A Follow-up Trial of Proglucamune® in the Treatment of Protective Qi Insufficiency, a TCM Condition

Protocol Number: 201878

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Statement of Compliance

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

USANA Health Sciences (USANA)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of USANA-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1. Protocol Summary

1.1 Synopsis

Title	A Follow-up Trial of Proglucamune® in the Treatment of Protective Qi Insufficiency, a TCM Condition
Study Description:	In this protocol, we will developed a novel, evidence-based approach to test the hypothesis that ß-glucan enhances Protective Qi (PQi), an important TCM concept which stipulates that a protective force circulates throughout the body surface and works as the first line of defense of against "external pernicious influences (外邪)".
Objective:	The primary objective of this study is to re-test the beneficial effects of Reishi for its Protective Qi (PQi) enhancing and immune-modulating effects in a double-blind, placebo-controlled study. The secondary objective of this study is to determine the effect of Proglucamune® on strengthening General Qi (GQi).
Endpoints	The primary endpoint is the change of PQi Deficiency (PQD) status accessed by a standardized multifactorial severity score and traditional method. The secondary endpoint is the change of GQi Deficiency (GQD) status accessed by a standardized multifactorial severity score and traditional method, the change of Global Health, Emotional Impact, Saliva sIgA, and Emotional and Behavioral Dyscontrol.
Study Population	130 male or females aged 18 to 65 will be enrolled without regard to race or ethnic background. All subjects should be generally healthy but exhibit an PQi Insufficiency score >1.8 (an empirical threshold derived from preliminary study that allows increased responsiveness to beta glucan).
Description of Sites/Facilities Enrolling Participants:	This study will be conducted at the Elegant and Olive Health Clinic, Unit3-505 Hood Rd., Markham, Ontario, L3R 5V6. Subjects for this study will be recruited through investigators of this trial, referral from other TCM practitioners, or via advertisement.
Description of Study Intervention:	Participants will be treated with 2 tablets of Proglucamune per day (containing 200mg of beta glucan).
Study Duration:	24 months
Participant Duration	3 months

1.2 Schema

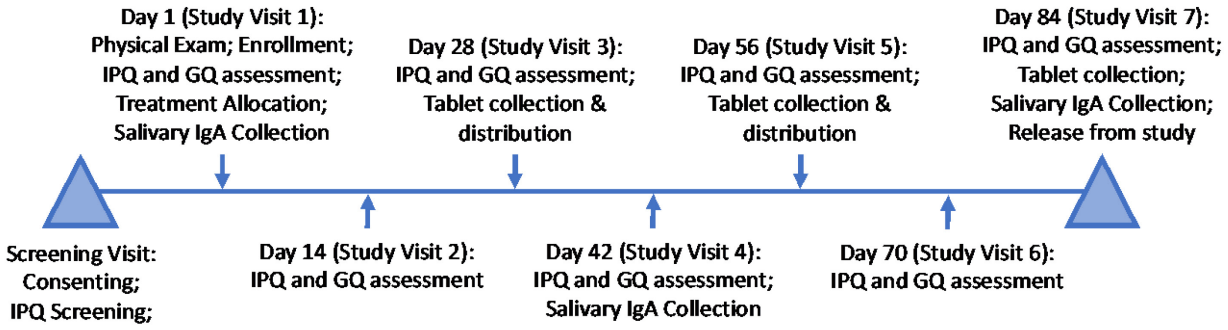

Figure 1 – Clinical Study Design. 130 subjects exhibiting insufficiency of Protective Qi (iPQ) will be enrolled in a 12-week (84 day) study. Subjects will visit the clinic on 8 separate occasions; Screening Visit: screening assessment for iPQ and General Qi (GQ) status, Study Visit 1: Physical examination (performed by an MD), consenting, treatment allocation and treatment initiation, Study Visits 3, 5 and 7: iPQ and GQ assessment only, visits 4 and 6: iPQ and GQ assessment and tablet collection/distribution, and visit 8: iPQ and GQ assessment, tablet collection, and subject release from the study. Salivary IgA will also be collected on Study Visits 1, 4 and 7

1.3 Schedule of Activities (SOA)

Procedures	Screening Day -14 to -1	Enrollment/Baseline Visit 1, Day 1	Study Visit 2 Day 14	Study Visit 3 Day 28	Study Visit 4 Day 42	Study Visit 5 Day 56	Study Visit 6 Day 70	Final Study Visit 7 Day 84
Informed consent	X							
Demographics	X							
Medical history	X							
Randomization	X							
Administer study intervention		X	X	X	X	X	X	X
Physical exam (including height and weight)	X	X	X	X	X	X	X	X
Protective Qi Deficiency	X	X	X	X	X	X	X	X
Generic Qi Deficiency	X	X	X	X	X	X	X	X
Global Health (including physical and mental)	X	X	X	X	X	X	X	X
Saliva sIgA	X	X			X			X
Emotional and Behavioral Dyscontrol	X	X	X	X	X	X	X	X
Emotional Impact	X	X	X	X	X	X	X	X
Adverse event review and evaluation	X	X	X	X	X	X	X	X
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X

2. Introduction

2.1 Study Rationale

TCM has developed a number of medicinal treatments to strengthen the PQi. Among these is the use of Reishi mushrooms, either alone or in combination with other TCM remedies. Although there are no definitive data on the treatment duration of Reishi or Reishi-containing formulas needed to improve PQi, anecdotal reports claim significant improvement within days. Notably, Western medicine has identified immune-boosting properties of Reishi, which may explain the PQi enhancing effects of this plant. Specifically, β-glucan – a component of Reishi - has been shown to activate macrophages [1-3], neutrophils [4, 5) and other immunocytes [6-8], and may exhibit particular benefits among macrophage-rich organs such as the lung, liver and spleen. In fact, β-glucans from sources other than Reishi, such as the baker's yeast, are able to initiate similar immune responses and clinical benefits [9].

2.2 Background

Qi is a central concept of traditional Chinese medicine (TCM) and was first documented in the oldest TCM writings more than 2000 years ago. Generally speaking, Qi refers to the vital energy of the body and is derived from two primary sources: 1) inborn Qi (that may be construed as genetics), and 2) pectoral Qi (can be construed as metabolism). Moreover, Qi manifests itself in two forms: Nutritive Qi and Protective Qi (PQi), which can be understood to reflect an individual's nutritional state and immune health, respectively. Regarding the latter, PQi functions to defend the body from the invasion of external pathogens. In this context, PQi is analogous to the anatomical barriers and immune cells of the innate immune system located for example, at the mucosal surfaces of the respiratory and digestive tract.

According to TCM, a Protective Qi Deficiency (PQD) manifests as a predisposition to cold* (*, as defined in TCM), susceptibility to wind* (that carries pathogens), abnormal sweating, and fatigue. Clinical examination of individuals with PQi reveals a feeble or weak pulse as well abnormal tongue features such as the appearance of a thin whitish coating, atypical thickness, and uncharacteristic teeth marks on the side. The individual's face often lacks gloss. Notably, these manifestations are mild, may happen to many people and, from the perspective of western medicine, may not in fact warrant diagnosis of an individual as being sick. If left untreated however, TCM indicates that a worsening of symptoms may ensue, such as the onset of coughing, fever, headache, delirium,

bleeding, etc. In this regard, the identification of an individual with PQD is viewed as an aspect of disease prevention in TCM.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

The risk of this trial is minimal due to the established safety profile of the active ingredients (beta glucan), which has been approved by FDA as a GRAS (Generally Considered As Safe) ingredient. In addition, the test formula has been used in market by the public for several years without adverse effects reported.

2.3.1 Known Potential Benefits

The finding of PQi-enhancing effect in PQD patients will avail TCM practitioner to prescribe PQD therapy based on principles of evidence-based medicine.

3. Objectives and Endpoints

Objective	Endpoints	Justification for endpoints
Primary		
To test ß-glucan enhances Protective Qi (PQi)	• PQi Deficiency (PQD) status accessed by a standardized multifactorial severity score • PQi Deficiency (PQD) status accessed by a traditional method	We have previously created and validated standardized score for assessing PQD severity. The traditional diagnosis method is also used as an additional way to evaluate the treatment.
Secondary		
To evaluate the effect of β-glucan on GQi severity score, salivary IgA, general health status through Patient-Reported Outcomes Measurement Information System (PROMIS), Emotional Impact, and Emotional, and Behavioral Dyscontrol.	• GQi Deficiency (GQD) status accessed by a standardized multifactorial severity score • GQi Deficiency (GQD) status accessed by a traditional method • Global Health - Physical • Global Health – Mental • Emotional Impact • Saliva sIgA • Emotional and Behavioral Dyscontrol	PQi is a component of GQ, β-glucan may improve GQi, too. Salivary IgA is a biomarker of immune. β-glucan's effect on immune defense may affect Salivary IgA. The improvement of PQi can be accompanied by improved life quality. Patient-Reported Outcomes Measurement Information System (PROMIS), Emotional Impact, Emotional and Behavioral Dyscontrol will be collected to evaluate the improvement of participants' life quality.

4. Study Design

4.1 Overall Design

The objective of this study is to expand upon our previous findings and, more specifically, to re-test our hypothesis in a triple-blind, placebo-controlled study with n=62 subjects in both the intervention (Proglucamune®) and placebo treatment groups. In addition, since TCM literature indicates that Reishi not only increases PQi but also the level of Qi in general (i.e., general Qi, GQi), and since PQi is a component of GQ, the secondary objective of this study is to determine the effect of Proglucamune® on strengthening GQi.

4.2 Scientific Rational for Study Design

The overlap of TCM and western medicine concerning the beneficial effects of Reishi for its Qi enhancing and immune-modulating effects, respectively, has prompted us to investigate whether or not Reishi, in conjunction with other natural products used in TCM, can enhance an individual's PQi. In a preliminary study [10], we investigated this subject using a commercial product (Proglucamune®, USANA Health Sciences) in a one-group, pre-test post-test design (n=30 subjects). The results of that work support our hypothesis that Proglucamune®, a Reishi and β-glucan containing product, enhances PQi in individuals with PQD.

In this triple-blind, placebo-controlled study, the control group will be treated with placebo. For the placebo tablets, the active ingredients will be replaced with equivalent amount of excipients (microcrystalline cellulose), and coated with the same material as β-glucan. The appearance and taste of the placebo are the same as that of treatment tablet. It will be able to minimize the influence of placebo effect.

