CLINICAL PROTOCOL COVER PAGE

Protocol Title:	A randomized, triple-blind, placebo-controlled, parallel clinical trial to investigate two products on supporting immune function in healthy adults
Protocol Number:	21UIHU
Protocol Date:	February 10th, 2021
Version:	4
Study Design:	Randomized, triple-blind, placebo-controlled, parallel study
Sponsor:	Unigen, Inc. 2121 South State Street Suite 400 Tacoma, Washington 98405 United States
Sponsor Contact:	Lidia Brownell Vice President of Clinical Research and Regulatory Compliance lbrownell@unigen.net 253-274-7166
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Medical Director:	David Crowley, M.D. KGK Science Inc. 519–438–9378

PROTOCOL SIGNATURE SHEET

The sponsor and the investigator agree to conduct the study in compliance with the clinical study protocol (and amendments), International Conference on Harmonization (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Name	Signature	Date
Sponsor: Lidia Brownell VP of Clinical Research and Regulatory Compliance Unigen, Inc. 2121 South State Street Suite 400 Tacoma, Washington 98405 United States		
Contract Research Organization: Malkanthi Evans, PhD Chief Scientific Officer KGK Science Inc. 255 Queens Ave., Suite 1440 London, ON N6A 5R8 Canada		

1 PROTOCOL SYNOPSIS

Population: Healthy adult males and females

Total number of participants: 75 enrolled participants (25 per group)

1.1 Inclusion Criteria

1. Males and females between 40 and 80 years of age, inclusive
2. Female participant is not of child-bearing potential, defined as females who have undergone a sterilization procedure (e.g. hysterectomy, bilateral oophorectomy, bilateral tubal ligation, complete endometrial ablation) or have been post-menopausal for at least 1 year prior to screening

   Or,

   Females of child-bearing potential must have a negative baseline urine pregnancy test and agree to use a medically approved method of birth control for the duration of the study. All hormonal birth control must have been in use for a minimum of three months. Acceptable methods of birth control include:
   - Hormonal contraceptives including oral contraceptives, hormone birth control patch (Ortho Evra), vaginal contraceptive ring (NuvaRing), injectable contraceptives (Depo-Provera, Lunelle), or hormone implant (Norplant System)
   - Double-barrier method
   - Intrauterine devices
   - Non-heterosexual lifestyle or agrees to use contraception if planning on changing to heterosexual partner(s)
   - Vasectomy of partner at least 6 months prior to screening
3. Participants who have not yet but are willing to receive the influenza vaccine
4. Agrees to provide a verbal history of flu vaccination
5. Agrees to maintain current lifestyle habits as much as possible throughout the study depending on your ability to maintain the following: diet, medications, supplements, exercise, and sleep and avoid taking new supplements
6. Healthy as determined by medical history and laboratory results as assessed by Qualified Investigator (QI)
7. Willingness to complete questionnaires and diaries associated with the study and to complete all clinic visits
8. Provided voluntary, written, informed consent to participate in the study

1.2 Exclusion Criteria

1. Women who are pregnant, breast feeding, or planning to become pregnant during the study
2. Participant has a known allergy to the active or inactive ingredients in UP360, UP446, placebo, or QIV
3. Unvaccinated participants with flu prior to baseline from September 2020 or prior to Day 28 vaccination
4. Participants self-reporting a diagnosis of COVID-19 prior to baseline or prior to Day 28 vaccination
5. Participants who have received the COVID-19 vaccine
6. Current use of prescribed immunomodulators (including corticosteroids) such as immunosuppressants or immunostimulants within 4 weeks of baseline (see Section 7.3)
7. Current use of dietary supplement or herbal medicines associated with boosting or modulating the immune system unless willing to washout (see Section 7.3.2)

8. Participation in other clinical research studies 30 days prior to enrollment will be assessed on a case-by-case basis by the QI
9. Individuals who are unable to give informed consent
10. Any other condition, chronic disease, or lifestyle factor, that, in the opinion of the QI, may adversely affect the participant's ability to complete the study or its measures or pose significant risk to the participant

1.3 Schedule of Assessments

Procedures/Assessments	Screening	Baseline Day 0	Day 28 ± 2 days	Day 56 ± 2 days
Informed consent	X			
Review inclusion/exclusion criteria	X	X		
Review medical history	X			
Urine pregnancy test		X		X
Review concomitant therapies	X	X	X	X
Heart rate and blood pressure		X	X	X
Height* and weight **only analyzed at baseline*		X		X
Randomization		X		
Blood collection for analysis of CBC, electrolytes (Na, K, Cl), HbA1c*, glucose, eGFR, creatinine, AST, ALT, ALP, and bilirubin **only analyzed at screening*	X	X	X	X
Blood collection for analysis of ESR, CRP, complement C3, complement C4, IgA, IgG, IgM, immune cell phenotypes (CD3+, CD8+, CD4+, CD45+, TCRγδ, CD3-CD16+CD56+)		X	X	X
Blood collection for future analysis of cytokines, HMGB1, NF-κB, Nrf-2, 8-iso-prostaglandin F2α, CAT, GSH-Px, SOD, MDA, AGEs, HI titers for specific strains of virus		X	X	X
Modified WURSS-24 Questionnaire dispensed	X	X	X	
Modified WURSS-24 Questionnaire returned		X	X	X
Vitality Questionnaire completed		X	X	X
COVID-19 Impact on QoL Questionnaire completed		X	X	X
Flu vaccine administered			X	
IP dispensed		X	X	
IP returned			X	X
Study Diary dispensed	X	X	X	
Study Diary returned		X	X	X
Compliance calculated			X	X
Adverse Events	X	X	X	X

2 LIST OF ABBREVIATIONS

º	Degrees
AE	Adverse Event
AGEs	advanced glycation end-products
ALT	Alanine Aminotransferase
ALP	Alkaline Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BP	Blood Pressure
C	Celsius
Ca	Calcium
CAT	catalase (CAT
CBC	Complete Blood Count
CD	Cluster of Differentiation
Cl	Chloride
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
DIN	Drug Identification Number
DOB	Date of Birth
EDTA	Ethylenediaminetetraacetic Acid
eCRF	Electronic Case Report Form
eGFR	Glomerular Filtration Rate
ESR	Erythrocyte Sedimentation Rate
etc.	“and so forth”
e.g.	“for example”
et al	“and others”
g	Gram
GCP	Good Clinical Practice
GSH-Px	glutathione peroxidase
HI	Hemagglutinin inhibition
HIV	Human Immunodeficiency Virus
HMGB1	High Mobility Group Box 1
HR	Heart Rate
lbs.	Pounds
ICF	Informed Consent Form
ICH	International Conference of Harmonization
i.e.	“in other words”
IEC	Independent Ethics Committee
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent to Treat
K	Potassium
kg	Kilogram
MCC	Microcrystalline cellulose

MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MDA	malondialdehyde
mg	milligram
mmHg	Millimeter of Mercury
mL	Milliliter
MS	Microsoft
Na	Sodium
NF-κB	Nuclear Factor Kappa B
Nrf-2	Nuclear Factor Erythroid 2-Related Factor 2
OTC	Over the Counter
PCP	Primary Care Physician
PP	Per Protocol
QI	Qualified Investigator
QIV	Quadrivalent Influenza Vaccine
QoL	Quality of Life
RBC	Red Blood Cells
RDW	Red Blood Cell Distribution Width
SAE	Serious Adverse Event
SOD	superoxide dismutase
SOP	Standard Operating Procedure
TCRγδ+	T-Cell Receptor Gamma Delta
TPD	Therapeutics Products Directorate
UAT	User Acceptance Testing
ULN	Upper Limit of Normal
URTI	Upper Respiratory Tract Infection
WBC	White Blood Cell
WHO	World Health Organization
WURSS	Wisconsin Upper Respiratory Symptom Survey

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4 INTRODUCTION

Acute respiratory tract infections are a leading cause of morbidity and mortality globally, illustrated by seasonal flu epidemics and most recently COVID-19, caused by the SARS-CoV2 infection. Every year influenza causes an estimated one billion infections leading to three to five million severe cases, and 290,000 to 650,000 deaths worldwide (1). In Canada, it is the leading cause of death due to a vaccine-preventable disease (2) with 3,500 mortalities per year (3). In the United States and Canada, the flu season occurs in the fall and winter, peaking anywhere from late November through March (2). During these months, influenza increases the demand on the healthcare system with 12,000 hospitalizations occurring annually (4). The prevalence of the flu during this period also translates into billions of dollars in lost revenue and worker productivity annually with over 45 million days of work lost annually due to the common cold, translating into an estimated $40 billion USD lost to both direct and indirect costs (5).

To combat this, vaccination against the flu has been adopted by many countries as the gold standard for prevention. In Canada, the national influenza vaccination coverage goal is 80% of those at risk of influenza-related complications or hospitalization are vaccinated. However, in the previous three years, only approximately 40% of Canadian adults received the flu vaccine, with the rate of vaccination amongst healthy adults between 18-64 years of age even lower at 27-31% (6).

This year, there is far greater strain on the health care system due to the COVID-19 pandemic as co-infection with COVID-19 and influenza or other respiratory pathogens is a significant risk factor for prolonged hospitalization (7, 8). Amid this public health crisis, it is critical to minimize the burden of influenza on the Canadian healthcare system so resources can be allocated appropriately. Further, a recent study has suggested that influenza vaccination in an older population over the age of 65 is negatively associated with COVID-19 mortality (9), supporting the importance of vaccination during this time. These significant public health implications point to the urgent need to increase vaccine adoption. In addition to low adoption rates, the Centers for Disease Control and Prevention estimated the current vaccine to be approximately 45% effective in preventing the influenza (10). This is consistent with previous years, with efficacy between 19-54% (11). This suggests that these is great need to find therapies that may increase the efficacy of the flu vaccine and reduce the severity and duration of upper respiratory tract infections (URTIs) including the flu and common cold.

