drink-mix packet into 6-8 oz of water and consume the whole drink.
- Participant will take the test product twice a day, at least 4-6 hours apart.
- The next day the participant will complete their symptom diary prior to taking the test product. Once completed they will mix 1 packet of the test product into 6-8 oz of water and consume the whole drink. They will take the test product again 4-6 hours later.
- The participant will complete this process daily until their cold symptoms resolve or for 18 days, whichever is shorter.
- If the participant takes ibuprofen or acetaminophen at any time, the participant will record this on their symptom diary.
- After taking the test product, the participant will be instructed to fill out an Adverse Event form for any side-effects experienced.
- The participant will be prompted, by email, to complete the study exit form once the participant's symptoms resolve completely or after 18 days, whichever is shorter.
- Neither the sponsor nor Hawthorne Effect, Inc. will make any attempt to collect any unused test 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 Start Date**	Days 1-18*	Study Exit***
Study Window							
Screening Survey	X						
Consent		X					
Baseline Survey			X				
Demographics			X				
Acknowledgement of Receipt of Test Product				X			
Test Product Consumed****					X	X	
Symptom Diary					X	X	X
Meds & Supplements			X				
AE Assessment					X	X	X
Study Exit Survey							X

*Participant will participate in the study starting on the day of the cold until the cold symptoms resolve or 18 days whichever is shorter.

** The day the participant experiences 2 or more of the protocol defined symptoms

*** The participant will exit the study at the time of complete cold symptom resolution, 18 days after the start of cold symptoms, or at 90 days if no cold is experienced by the participant.

**** The product will be consumed twice a day, 4-6 hours apart

6.3.Participant Enrollment and Follow-Up

Candidates will be screened using a HIPAA-secured screening survey to determine eligibility. All eligibility criteria must be met for candidates to be approved for enrollment into the study. Candidates will be provided an informed consent form and will be given the opportunity to ask questions related to the study procedures, risks and benefits, and rights related to participation in the study. Candidates 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 test product at the onset of colds symptoms and provide information related to their cold 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):

- epigastric pain
- nausea
- vomiting
- loss of appetite
- abdominal cramps
- diarrhea
- headaches

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 participant 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 cold 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 18-day supply of test product (36 packets) will be packaged and labeled with 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 participant 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 cold symptoms, and have taken the test product at least once. The primary analysis will be in the ITT population.

Primary Endpoint:

- The primary endpoint will be time to freedom from cold symptoms, with the clock starting at the onset of the cold. Where the onset is defined as the point in time when the participant experiences 2 or more cold symptoms. The primary analysis will be a Kaplan-Meier analysis of time to absence of all symptoms, based on the participant's self-report. There is no control group for the primary analysis.

Secondary Endpoints:

- Secondary endpoints involve the duration and severity of the separate cold symptoms.
- 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.

7.2.Sample Size Considerations

The referenced paper of Mossad, Macknin, et al. had a sample size of 100 patients with colds, of which 50 were in the treatment arm. Based on informal readings of various sources, we estimate that approximately 40% of the enrolled participants in this trial will experience a cold during the 90-day period. A sample size of 200 enrolled participants would then yield 80 participants with colds. Even with the uncertainties of compliance in this trial, the sample size should enable reasonable comparison of results against the Mossad, Mackin et al. study. [20]

As discussed above, the number 200 may be increased based on observed data concerning the number of participants with colds. 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

Time-dependent variable analysis

The primary analysis involves time dependent variables. The Kaplan-Meier algorithm will be used to analyze time to freedom from cold symptoms. Data presentation will include tables and graphs; in particular tables of participants at risk at various time points.

Censoring:

- Participants who do not have a cold during the trial will not be in the ITT population, and will not be included in the endpoint analysis.
- Participants who report the onset of a cold, but who do not complete the daily reports through 18 days will be censored as of the date of the last report.
- Participants who still have cold symptoms at 18 days will be censored at that time.
- Participants will also be censored if they withdraw from the trial.

Secondary Endpoints:

- Analysis of the individual cold symptoms will be a presentation of median time until the individual symptom resolves. The median for this purpose is the value computed as part of the Kaplan-Meier algorithm.
- An additional analysis will investigate the relation between baseline age and gender, and the time to resolution.
- Adverse events will be summarized.
- An additional data presentation will consist of side by side presentation 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.

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 at a later date. [23]

- Data analysis will largely consist of summary statistics and graphs. The only formal statistical 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.
- 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.
- 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.
- The exact items to be compared depend on what is reported in each historical control study. When possible, the items will include time to resolution of all cold symptoms, time to resolution of each individual cold symptom, proportion of cold symptoms resolved at each time, and reported baseline characteristics. When two-arm studies are compared, both arms will be reported in this comparison. Specific studies to be considered will include the Cleveland study, and other studies identified prior to the analysis of actual trial data.

8.Informed Consent Process

The study protocol and informed consent will be reviewed and 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 proved 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

This study will be registered on clinicaltrials.gov prior to commencement of enrollment the results will be analyzed and submitted for publication.

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 participants' subjective information and self-reporting; there is no medical review of symptoms, and no independent check on participant compliance. Some participant groups are not studied, including those under 18 years of age and pregnant women.

12.Bibliography

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13.Supplement and Appendix

13.1. Appendix

13.1.1. Appendix A Drug Interactions

Drug Interactions for Test Product

ECHINACEA

There are no Serious Drug Interactions known for Echinacea. There are some theoretical Moderate Interactions, where Echinacea may interact in the metabolism of certain drugs (which utilize the same enzymes it inhibits). See Below for List. Echinacea theoretically may also interfere with immunosuppressant therapy drugs due to its immune-stimulating activity.

CAFFEINE

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

Echinacea seems to increase plasma concentrations of caffeine by 30% (12155). This is likely due to inhibition of cytochrome P450 1A2 (CYP1A2) by echinacea.

CYTOCHROME P450 1A2 (CYP1A2) SUBSTRATES

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

Echinacea appears to inhibit CYP1A2 enzymes in humans (12155). Theoretically, echinacea might increase levels of drugs metabolized by CYP1A2. Some drugs metabolized by CYP1A2 include acetaminophen (Tylenol), amitriptyline (Elavil), clopidogrel (Plavix), clozapine (Clozaril), diazepam (Valium), estradiol, olanzapine (Zyprexa), ondansetron (Zofran), propranolol (Inderal), ropinirole (Requip), tacrine (Cognex), theophylline, verapamil (Calan, Covera-HS, Isoptin, Verelan), warfarin (Coumadin), and others.