4.3 Justification for Dose

The dose regimen (2 tablets daily that contain ~200mg beta glucan) in the trial has been tested previously in our preliminary trial and found to be effective [10].

4.4 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit shown in the Schedule of Activities (SoA), **Section 1.3**.

5. Study Population

5.1 Inclusion Criteria

1. Male or females aged 18 to 65 years (inclusive) without regard to race or ethnic background
2. Provide a signed Informed Consent prior to entry in the study.

3. Willing to follow all study instructions and consume the assigned investigational product for 12 weeks.
4. Not currently taking a β-glucan containing supplement or any other supplement that might interfere with the study design.
5. Ability to swallow tablets and pills.
6. Exhibit a PQD severity score > 1.8 (calculated by Table1 & Table 2)

5.2 Exclusion Criteria

1. Persons diagnosed by TCM as having medical conditions that interfere with the status of PQi.
2. Significant acute or chronic illness or other medical conditions that will prevent or interfere with giving an informed consent, or with participation in the study.
3. Scheduling difficulties or lack of transportation that will prevent or interfere with their ability to attend all of the necessary study visits.
4. Persons medically diagnosed with depression or anxiety disorders.
5. Persons with a history of alcohol abuse or other substance abuse within the previous 2 years.
6. Females who are attempting to become pregnant, pregnant, lactating or who have given birth within 1 year.
7. Persons who have had a medical surgery in the past 4 weeks or have scheduled a surgery during the study period.
8. Persons currently enrolled in a clinical trial, or who have completed a clinical trial within the last 4 weeks.
9. Allergies to mushrooms or other fungi.
10. Significant problems with constipation or diarrhea.
11. A lifestyle or schedule incompatible with the study protocol.
12. Persons who are allergic to yeast products, have autoimmune disease/an immune disorder, or take antidepressants, blood thinners (anticoagulants, acetylsalicylic acid), or immunosuppressant medication

5.3 Lifestyle Considerations

During this study, participants:

1. Must not have a lifestyle that will prevent or interfere with their ability to attend all of the necessary study visits
2. Must not have alcohol abuse
3. Must not use marijuana for recreational or medicinal purposes

5.4 Screening Failures

Individuals who do not meet the criteria for participation in this trial won't be enrolled.

5.5 Strategies for Recruitment and Retention

Subjects will be recruited through referral from other TCM practitioners and advertisement on social media. Individuals who were believed to have PQD by referring practitioners or by themselves will be encouraged to apply. Potential subjects recruited through TCM practitioners will not be referred without prior consent. All potential subjects will report to the TCM clinic for a screening visit (Visit 1, **Section 1.2**) prior to enrollment into the study. At screening, all potential subjects will be provided with an Information and Consent Form (ICF) and provided with sufficient time to read the ICF. Thereafter, a TCM practitioner will review the ICF with each potential subject and will address any questions the potential subject may have concerning the ICF and/or the clinical trial. The potential subject will also be provided with the option of taking the ICF home for review prior to making his or her decision to enroll or not enroll in the study. If potential subjects refuse consent, they will be asked to leave the clinic and will not be enrolled in the study. If they provide consent, the potential subject will sign the consent form, receive a duplicate for their own records, and will be considered as consented subjects.

Once consent has been obtained, a TCM practitioner will initiate the screening process (Appendix 1) that includes collection of information concerning anthropometric, general health status as well as PQi status. If the potential applicants exhibit a PQD severity score ≤ 1.8 (see Table 1& Table 2), which, according to our preliminary study, represents less responsiveness to the treatment, they will be excluded from the trial, whereas the applicants with a score >1.8 will begin the enrollment process.

Enrollment will be initiated by a TCM practitioner. Note that the enrollment process may occur on the same day as the Screening Visit, or at a date not more than 14 days from the Screening Visit. If enrollment is performed on the same day as the screening visit, the enrollment process will begin with a basic physical examination (to be conducted by the Qualified Investigator, Q.I.; see Appendix 2) immediately following the screening process and continue as outlined below. Note that subjects that complete screening and enrollment on the same day will be considered to have completed both the Screening Visit and Study Visit 1. However, if subject enrollment cannot be completed during the Screening Visit (i.e., due to time restrictions or other circumstances), subjects will return to the clinic within 14 days to initiate the enrollment procedure. During this visit (Study Visit 1), the TCM practitioner will re-assess the subjects' PQD status (Appendix 4). If the potential subject does not exhibit PQD, they will not be enrolled in the study. If the potential subject continues to exhibit PQD, they will continue the

enrollment process. (Note that for purposes of data analysis, subjects' PQD status characterized during Study Visit 1 will supersede their PQD status characterized during the Screening Visit). As outlined above, the enrollment process begins with a basic physical exam of the head, ears, eyes, nose, throat, etc. performed by the Q.I. If, in the estimation of the Q.I., the potential subject is deemed not to be in good general health, they will not be enrolled in the study. If potential participants are deemed to be otherwise healthy by the Q.I., the enrollment procedure will continue. The enrollment will start in Dec. 2018 and concluded in March 2019.

6. Study Intervention

6.1 Study Intervention Administration

6.1.1 Study Intervention Description

Proglucamune® lot No. AV2291 and Placebo lot No. AV2287.

6.1.2 Dosing and Administration

The Proglucamune® tablets and placebo tablets will be instructed to consume orally 2 tablets/day (containing ~200mg beta glucan) at one sitting, preferably with a meal. The study participants will be administered the study intervention during the course of study (84 days).

Subjects who are currently taking any prescribed medications must agree to maintain their current method and dosing regimen during the course of the study unless recommended otherwise by their physician. In such cases, they will be instructed to take the study treatment (placebo or Proglucamune®) at least 3 hours before or after the prescribed medication. The use of dietary supplements used for the purpose of combating low Qi are prohibited during the study. Chronic use of NSAIDs, laxative, antacids, as well as any lipid lowering medication (prescription, OTC, or herbal), insulin, metformin or other diabetes medication are prohibited in this study. Use of tobacco products including chewing tobacco and all types of cigarettes are prohibited. Any changes in medication schedules or prescription medication for concurrent conditions arising during the course of the study will be reviewed and noted in the case report form (CRF).

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

Subjects will be provided with the appropriate treatment tablets (i.e., either placebo or Proglucamune®) and instructed to consume 2 tablets/day at one sitting. Visits scheduled for day 28 (Visit 3) and day 56 (Visit 5) will

collect any unused tablets during the previous 28-day study period as well as distribution of another allotment of tablets (i.e., 60 tablets) sufficient for the forthcoming 28-day study period.

6.2.2 Formulation, Appearance, Packaging, and Labeling

Placebo formula contain excipients (831 mg per tablet) and coating materials. The placebo excipients include microcrystalline cellulose 806mg, Pregelatinized Starch 10.7 mg, croscarmellose sodium 7.11 mg. silicon dioxide: 3.57 mg, and Ascorbyl Palmitate 3.57 mg.
Treatment formula contain active ingredients and excipients (846 mg per tablet) and coating materials.
The treatment active ingredients include Beta-Glucan Complex (Baker's Yeast Extract [Saccharomyces cerevisiae, cell wall]) 125 mg (The w/w yield of prepared extracts in terms of starting crude material: 38%), Reishi Mushroom [Ganoderma lucidum, whole mushroom powder] 125 mg, Shiitaki Mushroom [Lentinula edodes, whole mushroom powder] 25 mg, and Zinc (as Zinc Gluconate) 25mg.
The treatment excipients include Microcrystalline cellulose 426 mg, modified cellulose 90 mg, vegetable fatty acid 10 mg, croscarmellose sodium 5 mg, and silicon dioxide 5 mg, and Hydroxy Propyl Cellulose 9mg.
Treatment and placebo formula contain the same coating materials (Opadry II Complete Film Coating System 57U150022 Red).

6.2.3 Product Storage and Stability

Treatments and placebo tablets should be stored at or blow 25^0C or 75^0F and kept out of reach of children.

6.2.4 Preparation

The study intervention and control product (tablets) can be used directly without any preparation.

6.3 Measures to Minimize Bias: Randomization and Blinding

This study will be a randomized, triple-blind, placebo-controlled, parallel arm design. The participants will be recruited and randomized in a 1:1 ratio to either of two interventions: 1) Daily consumption of the control supplement (placebo), and 2) Daily consumption of the treatment (β-glucan). For randomization, these participants will be first stratified based upon: 1) ethnicity, 2) whether or not the subject has had an influenza vaccine (flu shot) since October 1, 2018, and 3) whether or not the subject currently exhibit a 'cold' as defined by TCM (hereafter referred to as cold*). These factors will be deemed potential confounders of β-glucan effect. Throughout the trial, including the recruitment and the treatment, all participants and on-site investigators will be blinded to treatment.

Each participant has an emergency envelop, the information of this participant's allocation (treatment group or placebo group) will be include in, and PI will hold onto the envelops. If any participant needs to be unblinded, PI will open the corresponding envelop and notice the relevant physician.

6.4 Study Intervention Compliance

Protocol compliance will be evaluated based on study product returned. That is, compliance will be calculated by determining the number of dosage units taken divided by the number of dosage units expected to have been taken multiplied by 100.

$$\frac{number\ of\ dosage\ units\ taken}{number\ of\ dosage\ units\ expected\ to\ have\ been\ taken} \times 100\%$$

Subjects found to have a compliance of <80% or >120% will be censored from the study.

7. Study Intervention Discontinuation and Participant Discontinuation / Withdrawal

7.1 Discontinuation of Study Intervention

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

The data to be collected at the time of study intervention discontinuation will include the following: laboratory safety tests, anthropometrics, and vitals.

7.2 Participant Discontinuation/Withdrawal from Study

The following list of criteria will be used as guidelines concerning the discontinuation (i.e., removal and/or early withdrawal) of subjects from the study:

7.2.1 Personal Reasons

As stated in the Informed Consent Form, a subject may withdraw from the study for any reason at any time.

7.2.2 Removal by Qualified Investigator

The Investigator has the discretion to remove subjects from the study when deemed necessary. The circumstances of any discontinuation must be documented in detail in the subject file and final report. If possible, the evaluations planned for the end of study will be carried out at the time when the subject is withdrawn from the study. A subject leaving the study prematurely will be replaced by another if study attrition exceeds the planned 20%. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of subjects will be avoided.
Criteria for removal of subjects from the study by qualified investigator will include:

7.2.2.1 Clinical Reasons

A subject may be withdrawn from the study if, in the opinion of the Qualified Investigator, it is not in the subject's best interest to continue. Any subject who experiences a serious adverse event (SAE) will be withdrawn from the trial. A participant will also be withdrawn due to adverse events causing clinically significant illness or the need for prohibited medication(s) during the trial. Any female subject who becomes pregnant during the course of the trial will be withdrawn.