The immune system is comprised of two arms which differ in their response: innate which is fast acting and non-antigen specific, and adaptive, or acquired, which is slower to respond but antigen-specific. The innate immune system involves physical barriers such as skin, the complement system and immune cells with phagocytic capacity (neutrophils, macrophages, Natural Killer cells). These innate immune cells are able to quickly respond and destroy foreign pathogens generally through inflammatory process, however they lack the ability to increase efficacy or speed of response to a reoccurring pathogen (12). After the innate immune response, the adaptive immune system is engaged and able to develop immunological "memory" to repeated exposure. The cells of the adaptive immune system include T cells, or lymphocytes, which are responsible for initiating the adaptive response and killing virally-infected cells, and B lymphocytes which produce immunoglobulins (Ig) to target specific pathogens (12). Vaccines provide protection against repeated pathogen exposure through development of immunological memory (13).

It is well established that various nutrients including vitamin A, B12, folate, selenium, iron, copper and omeg-3 fatty acids play an important role in supporting the immune system and optimal nutritional status is key in protection against viral infections (14). Further, the addition of adjuvant supplements or nutritional

interventions have been investigated to improve the immune response to influenza and efficacy of the influenza vaccine (15-18). A vaccine model is used to examine if prophylactic supplementation modulates the immune response that is induced by the immunological challenge of administering the vaccine (17, 19).

To examine the role of dietary supplements in supporting immune function in response to influenza vaccination using this vaccine model, there are two investigational products (IPs) being used in the current study. One product, UP360, includes ingredients *aloe vera* gel powder, rosemary and *Poria cocos* extracts and the other, UP446, contains *Acacia catechu (Senegalia catechu)* and *Scutellaria baicalensis*. Through distinct mechanisms of action, these ingredients have been shown to activate the immune system, reduce inflammation and oxidative stress and protect against lung damage.

Aloe vera contains a variety of bioactive ingredients including vitamins, minerals, anthraquinones and polysaccharides that have antioxidant, anti-inflammatory and anti-bacterial effects (20-23). Studies *in vitro* have shown that aloe polysaccharide inhibits the replication of the H1N1 influenza virus (20) and animal models have demonstrated reduction in viral load and clinical symptoms of influenza infection (20) and increased survival and Ig production following influenza immunization (24). Several components of rosemary have been shown to have immunomodulatory effects *in vitro* and in animal models (25), primarily through increasing the IgM and IgG response following immune challenges (26). *Portia cocos* is a medicinal mushroom also known as fuling, matsuhodo, poria or China root. The major bioactive is the polysaccharide β-glucan that has been shown to have anti-inflammatory and immunomodulatory effects (27), with activation of T cells a potential mechanism of action. The adjuvant activity of *Portia cocos* has been examined in a variety of animal models with rabies, H1N1 influenza and hepatitis B vaccines (28, 29). The flavonoid extracts of *Senegalia catechu* and *Scutellaria baicalensis* has been demonstrated to reduce pro-inflammatory gene expression *in vitro* (30) and in rodent models *Senegalia catechu* has been shown to have anti-inflammatory activity and increase antibody titre after immunization (31). While these *in vitro and in vivo* studies suggest these ingredients have effects on immune function, there is a dearth of evidence on the immunomodulatory effects with human vaccine models in randomized, double-blind, placebo-controlled clinical trials.

The objective of this randomized, triple-blind, placebo-controlled, parallel study is to investigate two products, UP360 and UP446, compared to a placebo on supporting immune function in a healthy adult population. The increase in lymphocyte populations and Ig production with supplementation of the IPs compared to placebo will be compared in the 28-day pre- and post-vaccination periods to examine the immune boosting effects of the products. Other quantitative markers of immune function will be measured including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and complement C3 and C4 proteins. To support the alterations in immunity, the Wisconsin Upper Respiratory Symptom Survey (WURSS)-24 will be used as a subjective measure of signs and symptoms of URTI, inclusive of cold, flu and COVID-19. The impact of COVID-19 on wellbeing and quality of life will also be assessed to examine the potential confounder of the pandemic on immune function. The findings of this study will provide evidence for UP360 and UP446 to support immune function with flu vaccination, understand external factors that influence immunity during the cold and flu season and COVID-19 pandemic and potentially inform public health policy regarding community spread influenza and COVID-19.

Participants will be healthy men and women who have not been vaccinated with the quadrivalent influenza vaccine (QIV) but are willing to receive it during this study. Participants will be between the ages of 40 to 80 years old to include older adults that are the target of national vaccination programmes and those potentially most likely to have reductions in COVID-19 mortality with influenza vaccination. Participants'

medical history, lifestyle factors and laboratory results will be reviewed to assess eligibility and may be excluded if there is any condition or lifestyle factor that the QI determines may affect study measures or safety of the participant. To avoid interactions with the active ingredients in the IPs, participants on medications will be assessed on a case-by-case basis to ensure their eligibility and safety with special reference to the medications listed in the Investigational Brochure. All participants will be asked to maintain their current diet, medication, supplements, exercise and sleep while avoiding taking any new supplements during the study to avoid confounders. Information regarding occupation, social interactions, history of flu vaccination, URTIs, allergies, and lifestyle factors will be collected to account for inter-individual variability on study outcomes. The inclusions and exclusions in this study will ensure only participants who are healthy, stable, and have no comorbidities are enrolled.

5 STUDY OBJECTIVES

The objective of this study is to investigate the efficacy of two investigational products (IPs), UP360 and UP446, on supporting immune function in healthy adults.

Primary outcome:

The difference between UP360, UP446 and placebo in the increase in immune parameters as assessed by lymphocyte populations (CD3+, CD4+, CD8+, CD45+, TCRγδ+, CD3-CD16+56+) and immunoglobulins (IgG, IgM, and IgA) in blood from baseline at Day 28 and 56

Secondary outcomes:

The difference between UP360, UP446 and placebo at Day 28 and 56 in:

1. Number of confirmed COVID-19 infections
2. Number of confirmed flu cases
3. Impact of COVID-19 on quality of life assessed by the COVID-19 Impact on QoL Questionnaire
4. Over-the-counter cold and flu medication use

The difference between UP360, UP446 and placebo at Day 56 in:

1. Number of hospitalizations due to COVID-19
2. Number of hospitalizations due to flu

The difference in change between UP360, UP446 and placebo from baseline at Day 28 and 56 in:

1. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
2. Hematology parameters: white blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils), reticulocyte count, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count, RBC indices (mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red cell distribution width (RDW)
3. Complement C3 and C4 proteins
4. Mean global severity index, as measured by area under the curve (AUC) for the Modified Wisconsin Upper Respiratory Symptom Survey (WURSS)-24 daily symptom scores
5. Mean symptom severity scores, as measured by AUC for the WURSS-24 daily severity symptom scores
6. Number of well days (defined as days scored as 0 (not sick) for the question, “How sick do you feel today?”) as assessed by the Modified WURSS-24 Questionnaire
7. Number of sick days (defined as days scored as any number from 1 through 7 (sick) for the question, “How sick do you feel today?”) as assessed by the Modified WURSS-24 Questionnaire
8. Frequency of common upper respiratory tract infection (UTRI) symptoms as assessed by the Modified WURSS-24 Questionnaire
9. Duration of common UTRI symptoms as assessed by the Modified WURSS-24 Questionnaire
10. Severity of common UTRI symptoms as assessed by the Modified WURSS-24 Questionnaire
11. Vitality and quality of life as assessed by the Vitality and Quality of Life (QoL) Questionnaire

Outcomes for future analysis:

The difference in change between UP360, UP446 and placebo from baseline at Day 28 and 56 in:

1. Cytokines (GM-CSF; IFN-α; IFN-γ; IL-1α; IL-1β; IL-1RA; IL-2; IL-4; IL-5; IL-6; IL-7; IL-9; IL-10; IL-12 p70; IL-13; IL-15; IL17A; IL-18; IL-21; IL-22; IL-23; IL-27; IL-31; TNF-α; TNF-β/LTA 150)
2. High mobility group box 1 (HMGB1) protein, nuclear factor kappa B (NF-κB), nuclear factor erythroid 2-related factor 2 (Nrf-2)
3. Oxidative stress as assessed by 8-iso-prostaglandin F2α, catalase (CAT), glutathione peroxidase (GSH-Px), superoxide dismutase (SOD), malondialdehyde (MDA) and advanced glycation end-products (AGEs)
4. Hemagglutinin inhibition (HI) titers for specific strains of virus

Safety outcomes:

1. Clinical chemistry parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, creatinine, electrolytes (Na+, K+, Cl-), estimated glomerular filtration rate (eGFR), glucose
2. Incidence of pre-emergent and post-emergent adverse events
3. Vital signs (blood pressure (BP) and heart rate (HR))