CYTOCHROME P450 3A4 (CYP3A4) SUBSTRATES

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

Several clinical trials have shown that taking echinacea for up to one month does not significantly affect the metabolism of various cytochrome P450 3A4 (CYP3A4) substrates, including midazolam, docetaxel, etrovine, lopinavir-ritonavir, and darunavir-ritonavir (13712,48618,88164,88165). However, other clinical research shows that echinacea may increase the clearance of midazolam, suggesting that echinacea might induce CYP3A4 (48618). The discrepancy is thought to be due to differing effects of echinacea on intestinal versus

hepatic CYP3A4 enzymes. Echinacea appears to induce hepatic CYP3A4 and inhibit intestinal CYP3A4 (12155). In some cases, these effects might cancel out each other, resulting in little or no change in drug levels. In other cases, drug levels may be increased or decreased depending on the extraction of drugs at hepatic and intestinal sites. The effect of echinacea on CYP3A4 activity may differ depending on the CYP3A4 substrate (6450,11026,88162,88167). For now, closely monitor patients taking echinacea along with drugs metabolized by CYP3A4. Theoretically, echinacea may alter the effects and side effects of these drugs. Some drugs metabolized by CYP3A4 include lovastatin (Mevacor), clarithromycin (Biaxin), cyclosporine (Neoral, Sandimmune), diltiazem (Cardizem), estrogens, indinavir (Crixivan), triazolam (Halcion), and numerous others.

DARUNAVIR (Prezista)

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

Darunavir is metabolized by cytochrome P450 3A4 (CYP3A4) and is administered with the CYP3A4 inhibitor ritonavir to increase its plasma concentrations. Echinacea has variable effects on CYP3A4, but administration of an E. purpurea root extract (Arkocapsulas Echinacea, Arkopharma, Madrid, Spain) 500 mg four times daily for 14 days did not affect darunavir / ritonavir pharmacokinetics in 15 HIV-infected patients (88163,93578).

DOCETAXEL (Docefrez, Taxotere)

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

Docetaxel is metabolized by cytochrome P450 3A4 (CYP3A4). Echinacea has variable effects on CYP3A4, but taking E. purpurea whole plant extract (Echinaforce, A. Vogel Biopharma AG, Elburg, The Netherlands) 20 drops three times daily for 2 weeks did not alter the pharmacokinetics of docetaxel given as an intravenous infusion of 135 mg over one hour (88164).

ETOPOSIDE (VePesid)

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

In one report, concomitant use of etoposide and echinacea was associated with more severe thrombocytopenia than the use of etoposide alone, suggesting inhibition of etoposide metabolism (20082). Etoposide is a cytochrome P450 3A4 (CYP3A4) substrate. Echinacea has variable effects on CYP3A4, but some studies have reported inhibition of the enzyme (6450,11026,12155,88162,88167).

ETRAVIRINE (Intelence)

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

Etravirine is metabolized by cytochrome P450 3A4 (CYP3A4). Echinacea has variable effects on CYP3A4, but taking E. purpurea root extract (Arkocapsulas Echinacea, Arkopharma, Madrid, Spain) 500 mg three times daily for 14 days did not alter the pharmacokinetics of etravirine in HIV-infected patients (88165,93578).

IMMUNOSUPPRESSANTS

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

Theoretically, echinacea may interfere with immunosuppressant therapy because of its immunostimulating activity (3279,6388,6389,12639). 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).

LOPINAVIR/RITONAVIR (Kaletra)

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

Lopinavir is metabolized by cytochrome P450 3A4 (CYP3A4) and is administered with the CYP3A4 inhibitor ritonavir to increase its plasma concentrations. Echinacea has variable effects on CYP3A4, but taking E. purpurea (Echinamide, Natural Factors Nutritional Products, Inc., Everett, WA) 500 mg three times daily for 14 days did not alter the pharmacokinetics of lopinavir / ritonavir in healthy volunteers (48618,93578).

MIDAZOLAM (Versed)

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

Echinacea appears to inhibit intestinal cytochrome P450 3A4 (CYP3A4), leading to an increase in oral midazolam availability. Echinacea also appears to induce hepatic CYP3A4, increasing hepatic clearance of midazolam by 34%. Overall, plasma levels of midazolam after oral administration do not seem to be affected by echinacea. However, theoretically, echinacea might decrease the effectiveness of intravenous midazolam by inducing hepatic CYP3A4 and lowering plasma levels by about 20% (12155).

WARFARIN (Coumadin)

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

Preliminary clinical research in healthy male volunteers suggests that taking echinacea increases the clearance of the active S-isomer of warfarin after a single dose of warfarin, but there was not

a clinically significant effect on the international normalized ratio (INR) (20083). Patients taking warfarin should be advised to use echinacea cautiously.

Interactions with Herbs & Supplements

None known.

IVY EXTRACT

There are no Serious Drug Interactions known for Ivy Extract.

None known.

Interactions with Herbs & Supplements

None known.

ACEROLA, VITAMIN C

There are no Serious Drug Interactions known for Acerola. There are a couple theoretical Moderate Interactions having to do with its Vitamin C content, however.

ESTROGENS

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

Concomitant use of estrogens with acerola might increase absorption and therapeutic effects due to vitamin C content (129,130).

FLUPHENAZINE (Prolixin)

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

Concomitant use with acerola decreases blood levels due to vitamin C content (15).

WARFARIN (Coumadin)

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

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

Concomitant use with acerola can reduce anticoagulant activity of warfarin due to its vitamin C content (506).

Interactions with Herbs & Supplements

VITAMIN C: Due to vitamin C content in acerola, concomitant use of acerola with vitamin C supplements might increase the risk of adverse effects associated with vitamin C.

GINGER

There are no Serious Drug Interactions known for Ginger. There are some theoretical Moderate Interactions having to do with the potential of ginger in decreasing platelet aggregation. See Below for List.

ANTICOAGULANT/ANTIPLATELET DRUGS

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

Based on laboratory research, ginger is thought to inhibit thromboxane synthetase and decrease platelet aggregation (7622,12634,20321,20322,20323,96257). However, this has not been demonstrated unequivocally in humans, with mixed results from clinical trials (96257). Theoretically, excessive amounts of ginger might increase the risk of bleeding when used with anticoagulant/antiplatelet drugs. Some anticoagulant or antiplatelet drugs include aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, ticlopidine (Ticlid), warfarin (Coumadin), and others.

ANTIDIABETES DRUGS

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

Evidence from animal and human research suggests that ginger might increase insulin levels and/or decrease blood glucose levels (12636,20402,20403,20404,20405,89895,89896). Theoretically, ginger might have an additive effect with antidiabetes drugs and cause hypoglycemia. Some antidiabetes drugs include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, metformin (Glucophage), pioglitazone (Actos), rosiglitazone (Avandia), and others.

CALCIUM CHANNEL BLOCKERS

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

Preliminary research suggests ginger might have hypotensive and calcium channel-blocking effects (12633). Theoretically, ginger might have an additive effect with calcium channel blockers. Calcium channel blockers include nifedipine (Adalat, Procardia), verapamil (Calan, Isoptin, Verelan), diltiazem (Cardizem), isradipine (DynaCirc), felodipine (Plendil), amlodipine (Norvasc), and others.