7.2.2.2 Protocol Violation

Any subject found to have entered this study in violation of the protocol will be discontinued from the study at the discretion of the Qualified Investigator. This will include any subject found to have been inappropriately enrolled (did not meet eligibility criteria). Subject non-compliance includes not showing up for study visits, not taking the investigational product as directed, or refusing to undergo study visit procedures. Subjects who are found to be taking prohibited medications or supplements without the knowledge of the Qualified Investigator will also be withdrawn. Any major protocol deviations (i.e., those that increase the risk to subjects and/or compromise the integrity of the study or its results) will result in subject discontinuation.
In case of an early withdrawal or discontinuation, no follow-up other than recovery of the investigational product and an attempt to perform laboratory safety tests, anthropometrics, and vitals will be done for the subjects who decide to end their participation, except if the withdrawal was due to medical reasons related to the study. In this case, subjects will be followed-up until recovery. If a subject withdraws or is removed from the study, information collected up until the point of withdrawal will be used unless the subject requests otherwise. The circumstances of any discontinuation will be documented in detail. A subject leaving the study prematurely will be replaced by another if study attrition exceeds the planned 20%. Subjects will be compensated for the part of the study that has been performed.

8. Study Assessments and Procedures

8.1 Efficacy Assessments

The efficacy of Proglucamune® on PQi and GQi status will be quantified as outlined in the PQD scoring system (Table1 & Table 2) and the GQ scoring system (Table 3 & Table 4). Each subject's PQi and GQi status – as reflected in their PQD and GQD score – for each visit will be used to determine whether or not the subjects PQi or GQi status is improved by Proglucamune®. Treatment efficacy will also be evaluated by measuring and comparing salivary IgA levels at day 1 (Study Visit 1), day 42 (Study Visit 4) and day 84 (Study Visit 7).

8.2 Safety and Other Assessments

The active ingredients in treatment don't have safety information for pregnant. In order to protect participants, any participants who are pregnant or planning to become pregnant will be excluded. Since treatment product contains yeast, extract of mushroom, any participants, who are allergy to yeast, mushroom, and other fungi, will be excluded. The treatment in this study is a supplement, not a medicine. To avoid interrupting patients' treatment, participants will be evaluated whether he/she was extremely ill, immune deficient during the screening. Any participants who are extremely ill, immune deficient will be excluded too.

8.3 Adverse Events and Serious Adverse Events

Participants will be monitored for adverse events from the time of enrollment through the final visit. An adverse event (AE) is any untoward medical occurrence in a participant in a clinical investigation who has been administered an investigational product and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a product, whether or not it is considered related to that product. Pre-existing conditions which worsen during a study are to be reported as AEs.

During the study, participants will be asked to make a note of any adverse events. At each visit the participant will be asked "Have you experienced any difficulties or problems since I saw you last"? Any AEs will be documented and in the study record and will be classified according to the description, duration, intensity, frequency, and outcome. The Qualified Investigator will assess any AEs and decide causality.

8.3.1 Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 Definition of Serious Adverse Events (AE)

A serious adverse event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly/birth defect in the offspring of a participant who received the study treatment
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse.

8.3.3 Classification of An Adverse Event

8.3.3.1 Severity of Event

Intensity of AEs will be graded on a three-point scale (mild, moderate, severe) and reported in detail in the study record

1. Mild: Awareness of event but easily tolerated
2. Moderate: Discomfort enough to cause some interference with usual activity
3. Severe: Inability to carry out usual activity

8.3.3.2 Relationship to Study Intervention

The causality relationship of investigational product to the adverse event will be assessed by the Qualified Investigator as either:

1. Most probable: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge)

should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

2. Probable: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
3. Possible: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
4. Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
5. Not related: The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 Expectedness

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

8.3.4 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset,

clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Qualified Investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 Adverse Event Reporting

During the study, participants will be asked to make a note of any adverse events. At each visit the participant will be asked "Have you experienced any difficulties or problems since I saw you last"? Any AEs will be documented in the study record.

The Qualified Investigator will be responsible for classification of an AE as an SAE within 24 hours of notification. Causality will be signed off by the Qualified Investigator prior to reporting to ethics and regulatory bodies. Notification of any serious adverse events will be made in writing to the study sponsor. The IRB will be notified of all SAEs and unexpected adverse reactions. All SAEs will be reported to the Therapeutics Products Directorate (TPD) in an expedited manner.

The sponsor must notify the TPD of all serious adverse reactions as follows:

1. If it is neither fatal or life threatening, within 15 calendar days after the day on which the sponsor becomes aware of the information; and
2. If it is fatal or life threatening, must be reported as soon as possible, but not later than seven (7) days after the day on which the sponsor becomes aware of the information.

8.3.6 Serious Adverse Event Reporting

In accordance with Natural Health Products Directorate (NHPD) guidelines:

- If the serious unexpected adverse reaction is fatal or life threatening, the NHPD will be notified immediately if possible, and no later than seven days after the sponsor becomes aware of the information
- If the serious unexpected adverse reaction is neither fatal nor life threatening, the NHPD will be notified immediately if possible, and no later 15 days after the sponsor becomes aware of the information
- Within eight days after having informed the NHPD of a serious unexpected adverse reaction to the NHP, the sponsor must submit a report as complete as possible that includes an assessment of the importance and implication of any findings. The final report should include relevant previous experience with the same or similar health products.
- Serious adverse events unrelated to the NHP being studied do not require expedited reporting to the NHPD.
- In situations in which the cause of the adverse event is uncertain, the report will be submitted in the expedited manner and the problem in ascribing a cause should be addressed in a cover letter.

8.4 Unanticipated Problems

8.4.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

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

8.4.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

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

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the DCC/study sponsor within <insert timeline in accordance with policy> of the investigator becoming aware of the problem.

All UPs should be promptly reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP).

9. Statistical Considerations

9.1 Statistical Hypotheses

- **Primary Efficacy Endpoints:**
  - Change of Protective Qi after a total of 12 weeks follow-up
- **Secondary Efficacy Endpoints:**
  - Change of Generic Qi after a total of 12 weeks follow-up
  - Change of Global Health (Appendix 5) including physical health and mental health after a total of 12 weeks follow-up
  - Change of saliva secretary IgA after a total of 12 weeks follow-up
  - Change of Emotional and Behavioral Dyscontrol (Appendix 6) after a total of 12 weeks follow-up
  - Change of Emotional Impact (Appendix 7) after a total of 12 weeks follow-up

9.2 Sample Size Determination

A preliminary study was conducted prior to the current study for sample approximation [10]. We screened 47 volunteers and excluded those who were pregnant or planning to become pregnant, extremely ill, immune

deficient, taking medications/supplements known to affect Protective Qi status, or who consumed more than 28 g alcohol per day (i.e., the equivalent of more than 24 ounces of beer,10 ounces of wine, or 3 ounces of distilled alcohol daily). 30 participants diagnosed with PQD were enrolled and treated with β-glucan in a dose of ~200 mg/day for 8 weeks. The PQD status (severity score) was monitored biweekly and used to estimate the effect size of ß-glucan. Last Observation Carried Forward (LOCF) [15] imputation was used for handling missing data. When analyzing the data, we used matching techniques [11] to create a virtual control group that is essentially equivalent to the treatment group on observed pre-intervention characteristics. Nonetheless, any potential confounders were regarded as the effecters of Regression To Mean (RTM) [12] and were accounted for by Trochim's method ([13], P322) that adjusts an individual's pre-test score as follows:

$$x_{adj} = \bar{x} + r(x_{pre} - \bar{x}_{pre})$$

Where x_{adj} is the adjusted pretest value, $\bar{x}_{pre}$ is the treatment group pre-test mean, r is the pre-post correlation of the severity score for the treatment group, and x_{pre} is the original pretest value. We then used Cohen's d ([14], P276) to calculate the treatment effect size.

$$d = 2 * f = 2 * \sqrt{\frac{\frac{SS(x_{post} - x_{pre}),}{ss(x_{post})}}{1 - \frac{SS(x_{post} - x_{\mathrm{pre}}),}{SS(x_{post})}}} = 2 * \sqrt{\frac{\frac{7.479}{7.479 + 4.928}}{1 - \frac{7.479}{7.479 + 4.928}}} = 2 * 1.23 = 2.46$$

Where x_{post} is the post-treatment severity score, SS is the sum of square, and f is the F test on means in the analysis of variance and covariance.

Given the Cohen's d is a positively biased estimator of effect size when sample size are small [14], we adjusted Cohen's d to conventional "large effect size (0.8)".

Assuming an allowable Type I error (alpha) of 0.01 and power value of 0.9, we performed R package "pwr" and obtained a minimal sample size of 49 for each group.

9.3 Populations for Analyses

The intention-to-treat analysis method will be followed for trial outcomes. In the case of missing data due to participants that withdrew from the trial or missed visits, data from the previous visit will be used for the missing value (Last Observation Carried Forward, or LOCF).

9.4 Statistical Analyses

9.4.1 General Approach

Kolmogorov-Smirnov Test for Normality will be performed to check whether continuous baseline values are normal distribution. Continuous variables with normal distribution will be reported as mean and standard deviation (SD) and tested by t-test, otherwise will be reported as median and Interquartile range (IQR) and tested by Kruskal-Wallis rank sum test. Categorical variables will be presented as the participants' number and proportion (%) and tested by Chi-square or fisher's exact test.

9.4.2 Analysis of the Efficacy Endpoint(s)

Trial outcome measures, if they are continuous, will be evaluated by skewness and kurtosis for normality and expressed as mean (95% CI) if both measures were within the range of (2, -2); otherwise they will be expressed as median (95% CI) with specification. Given the potential effect of treatment time on trial outcomes, we will analyze the effect of ß-glucan with adjustment by treatment time. This will be conducted by linear mixed regression [16] or Aligned Rank Transformation ANOVA [17] if assumptions of the regression model were not satisfied. Categorical outcomes will be derived from conventional PQD diagnosis. The effect of ß-glucan will be analyzed using generalized mixed linear model [18] for conventional PQD diagnosis.

For all statistical analyses, differences with a $P < 0.05$ (two tailed) will be considered significant.