6 STUDY DESIGN

Figure 1: Study Design

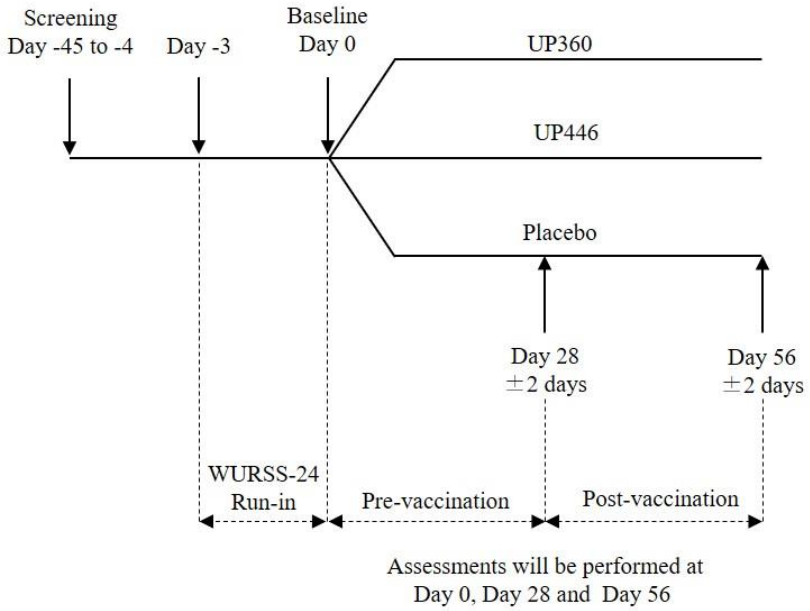
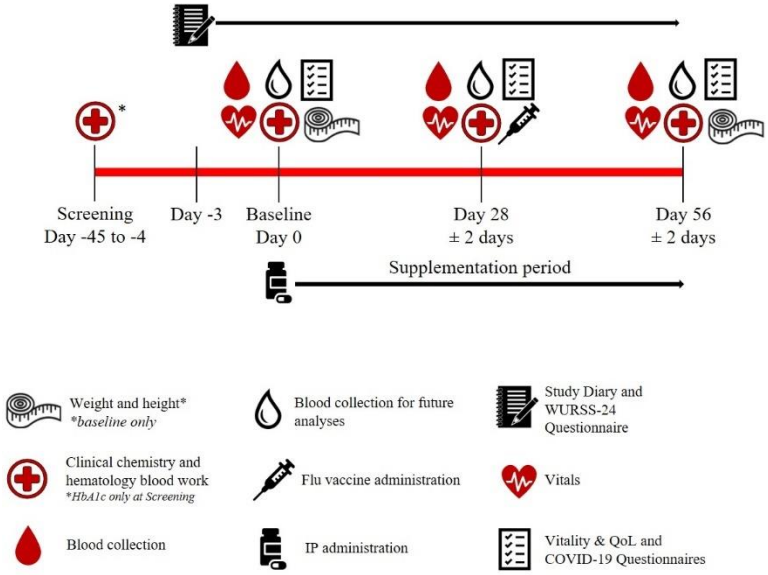


Figure 2: Timeline from screening to end-of-study period



The planned sample size for this study is 75. In order to evaluate study outcomes, study assessments will be conducted as per the Schedule of Assessments in Section 1.3.

Study Arm	Number of Participants
UP360 + Flu Vaccine	N = 25
UP446 + Flu Vaccine	N = 25
Placebo + Flu Vaccine	N = 25
Total	N = 75

7 SELECTION OF STUDY POPULATION

This study will enroll 75 healthy participants. One gender will not exceed 65%. Each participant must fulfill the inclusion criteria and not meet any of the exclusion criteria as described in Sections 7.1 and 7.2, respectively.

7.1 Inclusion Criteria

1. Males and females between 40 and 80 years of age, inclusive
2. Female participant is not of child-bearing potential, defined as females who have undergone a sterilization procedure (e.g. hysterectomy, bilateral oophorectomy, bilateral tubal ligation, complete endometrial ablation) or have been post-menopausal for at least 1 year prior to screening

   Or,

   Females of child-bearing potential must have a negative baseline urine pregnancy test and agree to use a medically approved method of birth control for the duration of the study. All hormonal birth control must have been in use for a minimum of three months. Acceptable methods of birth control include:
   - Hormonal contraceptives including oral contraceptives, hormone birth control patch (Ortho Evra), vaginal contraceptive ring (NuvaRing), injectable contraceptives (Depo-Provera, Lunelle), or hormone implant (Norplant System)
   - Double-barrier method
   - Intrauterine devices
   - Non-heterosexual lifestyle or agrees to use contraception if planning on changing to heterosexual partner(s)
   - Vasectomy of partner at least 6 months prior to screening
3. Participants who have not yet but are willing to receive the influenza vaccine
4. Agrees to provide a verbal history of flu vaccination
5. Agrees to maintain current lifestyle habits as much as possible throughout the study depending on your ability to maintain the following: diet, medications, supplements, exercise, and sleep and avoid taking new supplements
6. Healthy as determined by medical history and laboratory results as assessed by Qualified Investigator (QI)
7. Willingness to complete questionnaires and diaries associated with the study and to complete all clinic visits
8. Provided voluntary, written, informed consent to participate in the study

7.2 Exclusion Criteria

1. Women who are pregnant, breast feeding, or planning to become pregnant during the study
2. Participant has a known allergy to the active or inactive ingredients in UP360, UP446, placebo, or QIV
3. Unvaccinated participants with flu prior to baseline from September 2020 or prior to Day 28 vaccination
4. Participants self-reporting a diagnosis of COVID-19 prior to baseline or prior to Day 28 vaccination
5. Participants who have received the COVID-19 vaccine
6. Current use of prescribed immunomodulators (including corticosteroids) such as immunosuppressants or immunostimulants within 4 weeks of baseline (see Section 7.3)
7. Current use of dietary supplement or herbal medicines associated with boosting or modulating the immune system unless willing to washout (see Section 7.3.2)

8. Participation in other clinical research studies 30 days prior to enrollment will be assessed on a case-by-case basis by the QI
9. Individuals who are unable to give informed consent
10. Any other condition, chronic disease, or lifestyle factor, that, in the opinion of the QI, may adversely affect the participant's ability to complete the study or its measures or pose significant risk to the participant

7.3 Concomitant Medications, Over-the-counter Medications, Supplements and Food/Drinks

Participants who are taking any prescribed medications, over-the-counter (OTC) medications, supplements, or food/drinks that are considered not to affect the study outcomes and are on stable dosage must agree to maintain their current dosing regimen during the study unless otherwise recommended by their general practitioner/nurse practitioner. Participants on medications will be assessed on a case-by-case basis to ensure their eligibility and safety with special reference to the medications listed in the Investigator's Brochure.

7.3.1 Prescribed Medications

Participants on the following concurrent prescribed medications and/or treatments will be excluded during enrollment unless they have been taken off these therapies by their family physician. In the latter event, the frequency of use and/or dosage may be considered by the QI on a case-by-case basis prior to recommending an appropriate washout or their enrollment in the study.

1. HMG-CoA reductase inhibitors (statins)
2. Immunomodulators (including corticosteroids) such as immunosuppressants or immunostimulants
3. Thiazides and other potassium-wasting diuretics assessed by QI on a case-by-case basis

7.3.2 Dietary Supplements

Participants who are currently consuming the following supplements will not be allowed to participate unless willing to undergo the specified washout period prior to their baseline visit and agree not to take the supplements during the study. Other OTC supplements and food/drinks will require a case-by-case assessment by the QI based on dose and/or frequency of use to determine adequate washout. All washouts to be ensured to happen prior to enrollment.

1. Senegalia catechu (2-day washout)
2. Scutellaria baicalensis (7-day washout)
3. Aloe vera
4. Rosemary extract
5. Echinacea (2-day washout)
6. Astragalus (2-day washout)
7. Ginseng (25-day washout)
8. Turmeric (3-day washout)
9. Medicinal mushroom
10. Probiotics (30-day washout)
11. Beta-glucan (30-day washout)

7.4 Washout Periods

Please refer to Section 7.3.2 for washout periods for dietary supplements.

7.5 Early Withdrawal

Personal reasons

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

Removal by Qualified Investigator

Participant discontinuation should be considered at the discretion of the Qualified Investigator. The circumstances of any discontinuation must be documented in detail in the participant file and final report. If possible, the evaluations planned for the end of study will be carried out at the time when the participant is withdrawn from the study.

Criteria for removal of participants from the study includes:

Clinical reasons

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

Protocol violation

Any participant 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 participant found to have been inappropriately enrolled (did not meet eligibility criteria). Participant non-compliance includes failure to show up for study visits, failure to take the investigational product as directed, or refusal to undergo study visit procedures. Participants 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 participants and/or compromise the integrity of the study or its results) will result in participant discontinuation.

Participant Replacement

For all early withdrawals, a participant leaving the study prematurely or in the event of participant removal will be assessed at the time of dropout based on the rates of attrition at that time. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable, thus unnecessary withdrawal of participants should be avoided.

8 INVESTIGATIONAL PRODUCT

8.1 Manufacturing and Storage

The investigational product will be provided to KGK Science Inc. by the Sponsor. The investigational product will be carefully stored at the study site in a lockable, limited access area, accessible only to study team personnel in compliance with pertinent regulations. Only authorized persons will have access to the investigational product. The products will be stored at room temperature and will not be exposed to direct sunlight or heat. The investigational products will be kept in a locked investigational product storage room at KGK Science Inc. on receipt. An accountability log will be kept for the investigational products.

All unused investigational product will be returned to the study Sponsor by KGK Science Inc. (at the Sponsor's expense) or destroyed on receipt of written confirmation from the Sponsor at study closeout (within one month of last participant visit).

Manufactured by:

Rose City Nutritionals, LLC

8.2 Labelling and Coding

The investigational product will be labeled according to the requirements of ICH-GCP guidelines and applicable local regulatory guidelines. Investigational product will be randomized and coded by an unblinded person at KGK who is not involved in data collection or analysis.

8.3 UP360 (per 500 mg capsule)

Dietary Ingredient	Quantity
Aloe vera gel powder	150 mg
Rosemary extract	50 mg
Poria cocos extract	100 mg

Non-medical ingredients: Polydextrose, Microcrystalline cellulose (MCC), and magnesium stearate

8.4 UP446 (per 250 mg capsule)

Dietary Ingredient	Quantity
Acacia catechu (Senegalia catechu)	50 mg
Scutellaria baicalensis	200 mg

Non-medical ingredients: Maltodextrin, MCC, and magnesium stearate

8.5 Placebo

Ingredients: MCC and magnesium stearate

8.6 Directions for Investigational Products and Placebo

Participants will be instructed to take two capsules per day, one in the morning and one in the evening around mealtimes with food and 4-6 ounces of water for 56 days, beginning on Day 0. Clinic staff will instruct participants to save all unused and open packages and return them to KGK Science Inc. for a determination of compliance. If a dose is missed, participants are instructed to take the dose as soon as possible. Participants will be advised not to exceed 4 capsules daily.

8.7 Rescue Medication

Rescue medication is not applicable for this study.

8.8 Quadrivalent Influenza Vaccine

FLUCELVAX® QUAD, Drug Identification Number (DIN) 02494248, is a QIV designed for immunization of adults and children above the age of 9 for the prevention of influenza from subtypes A and B.