CYCLOSPORINE (Neoral, Sandimmune)

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

In an animal model, ginger juice taken 2 hours prior to cyclosporine administration reduced the maximum concentration and area under the curve of cyclosporine by 51.4% and 40.3%, respectively. This effect was not observed when ginger juice and cyclosporine were administered at the same time (20401).

METRONIDAZOLE (Flagyl)

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

In an animal model, ginger increased the absorption and plasma half-life of metronidazole. In addition, the elimination rate and clearance of metronidazole was significantly reduced (20350).

NIFEDIPINE

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

Clinical research shows that combined treatment with ginger 1 gram plus nifedipine 10 mg significantly inhibits platelet aggregation compared to nifedipine alone or ginger alone (20324).

PHENPROCOUMON

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

Phenprocoumon, a warfarin-related anticoagulant used in Europe, might increase the international normalized ratio (INR) when taken with ginger. There is one case report of a 76 year old woman with a stable INR on phenprocoumon that increased to greater than 10 when she began consuming dried ginger and ginger tea (12880).

WARFARIN (Coumadin)

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

Preliminary evidence suggests that ginger might inhibit thromboxane synthetase and decrease platelet aggregation (7622,12634,20321,20322,20323). In one case report, ginger increased the INR when taken with phenprocoumon, which has similar pharmacological effects as warfarin (12880). In another case report, ginger increased the INR when taken with a combination of warfarin, hydrochlorothiazide, and acetaminophen (20349). A longitudinal analysis suggests that taking ginger increases the risk of bleeding in patients taking warfarin for at least 4 months (20348). However, research in healthy people suggests that ginger has no effect on INR, or the pharmacokinetics or pharmacodynamics of warfarin (12881,15176). Until more is known, monitor INRs closely in patients taking significant amounts of ginger.

Interactions with Herbs & Supplements

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Based on laboratory research, ginger is thought to inhibit thromboxane synthetase and decrease platelet aggregation (7622,12634,20321,20322,20323). However, this has not been demonstrated unequivocally in humans with mixed results from clinical trials (96257). Concomitant use of ginger with other herbs that might affect platelet aggregation could theoretically increase the risk of bleeding in some people. These herbs include angelica, clove, danshen, garlic, ginkgo, Panax ginseng, red clover, turmeric, and others.

HERBS AND SUPPLEMENTS WITH HYPOGLYCEMIC POTENTIAL: Ginger might increase insulin levels and/or decrease blood glucose levels (12636,20402,20403,20404,20405,89895,89896). Theoretically, ginger might have additive effects with herbs that decrease blood glucose levels. Herbs with hypoglycemic potential include devil's claw, fenugreek, guar gum, Panax ginseng, and Siberian ginseng.

TURMERIC

There are no Serious Drug Interactions known for Turmeric. There are some theoretical Moderate Interactions, however, see below for list.

ANTICOAGULANT/ANTIPLATELET DRUGS

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

In vitro, turmeric has been shown to have antiplatelet effects (11143,81204,81271). However, results from human research are inconsistent. Turmeric has reportedly increased in the international normalized ratio (INR) in a patient using the vitamin K antagonist, fluindione (89718). However, use of a whole food supplement containing broccoli powder, turmeric

powder, pomegranate whole fruit powder, and green tea extract for 6 months does not influence INR in men taking warfarin (89730). Also, combining curcumin 500 mg with aspirin 100 mg does not appear to increase antiplatelet effects or bleeding risk (96137). Until more is known, use turmeric cautiously in combination with anticoagulant and antiplatelet drugs. Theoretically, concomitant use might increase the risk of bleeding due to decreased platelet aggregation. Some of these drugs include aspirin, clopidogrel (Plavix), dalteparin (Fragmin), enoxaparin (Lovenox), heparin, ticlopidine (Ticlid), warfarin (Coumadin), and others.

ANTIDIABETES DRUGS

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

Animal research and case reports suggests that the turmeric constituent, curcumin, can reduce levels of blood glucose and glycosylated hemoglobin (HbA1C) in patients with diabetes (79114,79573,79591,79692,79984,80155,80313,80315,80476,80553)(81048,81219). Furthermore, pharmacokinetic research shows that taking curcumin 475 mg daily for 10 days prior to taking glyburide 5 mg increases blood levels of glyburide by 12% at 2 hours after the dose in patients with type 2 diabetes. While maximal blood concentrations of glyburide were not affected by curcumin, the combination of curcumin and glyburide modestly decreased postprandial glucose levels for up to 24 hours compared to glyburide alone (96133). Theoretically, taking a combination of turmeric and antidiabetes drugs might have an additive effect and increase the risk of hypoglycemia. Some medications used for diabetes include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, pioglitazone (Actos), rosiglitazone (Avandia), chlorpropamide (Diabinese), glipizide (Glucotrol), tolbutamide (Orinase), and others.

CAMPTOTHECIN

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

One in vitro study suggests that curcumin inhibits camptothecin-induced apoptosis of breast cancer cells by up to 71% (96126). However, other in vitro research shows that curcumin can augment the cytotoxic effects of camptothecin. Reasons for the discrepancies may relate to the dose of curcumin and the timing of curcumin exposure (96125). It is not known if turmeric or its constituent curcumin inhibits or augments the cytotoxicity camptothecin in humans. Until more is known, use turmeric cautiously in combination with camptothecin. Theoretically, concomitant use of turmeric with camptothecin would reduce the efficacy of camptothecin.

CYCLOPHOSPHAMIDE

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

In an animal model of breast cancer, curcumin 25 grams/kg appears to inhibit cyclophosphamide-induced tumor regression (96126). However, other laboratory research shows that curcumin can augment the cytotoxic effects of cyclophosphamide. Reasons for the

discrepancies may relate to the dose and timing of curcumin exposure (96125). It is not known if turmeric or its constituent curcumin inhibits or augments the cytotoxicity cyclophosphamide in humans. Until more is known, use turmeric cautiously in combination with cyclophosphamide. Theoretically, concomitant use of turmeric with cyclophosphamide might reduce the efficacy of cyclophosphamide.

CYTOCHROME P450 1A1 (CYP1A1) SUBSTRATES

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

Most evidence from in vitro and animal research suggests that the turmeric constituent, curcumin, suppresses cytochrome P450 1A1 (CYP1A1) enzyme, primarily in the liver (15823,21495,80876,81411). However, some evidence from in vitro research suggests that curcumin may induce CYP1A1 in the intestines (21500). Theoretically, curcumin might increase or decrease levels of drugs metabolized by this enzyme. However, this interaction has not been reported in humans. Some medications metabolized by CYP1A1 include chlorzoxazone (Lorzone), theophylline, and bufuralol.