Other details analysis of the primary endpoints are described as follows:

- The PQi status of each participant at baseline and each follow-up visit will be measured by on-site investigators (licensed TCM practitioners) through a standardized quantitative assessment (Table 1 & Table 2). Each health condition relevant to PQD (i.e. cold frequency, symptoms, and signs) will be scored on a designed scale (ranging 1-10, with higher number indicating more severe deficiency) based on a set of standardized and specified criteria (Table 2). The sub-scores are then weighted (cold history 25%, symptoms 33.3%, signs: 41.7%) to arrive at a final PQD severity score. This score is on a 1-5 scale, with 5 being the most severe deficiency. The change of the score from baseline, indicating the treatment effect, will be calculated and analyzed by statistical means.
- PQi status of each participant at baseline and each follow-up visit will be measured by on site-investigators (licensed TCM practitioners) through non-standardized, qualitative traditional assessment. The status was characterized by non-PQD or PQD. The change of PQi status from baseline, indicating the treatment effect, will be calculated and analyzed by categorical statistic.

Other details analysis of the secondary endpoints are described as follows:

- The GQi status of participants at baseline and each follow-up visit will be assessed by on-site investigators (licensed TCM practitioners) through a standardize quantitative assessment (Table 3 & Table 4). Each health condition relevant to GQi Deficiency (GQD) (including symptoms, and signs) will be scored based

on a standardized criteria (Table 4), and then weighted to arrive at a final GQi severity score (Table 3). This score is on a 1-5 scale, with 5 being the most severe deficiency. The change of the score from baseline, indicating the treatment effect, will be calculated and analyzed by statistical means.

- The participants' Global Health will be assessed using the established PROMIS® Scale v1.2 (Please see the link https://www.healthmeasures.net/explore-measurement-systems/promis). This questionnaire consists of 10 global-health related questions. The answer for nine of ten questions are graded on 1-5 scale (with 5 being the best), and one question is graded on 1 to 10 scale (with 10 being the worst grade). The sub-scores are used to obtain a final combined score of Global Physical Health or Global Mental Health using a T-score metric in which 50 is the mean of a relevant reference population and 10 is the standard deviation (SD) of that population. The change of the score from baseline, indicating the treatment effect, will be calculated and analyzed by statistical means.
- The effect of Proglucamune on the participants' immunity will be assessed by the change of saliva secretary IgA, which will be normalized by the secretion rate (μg/min). The change of the score from baseline, indicating the treatment effect, will be calculated and analyzed by statistical means.
- Neuro-QoL (Quality of Life in Neurological Disorders) is a measurement system that evaluates and monitors the physical, mental, and social effects experienced by adults and children living with neurological conditions. Please see the link (http://www.healthmeasures.net/explore-measurement-systems/neuro-qol) for details. This questionnaire consists of 8 questions related to emotional and behavioral control. The answers for each of the questions are graded on five levels from best to worst. A combined score is generated using a T-score metric in which 50 is the mean of a relevant reference population and 10 is the standard deviation (SD) of that population.
- The participants' Emotional status will be assessed using the ASCO-Me® v2.0 Emotional Impact (Short Form). This questionnaire-based survey was established based on a Sickle-cell patient population (Please see the link http://www.ascq-me.org/Science or the citation below for detail). This questionnaire consists of 5 emotional-status related questions. The answer for each of the questions are graded on five levels from best to worst. A combined score is generated using a T-score metric in which 50 is the mean of a relevant reference population and 10 is the standard deviation (SD) of that population.

10. Supporting Documentation and Operational Considerations

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent and Other Informational Documents Provided to Participants

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

- Appendix 1 (Subject Record at Screening Participant questionnaire – General information & PQi and GQi Evaluation Questionnaire)
- Appendix 2 (Physical Examination for screening visit)
- Appendix 3 (Subject Record at Follow-up Participant questionnaire – General information)
- Appendix 4 (Subject Record at Follow-up Participant questionnaire – PQi and GQi Evaluation Questionnaire)
- Appendix 5 (Subject Record at Follow-up Global Health assessment)
- Appendix 6 (Subject Record at Follow-up Emotional and Behavioral Dyscontrol Assessment-Short Form)
- Appendix 7 (Subject Record at Follow-up Emotional Impact assessment– Short Form)
- Appendix 8 (Subject Record at Follow-up Information and Consent Form)

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 Study Discontinuation and Closure

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

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

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

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB

10.1.3 Confidentiality and Privacy

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

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

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

The study participant's contact information will be securely stored at clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the **ShareFile database** (an HIPPA compatible data sharing platform). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by statistician will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the **ShareFile database.**

10.1.4 Future Use of Stored Data

After completion of the study, documents and files generated from this trial will be shipped to and stored at the sponsor site (USANA). Digital, de-identified data collected for this study will be analyzed and stored at the **ShareFile Database**. After the study is completed, archived digital data will be transmitted to and stored at the **USANA Data Management Database**, for use by other researchers including those outside of the study. Permission to transmit data to the **USANA Data Management Database** will be included in the informed consent.

When the study is completed, access to study data and/or samples will be provided through the **USANA R&D**.

10.1.5 Quality Assurance and Quality Control

10.1.5.1 Regulatory Compliance

The investigators must agree to comply with the sponsor and regulatory requirements in terms of auditing of the study. This includes access to the source documents for source data verification at any time by the sponsor. In addition, the sponsor and investigators (as appropriate) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspections and will allow direct access to source data and documents for these purposes. An initiation meeting will be conducted by the sponsor. At this meeting, the protocol and logistical aspects of the study will be reviewed by the Sponsor with the investigators and all study staff.

10.1.5.2 Data Monitoring

Source documents will be reviewed during an audit performed by the sponsor at four to six weeks from the beginning of the study (i.e., as indicated by enrollment of the first participant) and at the conclusion of the study following the release of the final participant. This will be done to ensure that all data is being properly gathered and recorded in accordance with the manner specified in the protocol. The participant files will be reviewed to confirm that:

- Informed consent was obtained and documented;
- Enrolled participants fulfilled all inclusion criteria and did not meet any exclusion criteria;
- AE/SAE reporting has been performed as applicable;
- Study visits have been conducted as per protocol and information has been recorded in the appropriate place in the source document;
- The study product is being stored correctly and an accurate record of its dispensation to the study participants is being maintained (accountability).

Incorrect, inappropriate, or illegible entries in the participant files will be returned to the investigator for correction. No data disclosing the identity of participants will leave the study center. The Investigator and any designees will maintain confidentiality of all participant records.

10.1.6 Data Handling and Record Keeping

10.1.6.1 Data Collection and Management Responsibilities

All data collection and record storage will be done in compliance with ICH GCP Guidelines and applicable local regulatory guidelines. Data required for analysis will be acquired from source documentation (including laboratory reports) and entered into a Microsoft Excel and other statistical software (R) for this study. All data points entered into the study database are source data verified.

10.1.6.2 Study Records Retention

High safety standards for the transfer and storage of study data are guaranteed by the use of technologies such as password protection, firewalls and periodic backup to protect stored data. Writing access to the system will be limited to authorized personnel. All data is archived for a period not less than 20 years from the date of completion of the study.

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Table 1. Calculation of Standardized Protective Qi Deficiency (PQD)

Category	Parameter	Weight
Cold History	**TCM Inquiry (Cold frequency)**	25%
Symptoms of PQD	**TCM Inquiry (Spontaneous sweating)**	16.7%
	TCM Inquiry (Aversion to wind & cold)	16.7%
Sign of PQD	**TCM Inspection （Tongue）**	8.3%
	TCM Auscultation （Low voice & apathy）	6.7%
	TCM Palpation (Overall Pulse)	10%
	TCM Palpation (Cun Pulse)	16.7%

The PQD were obtained from the standardized protocol shown in Table 2, and the weighting coefficients were based on TCM investigators' clinical experience. The range of the PQD index is 1-5, with the higher value indicating more severe PQD.

Table 2: Standardized criteria for PQi severity score assessment

Candidate Parameter		Method of measurement and scores	
Cold Frequency	TCM Inquiry (Cold frequency)	No cold in the past 2 months	0
		Once in the past 2 months	1
		Twice in the past 2 months	2
		3 times or more in the past 2 months	3
Symptoms of PQD	TCM Inquiry (Spontaneous sweating)	No spontaneous sweating, sweat only with intense physical activities	0
		Sweat with routine physical activities	1
		Sweat heavily with routine physical activities	2
		Sweat with slight physical activities like walking	3
		Sweat spontaneously	4
	TCM Inquiry (Aversion to wind & cold)	No aversion to wind or cold	0
		Aversion to wind	1
		Aversion to cold, but relieved by adding light clothing	2
		Aversion to both cold (but relieved by light clothing) and wind, or susceptible to cold when exposed to wind or cold	3
		Aversion to cold (only relieved by think clothing that covers whole body); or very easily catch a cold when exposed to wind or cold	4
Sign of PQD	TCM Auscultation （Low voice & apathy）	The participant's voice is loud & clear at a distance of 2m from the investigator	0
		The participant can be heard & understood at 2m from the investigator, but the voice is recognizably weak.	1
		The participant's voice is clearly low at 2m from the investigator & needs much attention to understand.	2
		The participant can be heard from 2m but need repeated clarification.	3
		The participant cannot be heard with a clear understanding at a distance of 2m.	4
	TCM Inspection （Tongue）	The tongue looks light red with thin white coating and is of proper size.	0
		The tongue looks pale in color with white coating; however, the tongue is of proper size & has no tooth mark on the sides.	1
		The tongue looks pale with white coating. This size is slightly larger than normal. Tooth-marks are visible but are limited to part(s) of the tip and sides of the tongue.	2
		The tongue looks pale with white coating. This size is significantly larger than normal. Tooth-marks are visible along the full length of the tip and sides of the tongue.	3
	TCM Palpation (Overall Pulse[1])	Normal pulse	0
		Deficient Pulse is detectable but not apparent	1
		Apparent Deficient Pulse	2
	TCM Palpation (Cun Puls[1])	Normal pulse	0
		The pulse shows characteristics of Floating or Deficient Pulse, but not both.	1
		Floating pulse is present, Deficient Pulse is detectable but not apparent.	2
		Floating pulse is present, Deficient Pulse is apparent.	3

1. Overall pulse indicates the overall impression of pulse at the three locations: Cun, Guan, & Chi.

Table 3. Calculation of Standardized Generic Qi Deficiency (GQD)