Strains	Quantity/Dose
Haemagglutinin A/Hawaii/70/2019 (H1N1) pdm09-like virus (A/Nebraska/14/2019)	15 µg
Haemagglutinin A/Hong Kong/45/2019 (H3N2)-like virus (A/Delaware/39/2019)	15 µg
Haemagglutinin B/Washington/02/2019-like virus (B/Darwin/7/2019)	15 µg
Haemagglutinin B/Phuket/3073/2013-like virus (B/Singapore/INFTT-16-0610/2016)	15 µg

Non-medical ingredients: Disodium phosphate dihydrate, Magnesium chloride hexahydrate, Potassium chloride, Potassium dihydrogen phosphate, Sodium chloride, Water for injections, beta-propiolactone, cetyltrimethylammonium bromide, polysorbate 80

8.9 Directions for Quadrivalent Influenza Vaccine

The QIV will be kept under proper storage with refrigeration kept between 2 to 8ºC. The QIV will be administered via intramuscular injection using proper techniques and sanitation, preferably in the deltoid muscle of the upper arm, on Day 28.

8.10 Randomization

A randomization schedule will be created and provided to the Qualified Investigator indicating the order of randomization. Each participant will be assigned a randomization code according to the order of the randomization list generated using www.randomization.com. Enrolled participants will be randomized to the different study arms at day 0. One gender will not exceed 65%.

8.11 Blinding and Allocation Concealment

Concealment of the allocation of study arms will be employed through the use of opaque sealed envelopes, each labeled with a randomization number. Each envelope will contain information regarding the study arm associated with each randomization number. These envelopes will be readily available for the Qualified Investigator to open in the event that it becomes necessary to know which product a participant is taking for the sake of the participant health care.

Unblinding should not occur except in the case of emergency situations. In the event that a serious adverse event occurs, for which the identity of the investigational product administered is necessary to manage the participant's condition, the study arm assigned to the participant will be unblinded and the investigational product identified. The Sponsor must be notified of any unblinding within 24 hours. Details of participants who are unblinded during the study will be included in the Final Report.

9 STUDY ASSESSMENTS

9.1 Screening (Day -45 to Day -4)*

** At the discretion of the Qualified Investigator, any participants falling outside of the screening window (Day -45 to Day -4) due to scheduling issues will be asked to repeat eligibility/screening procedures prior to randomization at baseline.*

An informed consent form will be given to the potential volunteer. They will be required to read the information and will be given the opportunity to seek more information if needed or provided with the option of keeping a copy of the consent form to review prior to making their decision. If agreeable, the volunteer will sign the consent form and receive a duplicate of the signed copy. Once consent has been obtained, the screening visit will proceed. Each volunteer will be sequentially assigned a screening number to be entered in the screening and enrollment log.

Screening assessments include:

1. Review medical history, concomitant therapies and current health status
2. Assess inclusion and exclusion criteria
3. Collect information regarding demographics, alcohol, cannabis, and tobacco habits, diet, sleep, and exercise habits, allergy history, upper respiratory tract infection history, and flu vaccine history
4. Collect blood samples for the analysis of CBC, electrolytes (Na, K, Cl), HbA1c, glucose, eGFR, creatinine, AST, ALT, ALP, and total bilirubin
5. Dispense modified WURSS-24 Questionnaires and instruct participants on completion. The WURSS-24 Questionnaire is to be completed for the 3 days prior to baseline to establish a pre-intervention level of upper respiratory tract infection symptoms for each participant and ensure participants are not sick at the time of baseline (Section 9.9.3)
6. Dispense study diaries and instruct participants on completion to record the following during the run-in period:
    a. AEs
    b. Concomitant medication
    c. Hours of sleep
    d. Alcohol intake
    e. Tobacco use
    f. Cannabis use
    g. Hours and description of exercise
    h. Self-reported COVID-19 diagnosis based on positive COVID-19 test
7. Record any pre-emergent AEs

The next appointment will be scheduled within 45 days for potentially eligible participants for their baseline.

Participants will be reminded to follow all instructions provided prior to their next appointment.

9.2 Day -3 to -1 (Run-In)

1. Participants will complete the modified WURSS-24 Questionnaires and study diary during the run-in period.

9.3 Processing Participants who get COVID-19 or Flu Prior to Day 0

The modified WURSS-24 Questionnaires and daily diaries will be reviewed by clinic staff. As part of the run-in study diary, participants will be asked if between their screening and run-in period if they have had COVID-19 or flu. Clinic staff will identify those participants that self-report they have COVID-19 or flu. Regarding flu, participants will be queried on if they have a diagnosis from their primary care physician (PCP). In the absence of such a diagnosis, based on indicated symptoms, participants will be assessed on a case-by-case basis by the QI.

Both groups of participants will be removed from the study and followed up appropriately.

9.4 Day 0 (Baseline)

Eligible participants will be scheduled for the following assessments and will be required to be fasted (≥ 8 hours).

Baseline (Day 0) assessments include:

1. Return and review study diaries and modified WURSS-24 Questionnaires
2. Review concomitant therapies and current health status
3. Assess inclusion and exclusion criteria
4. Urine pregnancy test for female potential participants that are of child-bearing potential
5. Seated resting BP and HR measurements
6. Weight and height measurement
7. Randomization of eligible participants
8. Collection of blood samples for the analysis of:
    a. CBC, electrolytes (Na, K, Cl), glucose, eGFR, creatinine, AST, ALT, ALP, and total bilirubin
    b. ESR, CRP, complement C3, complement C4, IgG, IgM, IgA, CD3+, CD8+, CD4+, CD45+, TCRγδ+, CD3-CD16+CD56+
    c. Cytokines, HMGB1, NF-κB, Nrf-2, 8-iso-prostaglandin F2α, CAT, GSH-Px, SOD, MDA, AGEs, HI titers for specific strains of virus for the future analysis
9. Administer Vitality Questionnaire (Section 9.9.4)
10. Administer COVID-19 QoL (Section 9.9.5)
11. Dispense IP and instruct participants on use
12. Dispense new study diaries
13. Dispense new modified WURSS-24 Questionnaires (Section 9.9.3)
14. Record any pre-emergent AEs

The next appointment will be scheduled for Day 28 ± 2 days.

Participants will be reminded to follow all instructions provided prior to their next appointment.

9.5 Processing Participants who get COVID-19 or Flu Prior to Day 28 Vaccination

The WURSS-24 Questionnaires and daily diaries will be reviewed by clinic staff. Clinic staff will identify those participants that self-report they have COVID-19 or flu. Regarding flu, participants will be queried on if they have a diagnosis from their PCP. In the absence of such a diagnosis, based on indicated symptoms, participants will be assessed on a case-by-case basis by the QI.

Both group of participants will be removed from the study and followed up appropriately.

9.6 Day 28 ± 2 days

Participants will complete the following assessments and return unused investigational product, completed study diaries and modified WURSS-24 Questionnaires. Participants will be fasted (≥ 8 hours).

Assessments include:

1. Return and review study diaries and modified WURSS-24 Questionnaires
2. Return unused investigational product in the original packaging and remnants and calculate compliance by counting the returned unused investigational product
3. Review concomitant therapies and adverse events
4. Seated BP and HR measurements
5. Collection of blood samples for the analysis of:
    a. CBC, electrolytes (Na, K, Cl), glucose, eGFR, creatinine, AST, ALT, ALP, and total bilirubin
    b. ESR, CRP, complement C3, complement C4, IgG, IgM, IgA, CD3+, CD8+, CD4+, CD45+, TCRγδ+, CD3-CD16+CD56+
    c. Cytokines, HMGB1, NF-κB, Nrf-2, 8-iso-prostaglandin F2α, CAT, GSH-Px, SOD, MDA, AGEs, HI titers for specific strains of virus for future analysis
6. Administer Vitality Questionnaire (Section 9.9.4)
7. Administer COVID-19 QoL (Section 9.9.5)
8. Administer flu vaccine (QIV)
9. Dispense new IP
10. Dispense new study diaries
11. Dispense new modified WURSS-24 Questionnaires (Section 9.9.3)

The next appointment will be scheduled for Day 56 ± 2 days.

Participants will be reminded to follow all instructions provided prior to their next appointment.

9.7 Processing Participants who get COVID-19 or Flu After Vaccination and Prior to Day 56

The WURSS-24 Questionnaires and daily diaries will be reviewed by clinic staff. Clinic staff will identify those participants that self-report they have COVID-19 or flu. Regarding flu, participants will be queried on if they have a diagnosis from their PCP. In the absence of such a diagnosis, based on indicated symptoms, participants will be assessed on a case-by-case basis by the QI.

Participants with self-reported diagnosis COVID-19 will be removed from the study. A COVID-19 diagnosis will be considered an AE and AE follow-up procedures will be followed.

9.8 Day 56 ± 2 days

Participants will complete the following assessments and return unused investigational product, completed study diaries and modified WURSS-24 Questionnaires. Participants will be fasted (≥ 8 hours).

Assessments include:

1. Return and review study diaries and modified WURSS-24 Questionnaires

2. Return unused investigational product in the original packaging and remnants and calculate compliance by counting the returned unused investigational product
3. Review concomitant therapies and adverse events
4. Urine pregnancy test for female potential participants that are of child-bearing potential
5. Seated resting BP and HR measurements
6. Weight measurement
7. Collection of blood samples for the analysis of:
    a. CBC, electrolytes (Na, K, Cl), glucose, eGFR, creatinine, AST, ALT, ALP, and total bilirubin
    b. ESR, CRP, complement C3, complement C4, IgG, IgM, IgA, CD3+, CD8+, CD4+, CD45+, TCRγδ+, CD3-CD16+CD56+
    c. Cytokines, HMGB1, NF-κB, Nrf-2, 8-iso-prostaglandin F2α, CAT, GSH-Px, SOD, MDA, AGEs, HI titers for specific strains of virus for future analysis
8. Administer Vitality Questionnaire (Section 9.9.4)
9. Administer COVID-19 QoL (Section 9.9.5)

9.9 Clinical Assessments and Procedures

Calculations or measurements of specific parameters are required, as indicated in the Schedule of Assessments. Instructions for determining these parameters are provided in the following sections.