CYTOCHROME P450 1A2 (CYP1A2) SUBSTRATES

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

In vitro and animal research shows that the turmeric constituent, curcumin, inhibits cytochrome P450 1A2 (CYP1A2) enzyme (15823,21497,81304). Theoretically, curcumin might increase levels of drugs metabolized by this enzyme. However, other in vitro research suggests that curcumin does not significantly affect CYP1A2 (22000). Also, this interaction has not been reported in humans. Some substrates of 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 3A4 (CYP3A4) SUBSTRATES

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

In vitro and animal model research shows that turmeric and its constituent curcumin inhibits cytochrome P450 3A4 (CYP3A4) (21497,21498,21499). Additionally, in one case report, a transplant patient presented to an emergency room with acute nephrotoxicity and elevated tacrolimus levels of 29 ng/mL. The patient previously had tacrolimus levels within the therapeutic range at 9.7 ng/mL. Ten days prior to presenting at the emergency room the patient started consumption of turmeric powder, 15 or more spoonfuls daily. It was thought that turmeric increased levels of tacrolimus due to CYP3A4 inhibition (93544).

Theoretically, turmeric and curcumin might increase levels of other drugs metabolized by this enzyme. Some drugs metabolized by CYP3A4 include some calcium channel blockers

(diltiazem, nicardipine, verapamil), chemotherapeutic agents (etoposide, paclitaxel, vinblastine, vincristine, vindesine), antifungals (ketoconazole, itraconazole), glucocorticoids, alfentanil (Alfenta), cisapride (Propulsid), fentanyl (Sublimaze), lidocaine (Xylocaine), losartan (Cozaar), fexofenadine (Allegra), midazolam (Versed), and others.

DOCETAXEL (Docefrez, Taxotere)

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

Animal research suggests that the turmeric constituent, curcumin, enhances the oral bioavailability of docetaxel (80999). Theoretically, concomitant use might increase blood levels of orally administered docetaxel. However, the significance of this interaction is unclear, since this drug is typically administered intravenously in clinical settings.

DOXORUBICIN

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

One in vitro study suggests that curcumin inhibits doxorubicin-induced apoptosis of breast cancer cells by up to 65% (96126). However, other in vitro research shows that curcumin can augment the cytotoxic effects of doxorubicin. Reasons for the discrepancies may relate to the dose of curcumin and the timing of curcumin exposure (96125). It is not known if turmeric or its constituent curcumin inhibits or augments the cytotoxicity doxorubicin in humans. Until more is known, use turmeric cautiously in combination with doxorubicin. Theoretically, concomitant use of turmeric with doxorubicin would reduce the efficacy of doxorubicin.

ESTROGEN

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

In vitro research shows that curcumin displaces the binding of estrogen to its receptors (21486). Theoretically, concomitant use of large amounts of curcumin might interfere with hormone replacement therapy through competition for estrogen receptors.

GLYBURIDE

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

Pharmacokinetic research shows that taking curcumin 475 mg daily for 10 days prior to taking glyburide 5 mg increases blood levels of glyburide by 12% at 2 hours after the dose in patients with type 2 diabetes. While maximal blood concentrations of glyburide were not affected by curcumin, the combination of curcumin and glyburide modestly decreased postprandial glucose levels for up to 24 hours compared to glyburide alone (96133). Theoretically, taking a combination of turmeric and glyburide might increase the risk of hypoglycemia.

MECHLORETHAMINE

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

One in vitro study suggests that curcumin inhibits mechlorethamine-induced apoptosis of breast cancer cells by up to 70% (96126). However, other in vitro research shows that curcumin can augment the cytotoxic effects of mechlorethamine. Reasons for the discrepancies may relate to the dose of curcumin and the timing of curcumin exposure (96125). It is not known if turmeric or its constituent curcumin inhibits or augments the cytotoxicity mechlorethamine in humans. Until more is known, use turmeric cautiously in combination with mechlorethamine. Theoretically, concomitant use of turmeric with mechlorethamine would reduce the efficacy of mechlorethamine.

NORFLOXACIN (Noroxin)

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

Animal research shows that taking curcumin can increase blood levels of orally administered norfloxacin (80863). Theoretically, curcumin might increase the effects and adverse effects of norfloxacin. However, so far, this interaction has not been reported in humans.

P-GLYCOPROTEIN SUBSTRATES

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

In vitro and animal research shows that curcuminoids and other constituents found in turmeric can inhibit P-glycoprotein expression and activity (21472,21473,21474,21475,21476,21477,21478,21479,21480)(21482,21484). Theoretically, turmeric might increase the absorption of P-glycoprotein substrates. Drugs that might be affected include some chemotherapeutic agents (etoposide, paclitaxel, vinblastine, vincristine, vindesine), antifungals (ketoconazole, itraconazole), protease inhibitors (amprenavir, indinavir, nelfinavir, saquinavir), H2 antagonists (cimetidine, ranitidine), some calcium channel blockers (diltiazem, verapamil), digoxin, corticosteroids, erythromycin, cisapride (Propulsid), fexofenadine (Allegra), cyclosporine, loperamide (Imodium), quinidine, and others.

PACLITAXEL (Abraxane, Onxol)

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

Preliminary evidence from animal research suggests that curcumin enhances the oral bioavailability of paclitaxel (22005). Theoretically, concomitant use might increase blood levels of paclitaxel. However, the significance of this interaction is unclear, as this drug is typically administered intravenously in clinical settings.

SULFASALAZINE (Azulfidine EN-Tabs)

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

Preliminary clinical evidence shows that taking the turmeric constituent, curcumin, can increase blood levels of sulfasalazine by 3.2-fold (81131). This might increase the effects and adverse effects of sulfasalazine.

TACROLIMUS (Prograf)

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

In a case report, a transplant patient presented to an emergency room with acute nephrotoxicity and elevated tacrolimus levels of 29 ng/mL. The patient previously had tacrolimus levels within the therapeutic range at 9.7 ng/mL. Ten days prior to presenting at the emergency room the patient started consumption of turmeric powder, 15 or more spoonfuls daily. It was thought that turmeric increased levels of tacrolimus due to cytochrome P450 3A4 (CYP3A4) inhibition (93544). In vitro and animal model research shows that turmeric and its constituent curcumin inhibit CYP3A4 (21497,21498,21499) Advise patients taking tacrolimus to avoid large doses of turmeric.

TALINOLOL

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

Preliminary research in humans shows that taking curcumin for 6 days prior to taking talinolol can decrease the bioavailability of talinolol when taken together on the seventh day (80079).

Interactions with Herbs & Supplements

ANTICOAGULANT/ANTIPLATELET HERBS AND SUPPLEMENTS: Concomitant use of turmeric with herbs that might affect platelet aggregation could theoretically increase the risk of bleeding in some people (11143,81204,81217,81271). These herbs include angelica, clove, danshen, garlic, ginger, ginkgo, Panax ginseng, red clover, willow, and others.