Final Score	Subscore D	Subscore C	Subscore B	Subscore A
GQD Score **Weighted sum of Subscore Ds** **Symptom Score Wt: 40%** **Sing Score Wt: 60%**	Symptom Score Select the highest one among Subscore Cs of Part I-VI	**Part I :** **Symptoms of PQD Score** **Weighted sum of Subscore Bs** **Part Ia Wt: 47%** **Part Ib Wt: 53%**	Part I a: Score of cold history	TCM Inquiry (Cold frequency)
			Part I b: Score of other PQD symptoms Weighted sum of Subscore As. Ib 1 Wt. 50% Ib 2 Wt. 50%	Ib1: TCM Inquiry (Spontaneous sweating)
				Ib2 TCM Inquiry (Aversion to wind & cold)
		Part II: **Symptoms of Systemic Qi Deficiency Score** **Average subscore As of IIa-d**		IIa: TCM Inquiry (Limb weakness)
				IIb: TCM Inquiry (Lack of energy)
				IIc: TCM Inquiry (Low spirit)
				IId: TCM Inquiry (Unwilling to talk)
		Part III: **Symptoms of Lung Qi Deficiency Score** **Average subscore As of IIIa-d**		IIIa: TCM Inquiry (Shortness of Breath)
				IIIb: TCM Inquiry (Cough)
				IIIc: TCM Inquiry (Thin sputum)
				IIId: TCM Inquiry (Timidity)
		Part IV: **Symptoms of Spleen Qi Deficiency Score** **Average subscore As of IVa-c**		IVa: TCM Inquiry (Poor appetite)
				IVb: TCM Inquiry (Loose stools)
				IVc: TCM Inquiry (Abdominal discomfort feeling after eating)
		Part V: **Symptoms of Heart Qi Deficiency Score** **Average subscore As of Va-b**		Va: TCM Inquiry (Palpitations)
				Vb: TCM Inquiry (Depressed)
		Part VI: **Symptoms of Kidney Qi Deficiency Score** **Average subscore As of VIa-c**		VIa: TCM Inquiry (Urination)
				VIb: TCM Inquiry (Soreness of lower back)
				VIc: TCM Inquiry (Cold limbs especially legs)
	Sign of GQD **Weighted sum of Subscore As Part I-IV** **Part I Wt: 24%, Part II Wt: 40%, Part III Wt: 20%, Part IV Wt: 16%**			Part I: TCM Auscultation （Low voice & apathy）
				Part II: TCM Inspection （Tongue）
				Part III: TCM Palpation (Overall Pulse[1])
				Part IV: TCM Palpation (Cun Puls[1])

The GQD severity score were obtained from the standardized protocol shown in Table 4, and the weighting coefficients were based on TCM investigators' clinical experience. The range of the GQD index is 1-5, with the higher value indicating more severe GQD.

Table 4: Standardized criteria for GQi severity score assessment

Candidate Parameter		Method of measurement and scores	
Symptoms of PQD	Ia: TCM Inquiry (Cold frequency)	No cold in the past 2 months	0
		Once in the past 2 months	1
		Twice in the past 2 months	2
		3 times or more in the past 2 months	3
	1b1: TCM Inquiry (Spontaneous sweating)	No spontaneous sweating, sweat only with intense physical activities	0
		Sweat with routine physical activities	1
		Sweat heavily with routine physical activities	2
		Sweat with slight physical activities like walking	3
		Sweat spontaneously	4
	Ib2: TCM Inquiry (Aversion to wind & cold)	No aversion to wind or cold	0
		Aversion to wind	1
		Aversion to cold, but relieved by adding light clothing	2
		Aversion to both cold (but relieved by light clothing) and wind, or susceptible to cold when exposed to wind or cold	3
		Aversion to cold (only relieved by think clothing that covers whole body); or very easily catch a cold when exposed to wind or cold	4
Symptoms of Systemic Qi Deficiency	IIa: TCM Inquiry (Limb weakness)	1-5 scale, with 5 indicating the most symptomatic	
	IIb: TCM Inquiry (Lack of energy)		
	IIc: TCM Inquiry (Low spirit)		
	IId: TCM Inquiry (Unwilling to talk)		
Symptoms of Lung Qi Deficiency	IIa: TCM Inquiry (Shortness of Breath)	1-5 scale, with 5 indicating the most symptomatic	
	IIIb: TCM Inquiry (Cough)		
	IIIc; TCM Inquiry (Thin sputum)		
	IIId: TCM Inquiry (Timidity)		
Symptoms of Spleen Qi Deficiency	Iva: TCM Inquiry (Poor appetite)	1-5 scale, with 5 indicating the most symptomatic	
	IVb: TCM Inquiry (Loose stools)		
	IVc: TCM Inquiry (Abdominal discomfort feeling after eating)		
Symptoms of Heart Qi Deficiency	Va: TCM Inquiry (Palpitations)	1-5 scale, with 5 indicating the most symptomatic	
	Vb: TCM Inquiry (Depressed)		
Symptoms of Kidney Qi Deficiency	VIa: TCM Inquiry (Urination)	1-5 scale, with 5 indicating the most symptomatic	
	VIb: TCM Inquiry (Soreness of lower back)	1-5 scale, with 5 indicating the most symptomatic	
	Vic: TCM Inquiry (Cold limbs especially legs)	1-5 scale, with 5 indicating the most symptomatic	
Sign of GQD	ParI: TCM Auscultation （Low voice & apathy）	The participant's voice is loud & clear at a distance of 2m from the investigator	0
		The participant can be heard & understood at 2m from the investigator, but the voice is recognizably weak.	1
		The participant's voice is clearly low at 2m from the investigator & needs much attention to understand.	2
		The participant can be heard from 2m but need repeated clarification.	3
		The participant cannot be heard with a clear understanding at a distance of 2m.	4
	Part II: TCM Inspection （Tongue）	The tongue looks light red with thin white coating and is of proper size.	0
		The tongue looks pale in color with white coating; however, the tongue is of proper size & has no tooth mark on the sides.	1
		The tongue looks pale with white coating. This size is slightly larger than normal. Tooth-marks are visible but are limited to part(s) of the tip and sides of the tongue.	2
		The tongue looks pale with white coating. This size is significantly larger than normal. Tooth-marks are visible along the full length of the tip and sides of the tongue.	3
	Part III: TCM Palpation (Overall Pulse[1])	Normal pulse	0
		Deficient Pulse is detectable but not apparent	1
		Apparent Deficient Pulse	2
	Part IV: TCM Palpation (Cun Puls[1])	Normal pulse	0
		The pulse shows characteristics of Floating or Deficient Pulse, but not both.	1
		Floating pulse is present, Deficient Pulse is detectable but not apparent.	2
		Floating pulse is present, Deficient Pulse is apparent.	3

Overall pulse indicates the overall impression of pulse at the three locations: Cun, Guan, & Chi.

Appendix 1

Subject Record at Screening

Participant questionnaire – General Information

1. Date of birth:
2. Gender:
3. Ethnicity:
4. Telephone number:
5. Email:
6. What was the last time you were vaccinated?
    a. If yes, what vaccine?
7. Taking medications ? If yes:
    a. What is the name of the medication?
    b. When did you begin taking the medication?
    c. What is the dosage?
    d. How often do you take the medication?
8. Are you a female who is pregnant or is attempting to become pregnant, or is lactating?
9. Have you consumed other dietary supplements within 30 days? If yes:
    a. What is the name of the supplement?
    b. When did you begin taking the supplement?
    c. What is the dosage?
    d. How often do you take the supplement?
10. Have you participated as a subject in any other clinical study within 30 days?
11. Do you have any gastrointestinal conditions that may affect consumption of the treatment or placebo tablets?
12. Do you smoke? If yes, how often and how much do you smoke?
13. Do you have a history of alcohol consumption within the previous 2 years? If so, how many drinks do you have each week?

14. Are you fully able and willing to keep scheduled appointments (once every 2 weeks for the full 12 week duration)?

15. Do you have allergies to mushrooms or other fungi，or yeast products?

16. Do you have had a medical surgery in the past 4 weeks or have scheduled a surgery during the study period?

17. Do you have a history of substance abuse within the previous 2 years?

18. Please check any acute or chronic illnesses you currently have:

    Diabetes

    Acute infection, contagious diseases

    Chronic bronchitis

    Cardiopulmonary failure

    Cancer

    Immune dysfunction or disorder

    Significant constipation or diarrhea

    Alzheimer's and other neurodegenerative diseases

    depression or anxiety disorders

    Any other significant illnesses

19. If you have a cold during time of the trial, are you willing follow the investigating doctors' prescription and refrain from other medications?

Subject Record at Screening

Participant questionnaire – PQi and GQi Evaluation Questionnaire

Endpoint Part I

1. Did you ***catch*** any cold* (*as defined by TCM) in the past three months?
2. If no, please proceed to Part II
3. If yes:
    a. how many times, and how long did it last?
        i. Once — duration:
        ii. Twice — duration of cold #1:
            duration of cold #2:
        iii. 3 times or more — duration of cold #1:
            duration of cold #2:
            duration of cold #3:
            duration of other colds:
    b. how many days since you last experienced symptoms of a cold*? If you currently have an ongoing cold, write "ongoing".

Please rate each question on 1-10 scale

Endpoint Part II — Score

1. Do you have spontaneous perspiration ?
2. Does the perspiration worsen with activities?
3. Aversion to wind or chills

Score

Endpoint Part III

1. Do you often feel shortness of breath?
2. Do you often feel unwillingness to talk?

Score

Endpoint Part IV

1. Do you often feel limb weakness?
2. Do you often feel lack of energy?
3. Do you often feel low spirit?

Endpoint Part V Score

(Score each on a 1-10 scale)

1. weak or powerless pulse
2. cun-pulse superficial or weak
3. corpulent tongue or with white fur
4. low voice

Endpoint Part VI:

iPQ Scoring Summary Table

TCM Endpoint	Total Score	Average Score
Participant Questionnaire - Endpoint Part I		
Participant Questionnaire - Endpoint Part II		
Physical Examination – Endpoint Part II		
Overall Score		

Traditional Diagnosis of IPQ and IQ

	PQD	**GQD**
No Insufficiency		
Mild Insufficiency		
Moderate Insufficiency		
Severe Insufficiency		

Part VII: Base on what Exclusion Criteria is this subject excluded?