9.9.1 Height and Weight

Weight measurements will be performed with shoes removed and bladder empty on calibrated scales for all measurements.

At least two separate measurements will be taken. If the two measurements are more than 0.5 kg (1.1 lbs) apart, a third measurement will be taken. The two closest values will be selected for computation.
Measurement of height will be performed with the participant's shoes removed. The participant's knees will be straightened, and head held upright.

9.9.2 Blood Pressure and Heart Rate

Seated, resting blood pressure assessment:

The participant should be seated comfortably with their back supported and the upper arm bared without restrictive clothing. Feet should be flat on the floor and legs will not be crossed. The participant will rest in this position for at least five minutes prior to the first reading.

At baseline:

Seated blood pressure will be checked in both arms to ensure that the arm with the higher blood pressure reading will be used for BP measurements of the study. The arm chosen for use at the initial visit will be documented in the study file and used in all subsequent visits. Participant should be queried about their usual blood pressure. As per the QI's opinion, a high office blood pressure should be rechecked after the participant is given a glass of water and is rested for 15 minutes.

At subsequent study appointments:

Once enrolled in the study, BP will be measured in the chosen arm. Two readings will be made, and if there is questionable disparity a third reading will be taken.

Heart Rate (beats/min) will be measured simultaneously during blood pressure recording.

9.9.3 Modified WURSS-24 Questionnaire

The WURSS is a questionnaire used to evaluate the negative impact of acute URTIs. The WURSS-24 contains 24 items scored on a Likert-type severity scale. It contains the same items as the WURSS-21 along with headache, body ache, and fever to capture influenza-like illness symptoms (32, 33). The modified WURSS-24 used in this study include a revision that refer to "symptoms" rather than "cold" to clarify that symptoms may be due to any URTI not specific to cold. A new URTI episode is defined as the sudden appearance of 1 or more symptoms captured by questions 2 to 5 of the WURSS-24 Questionnaire, not attributed to allergies (as reported by participants) with at least 2 prior days of 'not sick' as defined by Murdoch et al. (32). The WURSS-24 Questionnaire was used to capture the incidence, frequency and severity of URTI symptoms and has been validated by Barrett et al. (34).

9.9.4 Vitality and Quality of Life Questionnaire

The Vitality and QoL Questionnaire will be used to assess the energy levels and quality of life of the participants. The 31-item questionnaire consists of a 7-point Likert scale, with answers ranging from 1 to 7 . The higher the summative score the more vitality that was subjectively perceived by the participants.

9.9.5 COVID-19 Impact on Quality of Life (QoL) Questionnaire

The impact of the COVID-19 pandemic on the wellbeing of participants will be assessed using the COVID-19-Impact on Quality of Life (COV19-QoL) scale v1.5 (35). This 6-item questionnaire consists of a 5-point Likert scale to assess the impact of COVID-19 on QoL. The higher the score, the greater impact on quality of life and related domains subjectively perceived by participants.

9.9.6 Blood Sample Collection

An appropriately trained and qualified personnel will perform the venipuncture procedure to collect the necessary blood samples as per standard phlebotomy techniques.

9.9.7 Compliance

Compliance will be assessed by counting the returned unused study product. Compliance is calculated by determining the number of dosage units taken divided by the number of dosage units expected to have been taken multiplied by 100.

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

In the event of discrepancy between the information in the study diary and the amount of study product returned, use will be based on the product returned unless an explanation for loss of product has been provided. Participants found to have a compliance of <80% or >120% will be counseled.

9.10 Laboratory Analyses

Blood samples will be drawn from the participants at screening, baseline (Day 0), Day 28, and at the end of the study (Day 56) as indicated in the Schedule of Assessments.

Protection of participant confidentiality will extend to all data generated from the assaying of these samples. These samples will be alphanumerically coded and the persons performing the analysis will not be aware of the participant's identity or the product they received.

The total blood volume collection for the laboratory assessments listed above will be approximately 183 mL, over the period from screening to end of study 56 days. At any study visit, blood loss per volunteer is not expected to exceed 58 mL. Additional blood samples may be collected during the study in order to perform or repeat laboratory tests outlined in the Schedule of Assessments if needed.

A central laboratory will be used in this study to measure blood parameters.

Urine pregnancy test will be performed.

9.11 Termination of the Study

In the case of premature termination of the Study, participating investigators/participants, and the Institutional Review Board must be promptly informed of the termination. In the event of early termination, as many assessments will be completed as agreed upon by participant.

9.12 Protocol Amendments

If amendments to the study protocol are required after approval such changes will be captured in writing, the reasons for the change documented, and signed and dated by the Sponsor. Any such amendments may be subject to IRB and Health Canada review/approval prior to implementation. Exception: if it becomes necessary to alter the protocol to eliminate an immediate hazard to participants, an amendment may be implemented prior to IRB approval. In this circumstance, the Qualified Investigator must notify IRB and Health Canada in writing within five (5) working days of the implementation.

10 SAFETY INSTRUCTIONS AND GUIDANCE

10.1 Adverse Events and Laboratory Abnormalities

10.1.1 Adverse Events

An AE is any untoward medical occurrence in a clinical investigation participant who has been administered an investigational product and does not necessarily have a causal relationship with this investigational product. 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 that worsen during a study are to be reported as AEs. In this study, symptoms associated with URTIs that are listed on the WURSS-24 Questionnaire will not be classified as an AE. Further, AEs due to the influenza vaccine rather than the investigational product will be assessed and documented.

During the study, participants should record any adverse effects in their diary. 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 and will be classified according to the description, duration, intensity, frequency, and outcome. The QI will assess any AEs and decide causality.

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

Mild: Awareness of event but easily tolerated

Moderate: Discomfort enough to cause some interference with usual activity

Severe: Inability to carry out usual activity

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

Most probable: There is a reasonable relationship between the investigational product and AEs. The event responds to withdrawal of investigational product (dechallenge) and recurs with rechallenge when clinically feasible.

Probable: There is a reasonable relationship between the investigational product and AEs. The event responds to dechallenge.

Possible: There is a reasonable relationship between the investigational product and AEs. Dechallenge information is lacking or unclear.

Unlikely: There is a temporal relationship to the investigational product administration but there is no reasonable causal relationship between the investigational product and the AEs.

Not related: There is no temporal relationship to investigational product administration or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AEs.

10.1.2 Serious Adverse Event

An 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:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalization or prolongation of existing hospitalization
4. A persistent or significant disability or incapacity
5. A congenital anomaly/birth defect in the offspring of a participant who received the study investigational product

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.

10.1.3 Unexpected Adverse Reaction

An unexpected adverse reaction is an adverse reaction, the nature and severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

10.1.4 Laboratory Test Abnormalities

The Qualified Investigator must assess the clinical significance of all abnormal laboratory values as defined by the compendium of normal values for the reference laboratory.

Any study emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the AEs form in the study record:

1. Accompanied by clinical symptoms
2. Leading to interruption or discontinuation of the investigational product
3. Requiring a change in concomitant therapy

This applies to any protocol and non-protocol specified laboratory result from tests performed after the first dose of the investigational product, which falls outside the laboratory reference range and meets the clinical significance criteria for liver and kidney tests as well as for hematology and clinical chemistry, etc. (i.e. AST and/or ALT > 2 x ULN).

This does not apply to any abnormal laboratory result which falls outside the laboratory reference range but which does not meet the clinical significance criteria or those which are a result of an AE which has already been reported.

Any laboratory result abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being reported as an AE in the study record.

10.2 Treatment and Follow-Up of AEs And Laboratory Abnormalities

10.2.1 Treatment and Follow-up of AEs

Adverse Events, especially those for which the relationship to the investigational product is suspected, should be followed up until they have returned to baseline status or stabilized.

If after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded in the study record.

10.2.2 Treatment and Follow-up of Laboratory Abnormalities

In the event of participant-initiated withdrawal or clinically significant unexplained abnormal laboratory test values, the participant will be withdrawn from the investigational product or placebo and will remain in the study and be required to attend all remaining study visits as part of a safety arm.

10.3 Reporting of SAEs And Unexpected Adverse Reactions

The Qualified Investigator will be responsible for classification of an AE as an SAE within 24 hours of notification. Causality should be signed off by the Qualified Investigator prior to reporting to ethics and regulatory bodies. Notification of any serious adverse events must be made in writing to the study Sponsor. The IRB will be notified of all product related SAEs and unexpected adverse reactions. All blinded SAE's or unblinded-participant-on-active product SAE's will be reported to the Therapeutics Products Directorate (TPD) in an expedited manner.

KGK Science Inc. must notify the TPD of all blinded or unblinded-participant-on-active product serious adverse events and reactions as follows:

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

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.

11 STATISTICAL EVALUTION

11.1 Determination of Sample Size

The planned total sample size will be 75 with 25 participants randomized to each study group. This sample size will enable detection of a difference in CD3+ of 10.8%, difference in CD4+ of 6.5%, difference in CD8+ of 4.9%, difference in CD45+ of 16.7% and difference in NK cells (CD56+) of 4.4% for lymphocytes; difference in IgA of 67 mg/dL (0.67 g/L), difference in IgG of 440 mg/dL (4.4 g/L), and difference in IgM of 133 mg/dL (1.33 g/L) for and immunoglobulins among the three arms at an overall 5% significance level and 80% power. This sample size takes into account a loss to follow up rate of 20%. The calculation is based on the studies by Olivares et al (19, 36, 37).

11.2 Analysis Plan

The **Safety Population** will consist of all participants who received any amount of study product or placebo, and on whom any pre- or post-randomization safety information is available.

The **Intent-to-Treat (ITT) Population** consists of all participants who received study product or placebo and on whom any post-randomization effectiveness information is available.

The **Per Protocol (PP) Population** consists of all participants who consumed at least 80% of study product or placebo doses, do not have any protocol deviations that affect primary outcomes and complete all study visits and procedures connected with measurement of the primary variables.