HERBS AND SUPPLEMENTS WITH HYPOGLYCEMIC POTENTIAL: The turmeric constituent, curcumin, might reduce levels of blood glucose and glycosylated hemoglobin (HbA1C) in patients with diabetes(79114,79573,79591,79692,79984,80313,80315,80476,80553,81219)(80155,81048,96133). Theoretically, taking turmeric with other herbs and supplements with hypoglycemic potential might have an additive effect and increase the risk of hypoglycemia. Herbs with hypoglycemic potential include devil's claw, fenugreek, garlic, guar gum, horse chestnut, Panax ginseng, psyllium, Siberian ginseng, and others.

IRON: Evidence from in vitro and animal research suggests that curcumin or turmeric may bind with iron and prevent its absorption (21467,21468,21469,21470). This does not appear to occur in humans when turmeric is used at levels commonly found in the diet (21471). However, theoretically, high doses of curcumin or turmeric may decrease the absorption of the iron.

ZINC

There is one Serious Drug Interaction known for Zinc—do not take with Cephalexin, as it reduces the amount of the Cephalexin drug metabolized. There are also some theoretical Moderate Interactions, where Zinc may interact in the metabolism of certain drugs, or have other effects that could interfere with their effect. See Below for List.

AMILORIDE (Midamor)

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

Amiloride can reduce urinary zinc excretion, especially at doses of 10 mg/day or more. This zinc-sparing effect can help to counteract zinc losses caused by thiazide diuretics, but it is unlikely to cause zinc toxicity at usual amiloride doses (830,11626,11627,11634). The other potassium-sparing diuretics, spironolactone (Aldactone) and triamterene (Dyrenium), do not seem to have a zinc-sparing effect.

ANTIDIABETES DRUGS

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

Clinical evidence suggests that zinc can lower blood glucose levels (86933,87520,90201). Theoretically, zinc can have additive effects in patients treated with antidiabetic agents; use with caution. Dose adjustments to diabetes medications might be necessary. Some antidiabetes drugs include glimepiride (Amaryl), glyburide (DiaBeta, Glynase PresTab, Micronase), insulin, metformin (Glucophage), pioglitazone (Actos), rosiglitazone (Avandia), and others.

ATAZANAVIR (Reyataz)

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

There is some concern that zinc might decrease serum atazanavir levels by chelating with atazanavir in the gut and preventing its absorption (93578). Although a single dose of zinc sulfate (Solvazinc tablets) 125 mg orally does not affect atazanavir concentrations in patients being treated with atazanavir / ritonavir, co-administration of zinc sulfate 125 mg daily for 2 weeks reduces plasma levels of atazanavir by about 22% in these patients. However, despite this decrease, atazanavir levels still remain at concentration that is high enough to be effective for

preventing HIV virus replication (90216). Therefore, the 22% decrease in atazanavir levels is probably not clinically significant.

CEPHALEXIN (Keflex)

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

There is concern that zinc might decrease cephalexin levels by chelating with cephalexin in the gut and preventing its absorption. A pharmacokinetic study shows that zinc sulfate 250 mg taken concomitantly with cephalexin 500 mg decreases peak levels of cephalexin by 31% and reduces the exposure to cephalexin by 27%. Also, taking zinc sulfate 250 mg 3 hours before cephalexin 500 mg decreases peak levels of cephalexin by 11% and reduces the exposure to cephalexin by 18%. By decreasing cephalexin levels, zinc might increase the risk of treatment failure. This effect does not occur when zinc is taken 3 hours after the cephalexin dose (94163). To avoid an interaction, advise patients to take zinc sulfate 3 hours after taking cephalexin.

CISPLATIN (Platinol-AQ)

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

Preliminary data suggest zinc stimulates tumor cell production of the protein metallothionein which binds and inactivates cisplatin (11624,11625). It is not known whether zinc supplements or high dietary zinc intake can cause clinically significant interference with cisplatin therapy. Cisplatin might also increase zinc excretion.

INTEGRASE INHIBITORS

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

Zinc is a divalent cation. Pharmacokinetic studies have shown that other divalent cations such as calcium and iron can decrease blood levels the integrase inhibitor dolutegravir through chelation (93578,93579). Theoretically, taking zinc along with dolutegravir or other integrase inhibitors might decrease the levels and effects of these drugs. Integrase inhibitors include dolutegravir (Tivicay), elvitegravir (Vitekta), and raltegravir (Isentress).

PENICILLAMINE (Cuprimine, Depen)

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

Zinc forms an insoluble complex with penicillamine, interfering with penicillamine absorption and activity. Zinc supplements reduce the efficacy of low-dose penicillamine (0.5-1 gram/day), but do not seem to affect higher doses (1-2.75 gram/day), provided dosing times are separated (2678,4534,11605). Advise patients to take zinc and penicillamine at least 2 hours apart. Penicillamine also reduces absorption of dietary zinc.

QUINOLONE ANTIBIOTICS

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

Quinolones form complexes with zinc in the gastrointestinal tract, reducing absorption of both the quinolone and zinc if taken at the same time (828,2682,3046,11600). Advise patients to take these drugs at least 2 hours before, or 4-6 hours after, zinc supplements. Quinolones include ciprofloxacin (Cipro), gemifloxacin (Factive), levofloxacin (Levaquin), moxifloxacin (Avelox), and others.

RITONAVIR (Norvir)

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

There is some concern that zinc might reduce serum ritonavir levels by chelating with ritonavir in the gut and preventing its absorption (93578). In patients with HIV, ritonavir is taken with atazanavir to prevent the metabolism and increase the effects of atazanavir. A pharmacokinetic study shows that, in patients being treated with atazanavir / ritonavir, co-administration of zinc sulfate (Solvazinc tablets) 125 mg as a single dose or as multiple daily doses for 2 weeks reduces plasma levels of ritonavir by about 16% (90216). However, despite the 16% decrease in ritonavir levels, atazanavir levels still remains high enough to prevent HIV virus replication. Therefore, the decrease in ritonavir levels is probably not clinically significant.

TETRACYCLINE ANTIBIOTICS

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

Tetracyclines form complexes with zinc in the gastrointestinal tract, which can reduce absorption of both the tetracycline and zinc when taken at the same time (3046,4945). Taking zinc sulfate 200 mg with tetracycline (Achromycin, Sumycin) reduces absorption of the antibiotic by 30% to 40% (11615). Demeclocycline (Declomycin) and minocycline (Minocin) cause a similar interaction (4945). However, doxycycline (Vibramycin) does not seem to interact significantly with zinc (11615). Advise patients to take tetracyclines at least 2 hours before, or 4-6 hours after zinc supplements to avoid any interactions.

Interactions with Herbs & Supplements

BETA-CAROTENE: Clinical research suggests that high doses of zinc supplements (600 mg/day) can decrease serum carotene levels (87325).