Appendix 2

Subject Record at Screening

PHYSICAL EXAMINATION

☐ NOT DONE

SITE	NORMAL	ABNORMAL	NOT DONE	DESCRIBE ABNORMALITIES
General Appearance	☐	☐	☐	
Head	☐	☐	☐	
Eyes	☐	☐	☐	
Nose	☐	☐	☐	
Mouth	☐	☐	☐	
Throat	☐	☐	☐	
Neck	☐	☐	☐	
Thyroid	☐	☐	☐	
Lungs	☐	☐	☐	
Heart	☐	☐	☐	
Breasts	☐	☐	☐	
Abdomen	☐	☐	☐	
Musculoskeletal	☐	☐	☐	

Investigator Signature _____

Appendix 3

Subject Record at Follow-up

Participant questionnaire – General information

1. Date of birth:
2. Gender:
3. Ethnicity:
4. Telephone number:
5. Email:
6. Height:
7. Weight:
8. Blood Pressure:
9. Heart Rate:
10. Respiration Rate:
11. Have you had a flu shot since October 1 of 2018?
12. How many days have elapsed since you last experienced symptoms of a cold*? If you currently have an ongoing cold, write “ongoing”.
13. What was the last time you were vaccinated with something other than the flu vaccine?
    a. If yes, what was vaccine?
14. Taking medications ? If yes:
    b. What is the name of the medication?
    c. When did you begin taking the medication?
    d. What is the dosage?
    e. How often do you take the medication?
15. Are you a female who is pregnant or is attempting to become pregnant, or is lactating?
16. Have you consumed other dietary supplements within 30 days? If yes:
    f. What is the name of the supplement?
    g. When did you begin taking the supplement?

h. What is the dosage?

i. How often do you take the supplement?

17. Have you participated as a subject in any other clinical study within 30 days?
18. Do you have any gastrointestinal conditions that may affect consumption of the treatment or placebo tablets?
19. Do you smoke? If yes, how often and how much do you smoke?
20. Do you consume alcohol? If so, in the past 2 months, how many drinks did you consume each week on average?
21. Are you fully able and willing to keep scheduled appointments (once every 2 weeks for the full 12 week duration)?
22. Do you have allergies to mushrooms, fungi or yeast products?
23. Have had a medical surgery in the past 4 weeks and/or do you have a medical surgery scheduled during the study period?
24. Do you have a history of substance abuse within the previous 2 years?
25. Have you suffered from allergic rhinitis, or pollinosis (hay fever), or asthma in the past year?
26. Did you eat any mushroom or oatmeal in the past two months?

    If yes, please state the approximate average quantity in a week (grams/week)?

27. Please check any acute or chronic illnesses you currently have:

    Diabetes

    Acute infection, contagious diseases

    Chronic bronchitis

    Cardiopulmonary failure

    Cancer

    Immune dysfunction or disorder

    Significant constipation or diarrhea

    Alzheimer's and other neurodegenerative diseases

    Depression or anxiety disorders

    Any other significant illnesses

28. If you have a cold during time of the trial, are you willing to inform and follow the study doctor's instructions?

Appendix 4

Subject Record at Follow-up

Participant questionnaire – PQi and GQi Evaluation Questionnaire

Part I

Do you have a history of **catching** a cold* (*, defined by TCM) in the past year? If no, please proceed to Part II of this section; if yes, please fill out the following blanks.

1. How many times did you **catch** a cold* in the **past year**?
   i. Once — duration:

   ii. Twice — duration of cold #1:
   duration of cold #2:

   iii. 3 times or more — duration of cold #1:
   duration of cold #2:
   duration of cold #3:
   duration of other colds:

   iv. During the above colds*, did you experience any of the following symptoms:
   - Sneezing
   - Coughing
   - Sweating
   - Nasal discharge or congestion
   - High fever (body temperature > 39.1^0C)
   - Itching or painful throat
   - Headache
   - Aversion to wind and cold
   - General pain and malaise

2. How many times did you **catch** a cold* **last winter (2017 – 2018)**?
   i. Once — duration:

   ii. Twice — duration of cold #1:
   duration of cold #2:

iii. 3 times or more

duration of cold #1:

duration of cold #2:

duration of cold #3:

duration of other colds:

iv. During the above colds*, did you experience any of the following symptoms:

- Sneezing
- Coughing
- Sweating
- Nasal discharge or congestion
- High fever (body temperature > 39.1^0C)
- Itching or painful throat
- Headache
- Aversion to wind and cold
- General pain and malaise

3. How many times did you **catch** a cold* in the **last two months**?

i. Once

duration:

ii. Twice

duration of cold #1:

duration of cold #2:

iii. 3 times or more

duration of cold #1:

duration of cold #2:

duration of cold #3:

duration of other colds:

iv. During the above colds*, did you experience any of the following symptoms:

- Sneezing
- Coughing
- Sweating
- Nasal discharge or congestion
- Itching or painful throat
- Headache
- Aversion to wind and cold
- General pain and malaise
- High fever (body temperature > 39.1^0C)

Part II

a. Do you have spontaneous perspiration?I don't readily sweat, or sweat only with intense physical activities
b. I sweat with some slight physical activities like walking
c. I sweat spontaneously
d. I sweat heavily and instantly with physical activities
e. I sweat even without any physical activities

4. Aversion to wind or cold
    a. No aversion to wind or cold
    b. Aversion to wind
    c. Aversion to cold, but relieved by adding clothing
    d. Aversion to both cold (but relieved by clothing) and wind, or susceptible to cold* when exposed to wind or cold weather
    e. Aversion to cold (only relieved by clothing that covers whole body), very readily catch a cold* when exposed to wind or cold weather

Part III

3. Do you often feel shortness of breath?
4. Do you often feel unwillingness to talk?

Part IV

1. Do you often feel limb weakness?
2. Do you often feel a lack of energy?
3. Do you often feel in low spirits?

Part V

1. Do you often have a cough?
2. Do you often have thin sputum
3. Do you often feel timidity

Part VI

1. Do you often have poor appetite?
2. Do you have loose stools
3. Do you often have uncomfortable feeling in the abdomen after eating?

Part VII

1. Do you often feel palpitations?
2. Do you often feel depressed?

Part VIII

1. Do you have frequency of urination?
2. Do you often feel soreness of lower back?
3. Do you have cold limbs, especially legs?

Part IX Score (Score each on a 1-5 scale)

5. weak or powerless pulse
6. cun-pulse superficial or weak
7. corpulent tongue or with white fur
8. low voice

Appendix 5

Subject Record at Follow-up

PROMIS® Scale v1.2 – Global Health

Global Health

Please respond to each question or statement by marking one box per row.

		Excellent	Very good	Good	Fair	Poor
Global01	In general, would you say your health is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global02	In general, would you say your quality of life is:	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global03	In general, how would you rate your physical health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global04	In general, how would you rate your mental health, including your mood and your ability to think?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global05	In general, how would you rate your satisfaction with your social activities and relationships?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Global09r	In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc.).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Completely	**Mostly**	**Moderately**	**A little**	**Not at all**
Global06	To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

In the past 7 days…

		Never	Rarely	Sometimes	Often	Always
Global10r	How often have you been bothered by emotional problems such as feeling anxious, depressed or irritable?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		None	**Mild**	**Moderate**	**Severe**	**Very severe**
Global08r	How would you rate your fatigue on average?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Global07r	How would you rate your pain on average?	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

Appendix 6

Subject Record at Follow-up

Emotional and Behavioral Dyscontrol – Short Form

Please respond to each question or statement by marking one box per row.

	In the past 7 days…	Never	Rarely	Sometimes	Often	Always
EDANG42	I had trouble controlling my temper……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPER05	It was hard to control my behavior…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPER06	I said or did things without thinking……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPER07	I got impatient with other people……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPER11	I was irritable around other people…….	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPER12	I was bothered by little things……	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPER17	I became easily upset……..	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
NQPER19	I was in conflict with others……...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix 7

Subject Record at Follow-up

ASCQ-Me® v2.0 Emotional Impact - Short Form

Emotional Impact - Short Form

Please respond to each question or statement by marking one box per row.

		Never	Rarely	Sometimes	Often	Always
EmotionalImpactQ11	In the past 7 days, how often did you feel completely hopeless because of your health?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**A little**	**Somewhat**	**Quite**	**Very**
EmotionalImpactQ12	In the past 7 days, how lonely did you feel because of your health problems? ..	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
EmotionalImpactQ16	In the past 7 days, how depressed were you about your health problems?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
EmotionalImpactQ9	In the past 7 days, how much did you worry about getting sick?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Never	**Rarely**	**Sometimes**	**Often**	**Always**
EmotionalImpactQ17	In the past 7 days, how often were you very worried about needing to go to the hospital?.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Appendix 8

Informed Consent Form

Sponsor / Study Title: USANA Health Sciences, Inc / "An evaluation of Proglucamune® in the treatment of Protective Qi"

Protocol Number: 201878

Study Doctor:	**Ira Bernstein B.Sc, M.D., C.C.F.P., F.C.F.P.**
Telephone:	**416-707-7552**
Additional Contact:	**Jianping Shi**
Address:	**Elegant and Olive Health Clinic** **505 Hood Rd.** **Markham, ON L3R 5V6**

You are being asked to participate in a clinical research study. To decide whether or not you want to be part of this research, you should understand the study risks and benefits in order to make an informed decision. This process is known as informed consent. This consent form describes the purpose, procedures, possible benefits and risks of the study.

This form will also describe how your medical information will be used and who may see it. This form is only one part of the informed consent process. In addition, the study doctor or study staff will explain this form and the study to you in detail.

You are being asked to take part in this study because the study doctor feels that you meet the qualifications of the study. Once you understand the study, you will be asked to sign this form if you wish to participate. You may have a copy of this form to review at your leisure or to ask advice from others prior to agreeing to participate in this study.

The study doctor or staff will answer any questions you may have about this form or about this study. You should also discuss your participation with anyone you choose in order to better understand this study and your options. Please read this document carefully and do not hesitate to ask any questions you may have regarding the information given and the study. This form may

contain words that you do not understand. Please ask the study doctor or staff to explain the words or information that you do not understand.

1.0 INTRODUCTION

Qi is a central concept of traditional Chinese medicine (TCM) and was first documented in the oldest TCM writings more than 2000 years ago. Generally speaking, Qi refers to the vital energy of the body and is derived from two primary sources: 1) inborn Qi (that may be construed as genetics), and 2) pectoral Qi (can be construed as metabolism).