11.3 Statistical Analysis Plan

All the primary and secondary endpoints will be analyzed as continuous variables.

For each primary and secondary endpoint, descriptive statistics including number of subjects, arithmetic mean, standard deviation, median, minimum and maximum values will be presented for each study day and for the changes from baseline (Day 0) to each subsequent study day.

Changes in continuous endpoints from baseline will be calculated as:

$$\text{Change to } V_i = \text{Value at } V_i - \text{Value at } V_{baseline}$$

Differences in changes between groups will be assessed by repeated measures mixed model ANOVA, with study group and visit as the fixed effects. Each model will include the baseline value as a covariate. Within group changes will be assessed by the paired t-test or Wilcoxon Sign Rank test, depending on the distribution of the data. All tests of significance for primary outcomes will be performed at one-sided, and for secondary outcomes will be performed at two-sided, alpha level = 0.05 unless otherwise specified.

The co-primary outcomes will be interpreted individually and together as a real-life global assessment of immune function. As such, there will be no adjustment for multiple outcomes (38-42). This is in accordance with the following principles of the American Statistical Association's statement on statistical significance

and p-values: #3 – "scientific conclusions and business or policy decisions should not be based only on whether a p-value passes a specific threshold;" #4 – "proper inference requires full reporting and transparency;" and #6 – "by itself, a p-value does not provide a good measure of evidence regarding a model or hypothesis" (43).

Missing data for the primary and secondary endpoints will be imputed with last-observation-carried-forward (LOCF) method or multiple imputation as a sensitivity analysis for ITT Population. No imputation will be performed for PP and Safety Population.

Probabilities ≤ 0.05 will be considered statistically significant. All statistical analysis will be completed using the R Statistical Software Package Version 3.6.3 or newer for Microsoft Windows (44).

11.3.1 Premature Discontinuation Description

For each premature discontinuation, the following parameters will be listed: participant number, dates of start and end of study, and the reason of premature discontinuation.

11.3.2 Safety

For adverse events, a descriptive analysis will be given. Adverse events will be presented in a frequency table by category and study arms. Furthermore, description, frequency, severity and causality will be reported for each adverse event.

Continuous safety parameters (e.g. hematology, clinical chemistry, HR and BP) will be summarized using a table including mean, standard deviation, median, minimum value, and maximum value for each measurement point. The changes from baseline will also be summarized similarly.

11.4 Protocol Deviation Description

Protocol deviations will be listed in the final study report.

11.5 Protocol Amendments

Once the protocol has been approved by the IRB and Health Canada, any changes to the protocol must be documented in the form of an amendment. All amendments will be documented in the final study report.

12 DATA COLLECTION AND STORAGE

All data collection and record storage will be done in compliance with ICH-GCP Guidelines and applicable local regulatory guidelines.

13 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (i.e., participants) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP.

13.1 IRB Approval

KGK Science Inc. will supply relevant documents for submission to an IRB for the protocol's review and approval. The following must be submitted to the IRB: this protocol, a copy of the informed consent form, and, if applicable, volunteer recruitment materials and/or advertisements and other documents required by all applicable laws and regulations. The IRB's written approval of the protocol and volunteer informed consent must be obtained before commencement of the study. The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g., informed consent form) reviewed; and state the approval date.

KGK Science Inc. must adhere to all requirements stipulated by the IRB. This may include notification to the IRB regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by volunteers, local safety reporting requirements and submission of the Qualified Investigator's annual/final status report to the IRB.

13.2 Volunteer Information and Informed Consent

Written consent documents will embody the elements of informed consent as described in the declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form describes the planned and permitted uses, transfers, and disclosures of the volunteer's personal and personal health information for purposes of conducting the study. The informed consent form further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is obtained. The informed consent form will detail the requirements of the volunteer and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

13.3 Potential Risks and Procedures to Minimize Risk

All potential risks are disclosed to study participants prior to their participation. The potential risks associated with this study include venipuncture, QIV, and their associated risks. Risks associated with venipuncture include pain, bruising, and infection at the site. Alcohol swabs and proper venipuncture procedure will be followed to minimize the risk of infection. Risks associated with the QIV are injection site pain, headache, fatigue, myalgia, injection site erythema, induration, and nausea.

14 QUALITY ASSURANCE AND QUALITY CONTROL

14.1 Auditing

All material used in clinical studies are subjected to quality control. Quality assurance audits may be performed by the Sponsor or any health authority during the course of the study or after its completion.

The Qualified Investigator agrees 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.

14.2 Monitoring

An initiation meeting will be conducted by the Sponsor or an approved representative (CRO). At this meeting, the protocol and logistical aspects of the study will be reviewed with the Qualified Investigator and all study staff.

Source documents will be reviewed to ensure that all items have been completed and that the data provided are accurate and obtained in the manner specified in the protocol. The participant files will be reviewed to confirm that:

1. Informed consent was obtained and documented
2. Enrolled participants fulfilled all inclusion criteria and did not meet any exclusion criteria;
3. AE/SAE reporting has been performed as applicable
4. Study visits have been conducted as per protocol and information has been recorded in the appropriate place in the source document
5. 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 Qualified Investigator or designee for correction. No data disclosing the identity of participants will leave the study center. The Qualified Investigator and any designees will maintain confidentiality of all participant records.

The Qualified Investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections and will allow direct access to source data and documents for these purposes.

14.3 Data Management

Data required for the analysis will be acquired from source documentation (including laboratory reports) and entered into Open Clinica Enterprise study instance designed specifically for this study. The two instances for the database would be created, test instance and production instance. A UAT (User Acceptance Testing) of the database would be performed in the test instance and then moved to the production instance. A password protected user id will be created which would give access to the limited authorized personnel. Only properly trained Data management staff will be granted access to perform database designing. A study specific Data Management Plan will be generated after the finalization of the database.

The standard data validation and edit checks would be performed on the production instance of the study by designing study specific rules and restrictions as defined in the eCRF. The discrepancies will be queried

and managed. Data tables will be created, queried and exported during and at the end of study using PostgreSQL tool (pgadminIII 9.5) and MS Access.

For Statistical analysis, the validated soft lock copy of the blinded study database will be sent to the Statistician to perform the analysis. The study database would be a read only file to ascertain changes in the data are not made during or after the analysis.

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.

All study data is archived for a period not less than 25 years from the date of completion of the study in accordance with Health Canada regulatory requirements.

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16 APPENDICES

16.1 Appendix I: Modified WURSS-24 Questionnaire

N.B. If participants report "Not Sick" for the first question, they should continue to complete the rest of the questionnaire.

Please note to participants: If you are not sick but still have symptoms please fill out the questionnaire.

Wisconsin Upper Respiratory Symptom Survey - WURSS-24 - *Daily Symptom Report*

Please fill in one circle for each of the following items:

	Not sick	Very mildly		Mildly		Moderately		Severely
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
How sick do you feel **today**?	O	O	O	O	O	O	O	O

Please rate the **average severity for each symptom over the last 24 hours**:

	Do not have this symptom	Very mild		Mild		Moderate		Severe
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Runny nose	O	O	O	O	O	O	O	O
Plugged nose	O	O	O	O	O	O	O	O
Sneezing	O	O	O	O	O	O	O	O
Sore throat	O	O	O	O	O	O	O	O
Scratchy throat	O	O	O	O	O	O	O	O
Cough	O	O	O	O	O	O	O	O
Hoarseness	O	O	O	O	O	O	O	O
Head congestion	O	O	O	O	O	O	O	O
Chest congestion	O	O	O	O	O	O	O	O
Feeling tired	O	O	O	O	O	O	O	O
Headache	O	O	O	O	O	O	O	O
Body aches	O	O	O	O	O	O	O	O
Fever	O	O	O	O	O	O	O	O

Over the last 24 hours, how much have your symptom(s) interfered with your ability to:

	Not at all	Very mildly		Mildly		Moderately		Severely
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Think clearly	O	O	O	O	O	O	O	O
Sleep well	O	O	O	O	O	O	O	O
Breathe easily	O	O	O	O	O	O	O	O
Walk, climb stairs, exercise	O	O	O	O	O	O	O	O
Accomplish daily activities	O	O	O	O	O	O	O	O
Work outside the home	O	O	O	O	O	O	O	O
Work inside the home	O	O	O	O	O	O	O	O
Interact with others	O	O	O	O	O	O	O	O
Live your personal life	O	O	O	O	O	O	O	O

Compared to yesterday, I feel that my symptom(s) are…

Very much better	Somewhat better	A little better	The same	A little worse	Somewhat worse	Very much worse
O	O	O	O	O	O	O

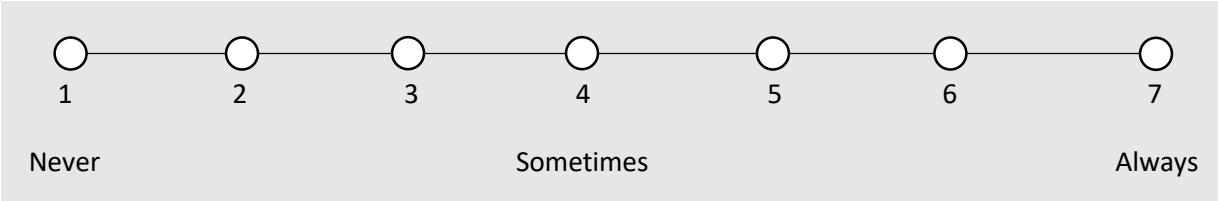
16.2 Appendix II: Vitality and Quality of Life Questionnaire

This self-assessment questionnaire has been developed to be administered to a healthy population.