BROMELAIN: Theoretically, metal ions such as zinc might inhibit the enzymatic activity of bromelain (11). However, there are no clinical reports of this interaction.

CALCIUM: Calcium supplements might decrease dietary zinc absorption (11590). This usually does not have a clinically significant effect on zinc balance (989,7135,7555). However, this interaction can be avoided by taking calcium supplements at bedtime instead of with meals (11590).

CHROMIUM: Preliminary evidence suggests that chromium and zinc share a transport site in the intestine, and each could reduce the absorption of the other (1950). This is not likely to be clinically significant at normal supplemental doses of zinc and chromium.

COPPER: Large amounts of zinc can decrease copper retention and competitively inhibit copper absorption (706,707,2693,24329,45976). Toxic levels of zinc intake can cause significant copper deficiency and associated anemia (706,11591). Some signs of copper deficiency have also occurred in adults and infants taking 150 mg/day or more of zinc for up to 2 years (2677).

EDTA: EDTA and its salts chelate metal ions, including zinc. Repeated infusions of high doses of EDTA, as used in chelation therapy, can increase urinary zinc excretion 10 to 25-fold and reduce serum zinc levels by up to 40% (5749,9630,11670,11671). Symptoms of zinc depletion have been reported, even when supplemental zinc (15mg/day) was used (11671). Monitor patients receiving repeated infusions of EDTA closely for symptoms of zinc depletion.

FOLIC ACID: The data on effects of folic acid supplements on dietary zinc absorption is conflicting (9389,9390,9391,9392,9393,9421). Normal supplemental doses of folic acid are not likely to affect zinc balance in people with adequate dietary zinc intake (7135,9391).

HERBS AND SUPPLEMENTS WITH HYPOGLYCEMIC POTENTIAL: Large amounts of zinc seem to lower blood glucose levels (86933,87520,90201). Theoretically, it might have additive effects when used with other herbs and supplements that also lower glucose levels. This might increase the risk of hypoglycemia in some patients. Some herbs and supplements with hypoglycemic effects include alpha-lipoic acid, bitter melon, chromium, devil's claw, fenugreek, garlic, guar gum, horse chestnut, Panax ginseng, psyllium, Siberian ginseng, and others.

IP-6 (Phytic acid): Phytic acid found naturally in foods can bind zinc and reduce its absorption (87206); however this interaction is modified by several other dietary factors. Symptomatic zinc deficiency due to high dietary phytic acid levels has not been reported in Western populations. The effect on zinc of increasing phytic acid intake with IP-6 supplements is not known. Avoid IP-6 supplements in people with other risk factors for zinc deficiency (1858).

IRON: Under some circumstances iron and zinc can interfere with each other's absorption. When high supplemental doses of zinc are taken on an empty stomach there is a measurable reduction in iron absorption. High supplemental doses of non-heme iron taken on an empty stomach can reduce zinc absorption, especially when dietary mineral intake is low (8856,9579,9580,9581,9582,9583,9584). This is probably because the carriers for iron and zinc in the gut become saturated at high doses, and the ions then compete for non-specific carriers. If one of the ions is present in excess, absorption of the other will be decreased (9580). When food is present, the ions become complexed with food components and do not compete for absorption (7357,9579). Therefore, there is not a significant interaction between dietary iron and zinc, or

between supplemental iron and zinc when taken with food (8866,9579,9581). Advise patients to take these supplements with food.

MAGNESIUM: High doses of zinc supplements (142 mg/day), or high dietary zinc intake (53mg/day) seem to decrease magnesium balance (9624,12424). This may be due to competition between zinc and magnesium for transport systems in the intestine. Conversely, high intakes of magnesium might enhance binding of zinc to dietary phytic acid, reducing its absorption (11617). The clinical significance of these effects isn't clear.

MANGANESE: Preliminary data suggests zinc supplements more than double the amount of manganese absorbed from supplements taken under fasting conditions (2000).

RIBOFLAVIN: Preliminary data suggests riboflavin and its active form, flavin adenine dinucleotide (FAD), improve zinc absorption. It is suggested that they form a complex with zinc, keeping it in solution in the gut, and acting as a carrier across the intestinal wall (11601). The clinical significance of this is not clear.

VITAMIN A: Clinical evidence suggests that zinc supplements can increase plasma levels of retinol (24333,86920,87307). Significant increases have occurred with doses of up to 30 mg/day for 6 months in children and adults (86920,24333).

VITAMIN D: Preliminary data suggests vitamin D is involved in zinc absorption (11602). However, data is conflicting on whether vitamin D supplements improve zinc absorption (11603,11604).

PEPPERMINT

There

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

ANTACIDS

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

Drugs that decrease stomach acid and raise gastric pH can cause premature dissolution of enteric-coated peppermint oil (4469). Separate dose administration times by at least 2 hours.

CYCLOSPORINE (Neoral, Sandimmune)

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

Preliminary research suggests that peppermint oil inhibits cyclosporine metabolism and may increase cyclosporine levels. Inhibition of CYP3A4 may be partially responsible for this interaction (11784). An interaction between peppermint oil and cyclosporine has not been reported in humans.

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 peppermint oil and leaf might inhibit cytochrome P450 1A2 (CYP1A2) (12479,12734). 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 peppermint oil. 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 peppermint oil cautiously or avoid in patients taking these drugs.

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 peppermint oil 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 peppermint oil. 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.

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 peppermint oil 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 peppermint oil. 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 peppermint oil cautiously or avoid in patients taking these drugs.

CYTOCHROME P450 3A4 (CYP3A4) SUBSTRATES

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

There's preliminary evidence that peppermint oil can inhibit cytochrome P450 3A4 (CYP3A4) enzymes (11783). Peppermint oil might increase levels of drugs metabolized by CYP3A4. However, other preliminary research suggests peppermint oil inhibits CYP3A4 only at very high concentrations (12479). Some drugs metabolized by CYP3A4 include lovastatin (Mevacor), ketoconazole (Nizoral), itraconazole (Sporanox), fexofenadine (Allegra), triazolam (Halcion), and numerous others. Use peppermint oil cautiously or avoid in patients taking these drugs.

H2-BLOCKERS

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

Drugs that decrease stomach acid and raise gastric pH can cause premature dissolution of enteric-coated peppermint oil (4469). The H2 blockers include cimetidine (Tagamet), ranitidine (Zantac), nizatidine (Axid), and famotidine (Pepcid).

PROTON PUMP INHIBITORS (PPIs)

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

Drugs that decrease stomach acid and raise gastric pH can cause premature dissolution of enteric-coated peppermint oil (4469). PPIs include omeprazole (Prilosec), lansoprazole (Prevacid), rabeprazole (Aciphex), pantoprazole (Protonix), and esomeprazole (Nexium).