Moreover, Qi manifests itself in two forms: Nutritive Qi and Protective Qi, which can be understood to reflect an individual's nutritional state and immune health, respectively. Regarding the latter, protective Qi functions to defend the body from the invasion of external pathogens. TCM also emphasizes that Protective Qi works primarily on the body surface as a defensive barrier. In this context, Protective Qi is analogous to anatomical barriers of the innate immune system located for example, at the skin surface and the mucosal surfaces of the respiratory and digestive tract.

TCM has developed a number of methods to strengthen the Qi. Prominent among these is the use of Reishi, either alone or in combination with other TCM remedies. The use of Reishi was described in detail in the first TCM pharmacopedia "Compendium of Materia Medica" published 1,600 years ago. Nonetheless, although Protective Qi is part of the general Qi, the specific effect of Reishi on Protective Qi is less documented. Anecdotal reports are available that claim significant improvement of Protective Qi with Reishi or Reishi-containing formulas within days. Notably, Western medicine has identified immune-boosting properties of Reishi, which may explain the Qi enhancing effects of this plant. Specifically, b-glucan – a component of Reishi - has been shown to activate macrophage (large white blood cells in the immune system that destroy bacteria and other harmful substances), neutrophil (type of white blood cells that are important for protection against infections), and other immunocytes (a type of cells capable of producing an immune response), and may exhibit particular benefits among macrophage-rich organs such as the lung, liver and spleen. In fact, ß-glucans from sources other than Reishi, such as baker's yeast, are able to initiate the same immune response and clinical benefits.

The overlap of TCM and western medicine concerning the beneficial effects of Reishi for its Qi enhancing and immune-modulating effects, respectively, has prompted us to investigate whether or not Reishi, in conjunction with other natural products used in TCM, can enhance an

individual's Protective Qi. More specifically, the objective of the current protocol is to determine if a commercially available dietary supplement (Proglucamune®, USANA Health Sciences) containing powdered Reishi and Shitake mushrooms as well as baker's yeast extract, and which is comprised of 25% ß-glucans by weight, will improve Protective Qi in subjects diagnosed by practitioners of TCM as having low or insufficient Protective Qi. Proglucamune® is approved by Health Canada as a natural health product to help maintain the immune function.
USANA is paying the study doctor to conduct this study.

2.0 STUDY PROCEDURE

You will be assigned by chance (like flipping a coin) to 1 of the 2 study groups:

- Proglucamune®
- Placebo

Neither you nor the study doctor will be able to pick which group you are in. You will not know and the study doctor will not know which study group you are in, but the study doctor can find out if it is necessary to know for your health.
The study product will be provided to you as tablets. You will be instructed to take 2 tablets per day with a meal. Take the tablets a few hours before or after taking other medications, and with plenty of fluids.
The content of the tablets is as follows:
A) Study Treatment (Proglucamune®)
1. Active ingredients:
a. Zinc (as Zinc Gluconate) 25mg
b. Beta-Glucan Complex (Baker's Yeast Extract [Saccharomyces cerevisiae, cell wall]) 125 mg,
c. Reishi Mushroom [Ganoderma lucidum, whole mushroom powder] 125 mg
d. Shiitaki Mushroom [Lentinula edodes, whole mushroom powder] 25 mg
2. Non-active ingredients:
a. Microcrystalline cellulose
b. Modified cellulose
c. Vegetable fatty acid
d. Organic maltodextrin
e. Croscarmellose sodium

f. Silicon dioxide

g. Vanilla extract

h. Organic sunflower lecithin

i. Organic palm olein

j. Organic guar gum

B) Placebo:

1. Active ingredients:

a. None

2. Non-active ingredients:

a. Microcrystalline cellulose

b. Modified cellulose

c. Vegetable fatty acid

d. Organic maltodextrin

e. Croscarmellose sodium

f. Silicon dioxide

g. Vanilla extract

h. Organic sunflower lecithin

i. Organic palm olein

j. Organic guar gum

2.1 Study Duration and number of subjects

• Your participation in this study will last approximately 84 days

• You will have a total of 7 study visits (including this first visit you are having). After today, you will return to the clinic every 14 days (two weeks) for a period of 12 weeks

• We anticipate that 130 adult women and men will enroll in this study

2.2 Subject Responsibilities:

While participating in this research study, you will need to:

• Understand the nature of the study and provide voluntary, written informed consent

• Be willing and able to complete all the study records and attend all clinic visits

• Tell the study staff about any changes in health or any problems you experience during the study

• Tell the study staff about any changes to your medications (if taking any) during the

study

• Ask questions as you think of them

• Tell the study doctor or the study staff if you change your mind about staying in the study

• Maintain your same lifestyle routine such as exercise and activity levels throughout the study period

• Abstain from any alcohol abuse (>2 standard alcoholic drinks per day) or drug abuse

• Abstain from the use of recreational or medical marijuana

• Agree to not use another investigational product during the trial

• Agree to not have any flu vaccine during the trial

• In case you catch a cold, agree to notify and follow the instructions from the study doctor

2.2.1 Entry Requirements:

• You must be a male or female between the ages of 18 and 65 years (females please see the section below titled “Birth Control, Pregnancy and Breastfeeding”)

•You must be willing to follow all study instructions and consume the assigned dietary supplements for 12 weeks

• You must not be pregnant and/or lactating or trying to become pregnant

• You must not have chronic use of prescription or over the counter (OTC) medications that may interfere with study results including immune suppressants. Chronic use is defined as routine consumption at least three to four times per week, every week or if prescribed by a medical doctor. It does not include occasional use of medications to alleviate symptoms, for example, of menstrual cramps, occasional headaches, or for acute viral infections (eg. a cold or the flu)

• You must not have participated in TCM therapies designed to combat protective Qi or Qi in general in the 4 weeks preceding enrollment

• You must not have consumed supplements (including the current treatment - Proglucamune®) designed to combat protective Qi or Qi in general in the 4 weeks preceding enrollment

• You must not have difficulty swallowing pills

• You must not have chronic gastrointestinal conditions (inflammatory bowel disease, or other gastro-intestinal diseases) that may hinder digestion of the study treatment supplements

• You must not have any illnesses or conditions that the study doctors deem significant and will interfere with your ability to participate in the study

• You must not have cancer except skin cancers that have been completely excised with

no chemo therapy or radiation follow up. You must not have a history or current diagnosis of cancer diagnosed less than 5 years prior to screening.

• You must not have a history of alcohol abuse or other substance abuse within the previous 2 years

• You must not use marijuana for recreational or medicinal purposes

• You ust not have a history of unstable depression or mental illness requiring treatment within the previous 6 months

• You must not have any planned surgery during the study period

• You must not be currently using tobacco products including chewing tobacco and all types of cigarettes including vaporizers

• You must not have any significant problems with constipation or diarrhea (chronic constipation, chronic diarrhea)

• You must not have a lifestyle, scheduling difficulties or lack of transportation that will prevent or interfere with your ability to attend all of the necessary study visits

• You must not have participated as a subject in any other clinical trial within 30 days of enrollment

• You must not be cognitively impaired and/or be unable to give informed consent

• You must not have any other condition which in the study doctor's opinion may adversely affect your ability to complete the study or its measures or which may pose significant risk to you

• You must not have allergies to mushrooms or other fungi.

• You must not have autoimmune disease/an immune disorder, nor take antidepressants, blood thinners (anticoagulants), or immunosuppressant medication.

• You must not have a history of anemia or migraines.

Please be prepared to discuss with your study doctor your use of all prescription and over-the-counter medications (including vitamins, nutritional supplements, “natural” remedies and herbal preparations) and functional foods (i.e. probiotic containing foods, high fiber foods). The study doctor will discuss other specific study enrollment requirements with you. Birth control, pregnancy and breast feeding:

• You may not participate if you are pregnant, breastfeeding or planning to become pregnant during the course of the study.

• If you become pregnant during the study, you must stop taking the study product immediately and contact the study doctor.

Concomitant Medications

• If you are currently taking any prescribed medications (including thyroid hormone), you must agree to maintain your current method and dosing regimen during the course of the study unless recommended by your physician.

• If you are currently taking prescribed birth control, you must agree to maintain your current method and dosing regimen during the course of the study.

2.2.2 Clinic Visit Requirements:

You will be required to return to the clinic on seven (7) separate occasions. The purpose and procedures of each visit is detailed below:

Screening Visit (Duration: approximately 1 hour)

Before the study starts, you will be asked to review and sign this Information and Consent Form (ICF) if you agree to participate in this study. You will undergo the following procedures (listed below) to determine if you are eligible to participate in this study:

• Review of medical history, medication and supplement use

• Evaluation of IPQ (insufficiency of Protective Qi) status

• If you qualify for the study and agree to participate, you will sign this consent form and will be asked to begin the enrollment process during Study Visit 1 in which you will undergo further examinations by the study doctor.

Study Visit 1 (Duration: approximately 1 hour)

Study Visit 1 consists of the following:

• Review of your health conditions, concomitant medications and supplement use

• Evaluation of IPQ and IQ (general Qi) status

• Physical Exam (including measurement of height, weight, blood pressure and heart rate, respiration rate, temperature, and examination of head, ears, eyes, nose, and throat, etc.)

• Collection of saliva sample for IgA (a class of antibody found in external bodily secretions, such as saliva) evaluation

• You will meet with a study doctor and be given the opportunity to ask questions and review the study requirements. If you qualify for the study and agree to participate, you will be enrolled in the study and will be given a bottle that contains 60 tablets. You will take two tablets a day with

food for the ensuing 4 weeks. If you are taking medications, you will take the tablets at least 3 hours before or after any medications.

• An individual schedule of clinic visits will be provided to you at this time. You will be asked to maintain your typical diet for the entire 12 weeks of the study. If you need to reschedule during the following two week period, please call the study doctor at your earliest convenience. A phone call will be made to you at around one week prior to the appointment as a reminder.

Study Visit 2 (Duration: approximately 0.5 hour)

This visit happens approximately two weeks (± 2 days) after Study Visit 1. The following will be done at this visit:

• Review of health conditions, concomitant medications and supplement use

• Evaluation of IPQ and IQ status

• Physical Exam (including measurement of, weight, blood pressure, heart rate, respiration rate and temperature)

Study Visit 3 (Duration: approximately 0.5 hour)

This visit happens approximately two weeks after (± 2 days) Study Visit 2. The following will be performed at this visit:

• You will be asked to return all unused study product tablets in the original packaging to the study doctor.