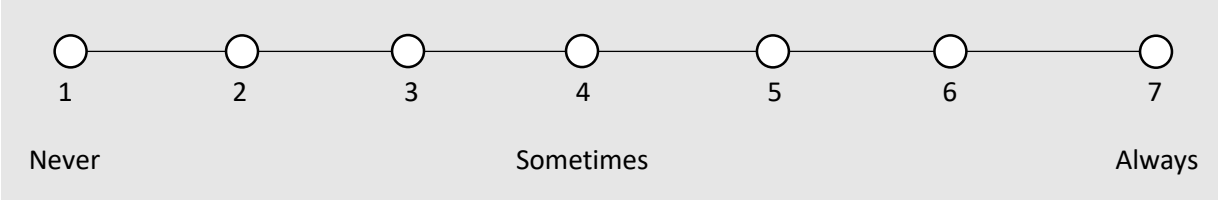
Vitality and Quality of Life Questionnaire

Please respond to each of the following statements by indicating the degree to which the statement is true for you in general in your life in the past month.

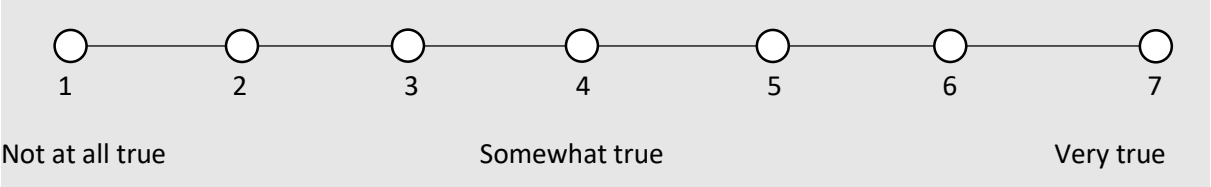
1. **I feel alive and vital**



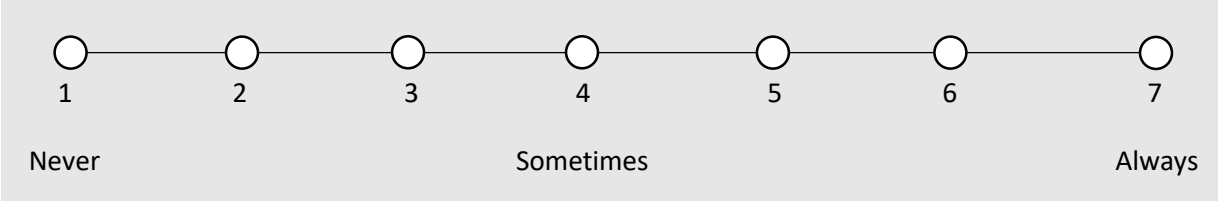
2. **I don't feel very energetic**



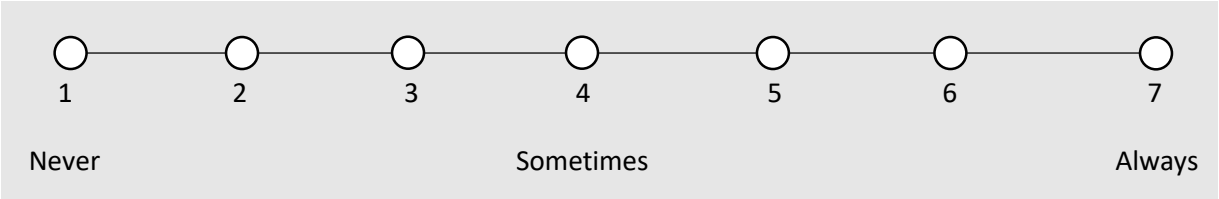
3. **Sometimes I feel so alive I just want to burst**



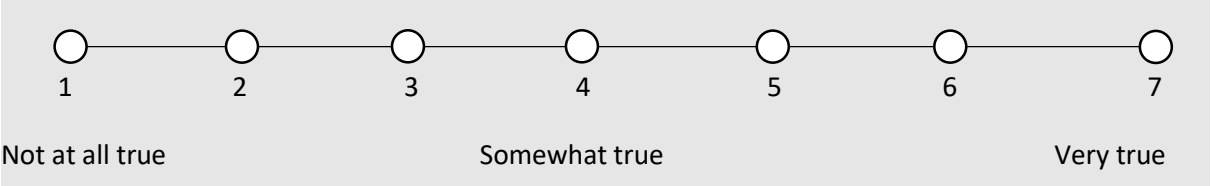
4. **I have energy and spirit**



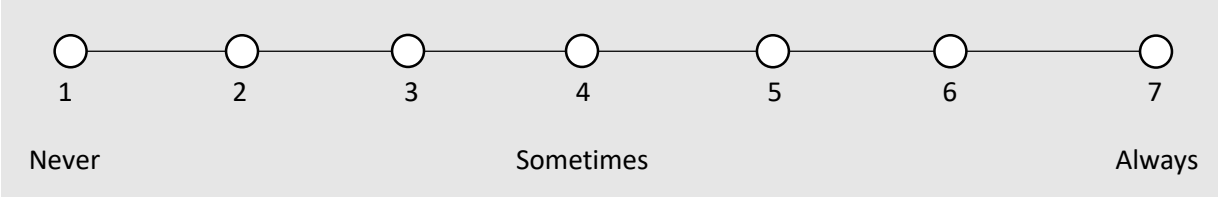
5. I look forward to each new day



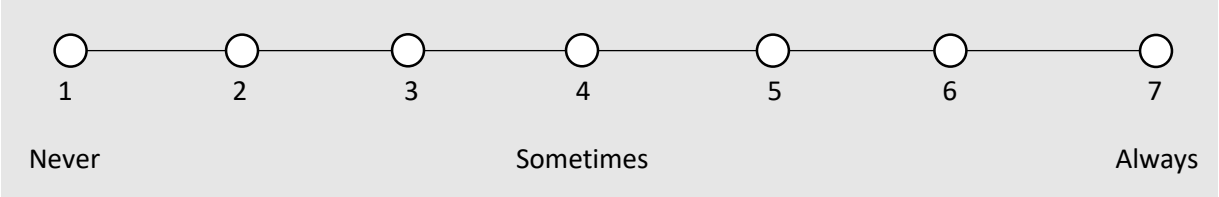
6. I always feel alert and awake



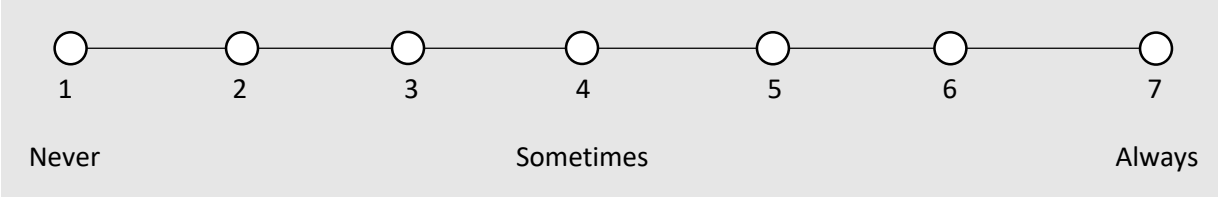
7. I feel energized when I wake up



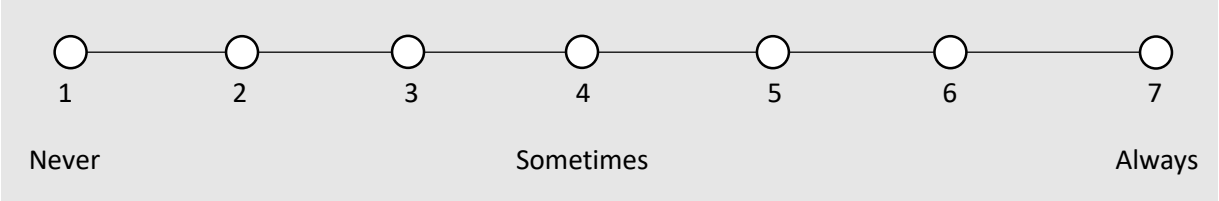
8. I feel energy and vitality throughout the day



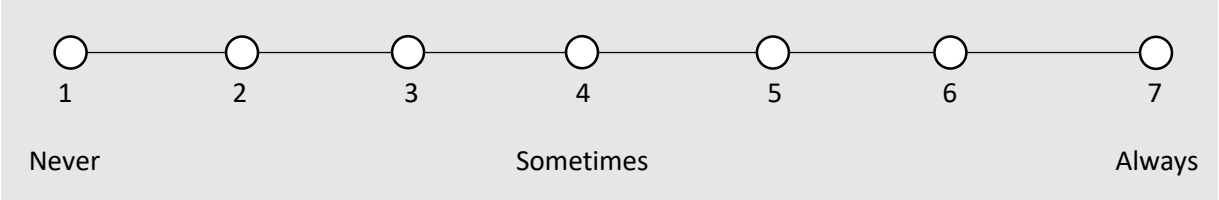
9. I have a midday slump in energy



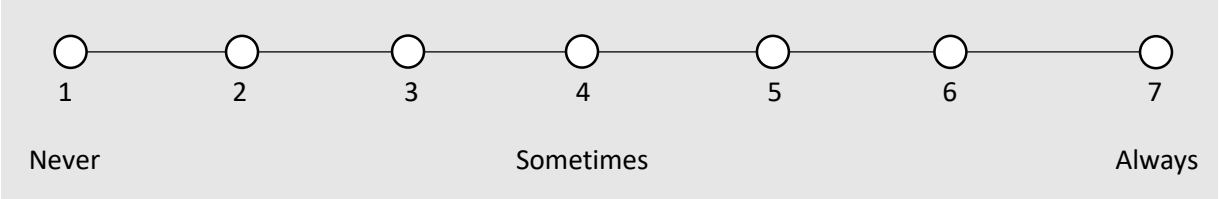
10. I feel engaged and enthusiastic in my personal relationships (friends and family)



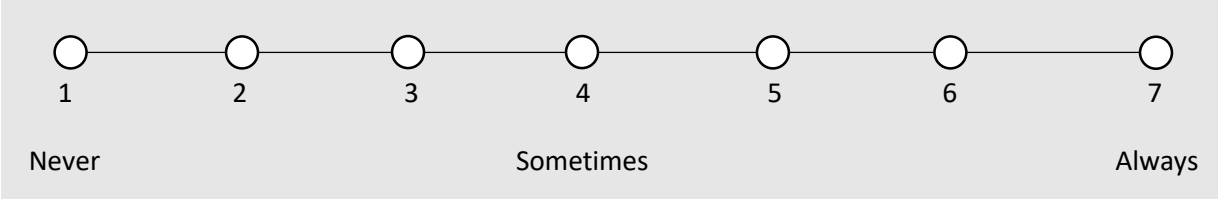
11. I have good mental clarity and focus