Interactions with Herbs & Supplements

IRON: Peppermint tea dose-dependently inhibited iron absorption in both animal and human research (19337,21711).

QUERCETIN: Evidence from animal research suggests that menthol from peppermint oil enhances the absorption of topical quercetin (21713).

13.1.2. Appendix B Instructions for Use

Instructions for Use

The test product combines whole food sourced Vitamin C, quality Echinacea, Ivy Extract, Zinc, Ginger and Turmeric. This formula is designed to support the immune system while soothing & clearing cough, with the main active components of Echinacea fresh pressed juice, Ivy Extract and Zinc

Daily Dosage:

1 Packet contain: Active Ingredients: Echinacea, Ivy Extract, Camu Camu, Ginger, Turmeric, Zinc

Inactive Ingredients: Natural Flavor, Guar Gum, Monk Fruit Sweetener, Citric Acid

Supplement Facts

Serving Size 1 Sachet (5.4g)

Servings per Container 3

	Amount Per Serving	% Daily Value
Calories	5	
Total Carbohydrate	1 g	<1% *
Total Sugars	<1 g	†
Vitamin C (as Camu-camu (Fruit) Powder & Ascorbic Acid)	500 mg	833%
Zinc (as Zinc Gluconate)	15 mg	100%
Organic Turmeric Powder (Rhizome)	500 mg	†
Echinacea purpurea Extract (Aerial)	400 mg	†
Organic Ginger Powder (Root)	250 mg	†
English Ivy Extract (Leaf)	25 mg	†

*Percent Daily Values are based on a 2,000 calorie diet.

† Daily Value Not Established

OTHER INGREDIENTS: Natural Flavor, Guar Gum, Monk Fruit Extract, Citric Acid

Directions: Mix 1 packet with 6-8 oz of hot water at the onset of symptoms and repeat twice a day, 4-6 hours apart, for the duration of your cold 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.

13.1.3. Appendix C Screening Form

Screening

1. Are you at least 18 years old? (DOB?) (Y/N)
2. Have you ever been diagnosed with any chronic liver disease? (Y/N)
3. Have you ever been diagnosed with any chronic renal disease? (Y/N)
4. Are you pregnant or breastfeeding? (Y/N)
5. Do you have any allergies to any of the following? (Y/N)
    a. Echinacea
    b. Ivy Extract
    c. Camu Camu
    d. Vitamin C
    e. Ginger
    f. Turmeric
    g. Zinc
    h. Monk fruit
    i. Guar Gum
    j. Citric Acid
    k. Natural Flavoring
6. Have you ever been diagnosed with an autoimmune or immunodeficiency disease? (Y/N)
7. Do you have more than 10 alcoholic beverages per week? (Y/N)
8. Are you willing to try the test product for relief of your symptoms? (Y/N)
9. Are you comfortable taking your own temperature with a digital thermometer? (Y/N)

13.1.4. Appendix D Baseline Form

Baseline

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 many colds do you get a year?
3. On average How long do your colds usually last? (1-3 days, 4-6 days, 7-9 days, >10 days)
4. When you have a cold what Cold Symptoms do you usually experience? (check all that apply)
    a. Cough
    b. Hoarseness
    c. Muscle aches
    d. Runny Nose
    e. Nasal Congestion
    f. Scratchy Throat
    g. Sore throat
    h. Sneezing
    i. Oral Temp > than 37.7 °C (99.9 °F)
    j. Other: _____
5. Do you take any medication when you have a cold (i.e. Dayquil/Nyquil, Advil, or Prescription etc.)?
    a. If so, which medications do you take?
    b. How often do you normally take them? (once a day, as needed, or as instructed)
    c. Are they successful in treating your symptoms?
6. Do you take any supplements when you have a cold (Emergen-C, Vitamin C, Airborne, Nettipot, etc.)?
    a. If so, which supplements do you take?
    b. How often do you take the supplement when you have a cold? (once a day, several times a day, every other day, once in a while)
    c. Are they successful in helping with your symptoms?

13.1.5. Appendix E Symptom Diary

Daily Symptom Survey

BEFOREtaking the test product OR any allowed medication, please answer all of the following questions daily for the duration of your cold symptoms.

REMINDER: DURING THE TRIAL, YOU ARE NOT ALLOWED TO TAKE ANY COLD MEDICATIONS (NYQUIL/DAYQUIL, TYLENOL COLD, COUGH SYRUP/LOZENGES, ETC.)

1. Cough

0	1	2	3
No Symptom	Slight	Moderate	Severe

2. Hoarseness

0	1	2	3
No Symptom	Slight	Moderate	Severe

3. Muscle aches

0	1	2	3
No Symptom	Slight	Moderate	Severe

4. Runny Nose

0	1	2	3
No Symptom	Slight	Moderate	Severe

5. Nasal Congestion

0	1	2	3
No Symptom	Slight	Moderate	Severe

6. Scratchy Throat

0	1	2	3
No Symptom	Slight	Moderate	Severe

7. Sore throat

0	1	2	3
No Symptom	Slight	Moderate	Severe

8. Sneezing

0	1	2	3
No Symptom	Slight	Moderate	Severe

9. Did you take any pain/fever reducer (ibuprofen/acetaminophen today? (Y/N)
    a. Why?
    b. Did it work? (Y/N)
10. Have you taken any other cold medications (Nyquil, Dayquil, other cold medication, cough drop, cough syrup, etc.)? (Y/N)
    a. If yes, please exit from the study
11. Have you seen a doctor for your symptoms? (Y/N)
    a. If yes, were you prescribed anything? (Y/N) → if yes please exit from the study
12. Did you experience any side effects after taking the product? (Y/N)
    a. If yes, please fill out the Adverse Event form.

13.1.6. Appendix 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 cold?

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 the elements?

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

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

13.1.7. Appendix G Adverse Event Form

Immune 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.

13.1.8. Appendix H Test Product Insert

Welcome to the Immune Support Trial!

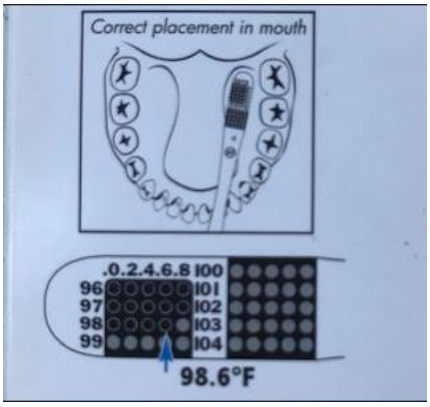
We appreciate you taking the time to participate in this trial. As you may already know, the aim of this study is to measure the impact the test product has on the duration and severity of your cold symptoms. Please take the time to read the following information below to become acquainted with the trial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

Instructions upon Test 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 an 18-day supply (36 packets) of the test product.
3. You will start taking the test product at the onset of your next cold.
    a. This will be the day that you experience 2 or more cold symptoms (cough, hoarseness, muscle ache, runny nose, stuffy nose, scratchy/itchy throat, sore throat, sneezing, or an oral temperature greater than 37.7 °C (99.9 °F).
4. Also included in the study bag is a disposable thermometer. This will be used to take your temperature If you feel that you have a fever with your cold at onset.