• Review of health conditions, concomitant medications and supplement use

• Evaluation of IPQ and IQ status

• Physical Exam (including measurement of, weight, blood pressure, heart rate, respiration rate and temperature)

• A new bottle of study product will be provided to you at the end of the visit. You will take two tablets a day or as instructed by the study doctor for the ensuing four weeks.

Study Visit 4 (Duration: approximately 0.5 hour)

This visit happens approximately two weeks (± 2 days) after Study Visit 3. The following will be done at this visit:

• Review of health conditions, concomitant medications and supplement use

• Evaluation of IPQ and IQ status

• Physical Exam (including measurement of, weight, blood pressure, heart rate, respiration rate and temperature)

• Collection of saliva sample for IgA evaluation

Study Visit 5 (Duration: approximately 0.5 hour)

This visit happens approximately two weeks after (± 2 days) Study Visit 4. The following will be performed at this visit:

• You will return all unused study product tablets in the original packaging to the study doctor.

• Review of health conditions, concomitant medications and supplement use

• Evaluation of IPQ and IQ status

• Physical Exam (including measurement of, weight, blood pressure, heart rate, respiration rate and temperature)

• A new bottle of study product will be provided to you at the end of the visit. You will take two tablets a day or as instructed by the study doctor for the ensuing four weeks.

Study Visit 6 (Duration: approximately 0.5 hour)

This visit happens approximately two weeks (± 2 days) after Study Visit 5. The following will be done at this visit:

• Review of health conditions, concomitant medications and supplement use

• Evaluation of IPQ and IQ status

• Physical Exam (including measurement of, weight, blood pressure, heart rate, respiration rate and temperature)

Study Visit 7 (Duration: approximately 0.5 hour)

This visit happens approximately two weeks after (± 2 days) Study Visit 6, and marks the end of the study. The following will be performed at this visit:

• You will return all unused study product tablets in the original packaging to the study doctor.

• Review of health conditions, concomitant medications and supplement use

• Evaluation of IPQ and IQ status

• Collection of saliva sample for IgA evaluation

• Physical Exam (including measurement of, weight, blood pressure, heart rate, respiration rate and temperature)

2.2.3 Risks to You

Any side effects (unwanted effects or health problems), including changes in medical conditions you had when you started the study, should be reported to the study doctor or study staff. In

addition, if you need to take any new medications during the study, you should report this to the study doctor or study staff.

Proglucamune® has been on the market for over three (3) years. The dose in this study is the same as is used in the market. To avoid digestive upsent, take the study drug with food.

Proglucamune® may cause migraine-like headaches in sensitive individuals. It is possible that you could have problems and side effects of the study product that nobody knows about yet, which include your health getting worse.

2.2.3.1 Allergic reactions

Do not participate in this study if you are allergic to yeast products. Hypersensitivity or an allergic reaction can occur with Proglucamune®.

If you have a very bad allergic reaction, you could die. Some things that happen during an allergic reaction that could be a sign or symptom of a life-threatening allergic reaction (anaphylaxis) are:

• a rash
• having a hard time breathing
• wheezing
• a sudden drop in blood pressure (making you feel dizzy or lightheaded)
• swelling around the mouth, throat, or eyes
• a fast pulse
• sweating

You should get medical help immediately and then contact the study doctor or study staff if you have any of these or any other side effects during the study. Please also refer to section “Contact Information”, for instructions on what to do in an emergency.

Ask the study doctor or study staff if you have questions about the signs or symptoms of any side effects, you read about in this consent form.

Please tell the study doctor or study staff right away if you have any side effects. Please tell them if you have any other problems with your health or the way you feel during the study, whether or not you think these problems are related to the study product.

2.2.3.2 Stopping regular medication use - what are the risks?

You should not stop your regular medication to be in the study without discussing this with

your regular health care physician.Your health might get worse. Please tell the study doctor or study staff right away if you have any problems.

2.2.4 Withdrawal From the Study

• You are free to choose to stop your participation in the study at any time without penalty or loss of benefits to which you are otherwise entitled.

• If you do discontinue the study for whatever reason, you are expected to return all study materials to the clinic.

• You may be asked to undergo some final visit procedures. This may include returning to the clinic to complete a questionnaire.

• If the study doctor or study staff finds out any non-study related information that may greatly affect your well-being (for example, information related to your future health condition), they will share it with you.

2.2.5 New Findings

• Any significant new findings that become available during the course of the study which may influence your continued participation in the study will be disclosed to you as soon as possible.

• While there may be no immediate benefit to you, the results of this study will provide some of the required scientific evidence in order for it to be analyzed by scientists.

• Regulatory bodies such as Food and Drug Administration (FDA) and Health Canada require that all natural products that are sold at your local health food stores and pharmacies should have good scientific evidence for the claims that are being made on the labels of these products.

• Your participation in this study provides the research that is required to bring the science behind the investigational product.

2.2.6 Study Alternatives

• Your alternative is not to participate in this study.

2.2.7 Costs to You

• Your usual health care benefits will not be altered due to your participation in this study.

• All of the tests and study product, examinations, and medical care required as part of this study are provided at no cost to you, the public health plan, or your private medical insurance (if any) and will be paid for by the study sponsor.

• You, the public health plan, or your personal medical insurance (if any) should continue to pay for expenses for your current medical care and/or prescriptions. These expenses will not be paid as part of your participation in this study.
• The sponsor of this study is paying your study doctor for the time, effort and expenses to conduct this study.

2.2.8 Compensation for Participation

For your time and participation in the study, you will be compensated up to $380 if you complete the study. If you are unable to complete the entire study, compensation will be given based on the portion of the study completed as described below:

• Study Visit 1: $40
• Study Visit 2: $40
• Study Visit 3: $40
• Study Visit 4: $40
• Study Visit 5: $40
• Study Visit 6: $40
• Study Visit 7: $40
• Study Bonus: $100 (Available only to subjects who complete all study visits).

Each of your compensations will be provided to you as a check card that can be redeemed at most commercial or financial institutions. You will be paid following each completed visit.

2.2.9 Compensation and Treatment for Injury

In case of an injury or illness suffered by participation in this study, you will receive appropriate medical care. By signing this form, you are not giving up your legal rights, nor releasing the study doctor or sponsors from their legal and professional obligations.

Be aware that the provincial health plan or your health care payer/insurer might not cover the costs of study-related injuries or illnesses.

2.2.10 Voluntary Participation

Your participation in this research is strictly voluntary. You have the right to choose not to be in the study or leave the study at any time for any reason without affecting your relationship with the study doctor or medical staff and without penalty or loss of benefits to which you are otherwise entitled.

The study doctor may also stop your participation in this study at any time without your consent. Reasons for this may include, but are not limited to:

• missing scheduled study visits

• not taking study product as directed

• choosing not to complete required tests and documents

• development of medical conditions or serious side effects that may pose a health risk to you as directed by USANA Health Sciences Inc.

3.0 CONFIDENTIALITY OF RECORDS

• The study doctor and representatives of the sponsors, USANA Health Sciences Inc, will keep all of your medical information confidential to the extent permitted by law.

• All research data (health information such as past medical history and test results from this study) will be kept in a locked file. Forms on which your information is entered will not contain your name (with the exception of the study intake form).

• Any of your personal information that is stored electronically will be password protected, accessible only to authorized personnel and de-identified wherever possible. Electronic data may be stored on secure servers which are physically located in Canada or the United States.

• You will not be identified in any publication that might result from the study.

• Unless required by law, only the study doctor, the sponsor, members of the Institutional Review Board - Advarra IRB (an independent ethics committee that reviewed the ethical aspects of this study to help protect the rights and welfare of study participants), and government regulatory drug agencies (e.g. Health Canada and/or the US Food and Drug Administration - FDA) can have access to this confidential study data at the study site. This inspection is to check the accuracy of study records.

• Study records will be kept by the sponsor for a minimum of 25 years after study completion.

• The sub-investigators will transfer the data to the study doctor after study completion who will retain it for at least 25 years.

• Information from this study will be submitted to the sponsor and possibly to governmental agencies in Canada and other countries (e.g. US Food and Drug Administration - FDA). Information sent from the study site will not contain your name.

• You have the right to check your study records and request changes if the information is not correct.

• While reasonable effort will be made to protect the privacy of your information, absolute confidentiality cannot be guaranteed. This does not limit the duty of the researchers and others to protect your privacy.

• By signing this information and consent form, you consent to the collection, access, use and disclosure of your information as described above.

4.0 CONTACT INFORMATION

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: Pro00030792.

5.0 CONSENT QUESTIONS

1 Have you been given enough time to read and understand this Information and Consent form and the information it contains regarding study?

Yes / No

2 Have you been given enough time to consider whether or not to participate?

Yes / No

3 Is this document in a language you understand? Yes / No

4 Have you been given the opportunity to ask any and all of your questions you have regarding this study?

Yes / No

5 Have all of your questions been answered to your satisfaction? Yes / No

6 Do you understand that you may consult the study doctor or his/her staff should anything become unclear or if you have any more questions?

Yes / No

7 Do you volunteer to be in this study of your own free will and without being pressured by the study doctor or the study staff?

Yes / No

8 Do you understand that you can leave the study at any time without giving a reason and without affecting your health care?

Yes / No

9 Do you understand the risks involved with participating in this study? Yes / No

10 Do you agree to follow the medical instructions provided to you by the Study Doctor and staff?

Yes / No

11 Do you understand that you may not participate in another study while are you are enrolled in this study?

Yes / No

12 Do you understand that your data derived from this study will be kept confidential, and may be reviewed by USANA Health Sciences Inc, the Institutional Review Board (Research Ethics Review Board) and by Regulatory Authorities (e.g. Health Canada, FDA)?

Yes / No

13 Do you understand that all of your personal information will be treated as strictly confidential, except where disclosure is required by law, and will not made publicly available; however, absolute confidentiality cannot be guaranteed?

Yes / No

14 The study doctor has my permission to tell my regular doctor about my being in this study.

Yes / No

6.0 VOLUNTARY CONSENT TO PARTICIPATE

Effect of Phytochemical-based Dietary Supplement on Protective Qi By signing this document, I do not waive any of my rights under the law, or release the study doctor or sponsors from their legal and professional obligations.

I know that the study product is for my use only. I will not share it with anyone, and will store it in a safe place away from children or others for whom it is not intended. I will be given a signed copy of this Information and Consent Form.

_____

Printed Name of Study Subject

_____ _____/_____/_____

Signature of Study Subject Date