Instructions Once Product Intake Begins:

1. Once you experience 2 or more cold symptoms, this will be the date your cold starts and you will record this.
    - You will complete the Cold Start Form. If you meet the criteria for having a cold you will proceed through the rest of the instructions.
    - If a fever is present, please measure and record using the disposable thermometer. **This is only needed on the first day of your cold.**
        - Place thermometer under the tongue as seen below.
        - Close your mouth and ensure your tongue is pressed against the thermometer.
        - Keep the thermometer in this position between 60-30 seconds.
        - Take the reading immediately after removing from your mouth as the thermometer will reset. If you need you to repeat this repeat these steps.



2. Next, you will complete the symptom diary by:
    - Rating the severity of each symptom you are experiencing.
    - Recording any medications, you are taking.

- Side-Effects of the test product.
- Recording any visits to your physician and if any prescriptions given.

3. Take the test product twice a day
    - 1 packet mixed into 6-8 oz of hot water.
    - The second dose should be taken 4-6 hours after the first dose
4. Repeat the above steps every day for the duration of your cold.
5. **REMEMBER: Once you have started the trial, and recorded the first day of your cold symptoms, you are not allowed to take any cold medications for the duration of the trial other than the test product. You are allowed to take Ibuprofen (Advil) and Tylenol but you are not allowed to take: Dayquil, Nyquil, Tylenol Cold, etc.**
    - If you have any questions regarding what medications, you can take please call/text/email the research personnel at Hawthorne Effect.
    - You are allowed to take Ibuprofen (Advil, Motrin, Aleve, etc.) or Acetaminophen (Tylenol).
        - **Please complete your daily symptoms survey BEFORE taking any medications or the test product.**
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. You will complete the study on the day that you are no longer experiencing symptoms. On this day you will be prompted to complete a study exit form.
8. Upon receipt of study exit survey and review of completed study forms, you will receive an Amazon gift card of $25 via email.

Thank you again for participating in this trial!

If you have any questions, please contact:
Nnenna Udensi, Remote Trial Coordinator
Nnenna.udensi@hawthorne-effect.com

13.1.9. Appendix I Informed Consent Form

RESEARCH PARTICIPANT
INFORMED CONSENT FORM & HIPAA AUTHORIZATION

Sponsor / Study Title:	HLNatural, Inc. / "Evaluation of the impact of the HLNatural, Inc. Immunity product in reducing the length of cold symptoms in adults suffering from the common cold"
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 immune support and cold relief. The test product contains all-natural ingredients which have been combined into a powder to be taken in water at the first sign of a cold. 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

According to the Centers of Disease Control and Prevention (CDC) adults will have an average of 2-3 colds per year. Most colds will last approximately 7-10 days. The symptoms of colds could include cough, sore throat, runny nose, body aches, fevers, headaches and fatigue. A cold can affect your activity such as going to work, interrupting your sleep and your day-to-day activities.

Who can participate?

Anyone who is at least 18 years of age and who does not have any major health problems. Participants, although they may not have a cold currently, can be interested in using all-natural substances to reduce the duration of common cold symptoms when they should arise.

Potential participants will be asked screening questions to determine if they can be 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 measure whether or not the test product, when taken twice daily at the first sign of cold symptoms, will shorten the duration of cold symptoms.

How long is the study?

You will participate in the study for 90 days. If you experience a cold in this 90-day period you will conduct study-related tasks until all of your symptoms go away or 18 days, whichever is shorter. If you do not experience a cold in this 90-day period, you will exit the study on day 90.

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. 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 powder?

Active Ingredients: Echinacea Fresh, Ivy Extract, Camu Camu (Vitamin C), Ginger, Turmeric, Zinc
Inactive Ingredients: Natural Flavor, Guar Gum, Monk Fruit Sweetener, Citric Acid

Instructions to prepare the mixture

At the onset of a cold, mix 1 packet of the drink-mix product in 6-8 oz. of hot water. Drink the drink mix twice a day until symptoms are gone or 18 days, whichever comes first.

What will we ask you to do?

Once you are enrolled in the study, you will wait to see if you catch a cold. A cold is defined as two or more symptoms, and a list of symptoms will be provided.

Once you have a cold, you will be asked to start taking the test product, a powder drink-mix, mixed in 6-8 oz of water, twice a day. You will continue to take the test product until your cold symptoms resolve, or for 18 days, whichever is shorter. You will be asked to complete a symptom survey including questions on the severity of your cold symptoms, list any medications or supplements you took, and report any unfavorable effect while taking the test product.

1. Complete the screening survey.
2. Sign and date the eConsent.
3. Complete the baseline survey, demographic form, and Medication and Supplements form.
4. Receive test product, log into study portal, and complete supplement receipt form. This will mark the start of your participation in this study.
5. Once you have a cold, complete the cold start form.
6. If you meet the criteria for having a cold, you will then completethe symptom survey.
7. Take test product.
8. Write down any adverse or ill effects any time after taking the test product.
9. Record if you took any additional medications or supplements daily during the course of your cold.
10. Note any final adverse events and complete the exit form.

You will be considered in the study for 90 days. If, during the 90 days, you experience 2 or more of the following lists of symptoms you will be asked to take the test product until all your symptoms resolve. You will exit the study at 90 days even if you did not experience signs of a cold.

Other Instructions:

- If you are prescribed antibiotics for any reason, please report this to the study manager and you will be withdrawn from the study.
- You are asked not to take any other form of cold remedy (over-the-counter [Nyquil/Dayquil/Cough Syrup/Cough Drops/Emergen-C/Airborne/Zarbees] or prescription drugs) during the study period (for example, during your cold).
- You will be allowed to take Advil and Tylenol, but will need to record this as part of your daily survey.
- You are asked to limit the number of alcoholic beverages to less than or equal to two

drinks per day and avoid recreational drugs during the study period.

Cold symptoms are:

- cough
- headache
- hoarseness
- muscle ache
- runny nose
- nasal congestion
- scratchy throat
- sore throat
- sneezing
- an oral temperature greater than 37.7 °C (99.9 °F)

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 are:

- epigastric pain (pain in the upper abdomen, just below the ribcage)
- nausea
- vomiting
- loss of appetite
- abdominal cramps
- diarrhea
- headaches

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?

Participants may benefit from the test product by achieving symptom relief and reducing the duration of their cold. 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, which includes 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 correlate with the product provided to you as part of this study, HLNatural, Inc. will compensate you for all 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 login 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 confirm 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: Pro00037635.

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