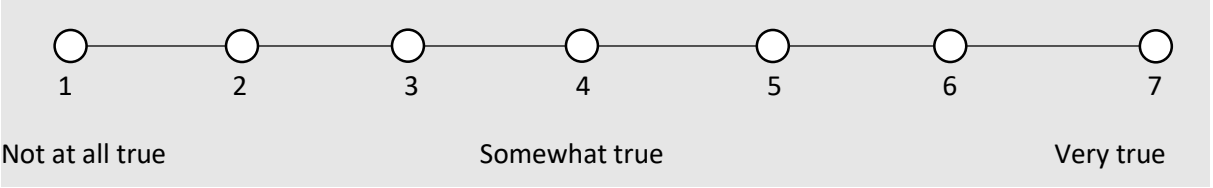
12. I feel I have a good sense of purpose and meaning in my life



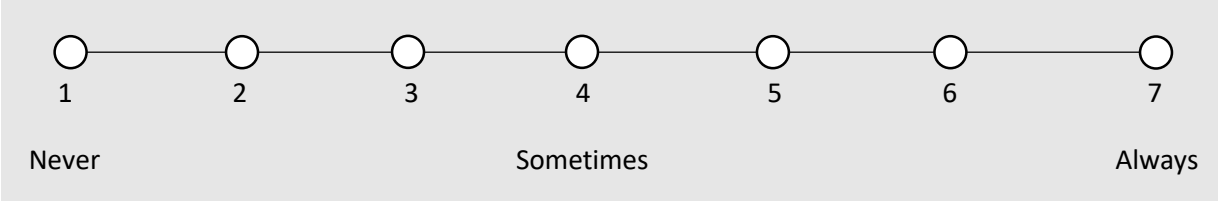
13. It takes a great effort to start things. This applies to every day activities such as getting out of bed, washing myself, and eating



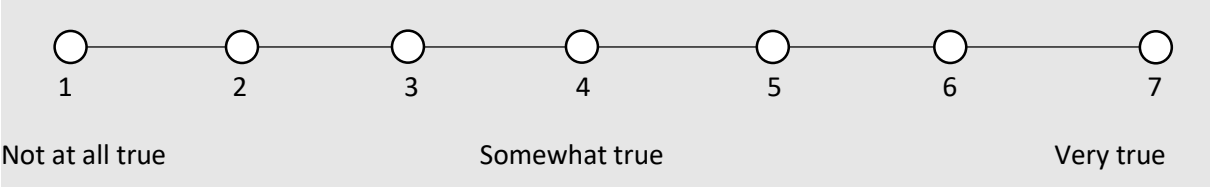
14. I forget things slightly more often than I should, but I am able to manage by making notes



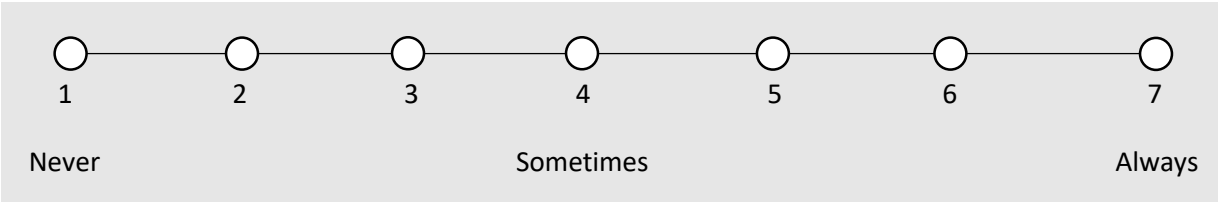
15. My thoughts are neither slow nor sluggish when it comes to work involving mental effort



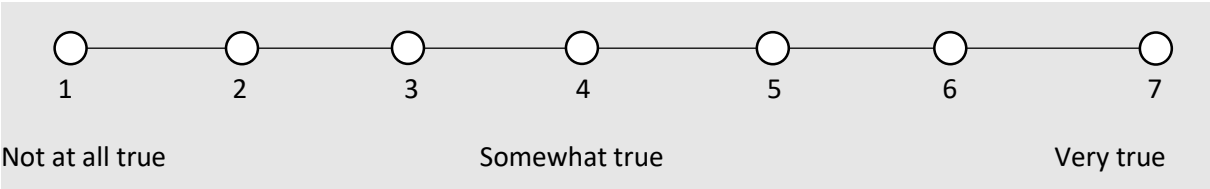
16. My thoughts often feel slow and sluggish, even when carrying out everyday activities, for example, a conversation with a person or when reading the newspaper



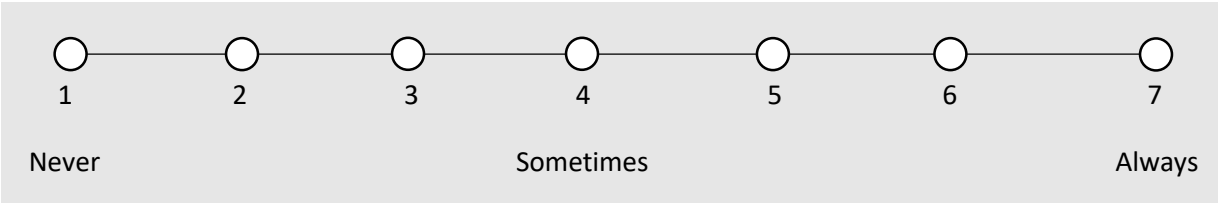
17. I become stressed easily



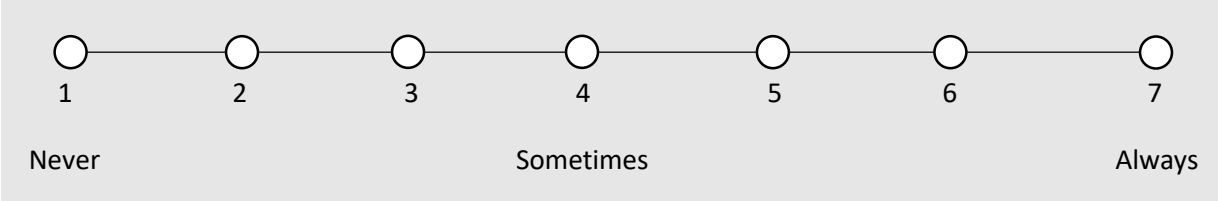
18. I am often short-tempered or irritable



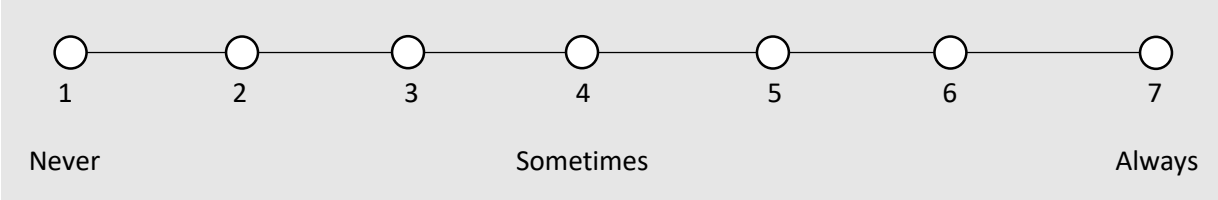
19. I become irritated very quickly about small things or things that do not bother other people



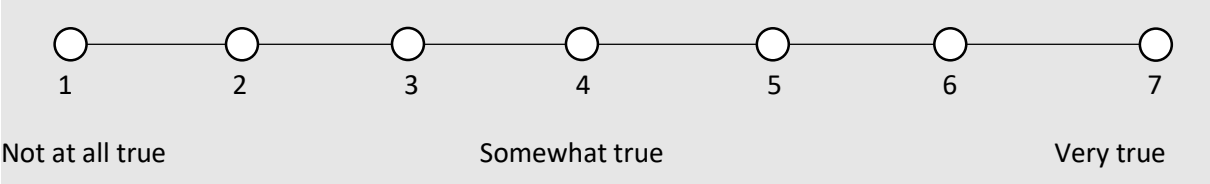
20. I do not get enough sleep



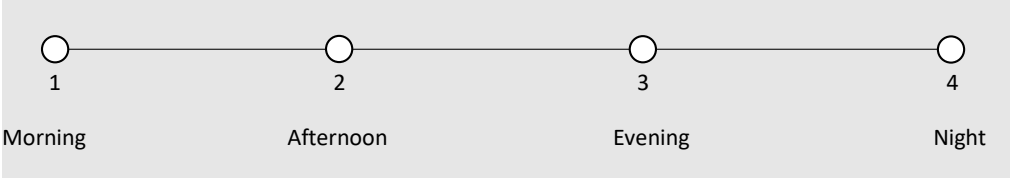
21. I have slight problems falling asleep or my sleep is shorter, lighter, or more restless



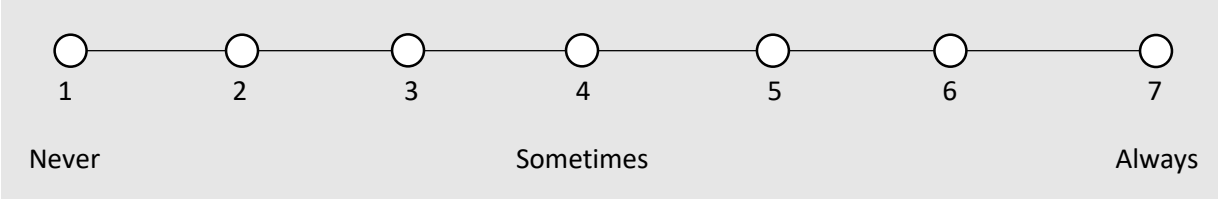
22. My energy level fluctuates throughout the day. I can predict that I will feel better at certain times and worse at other times



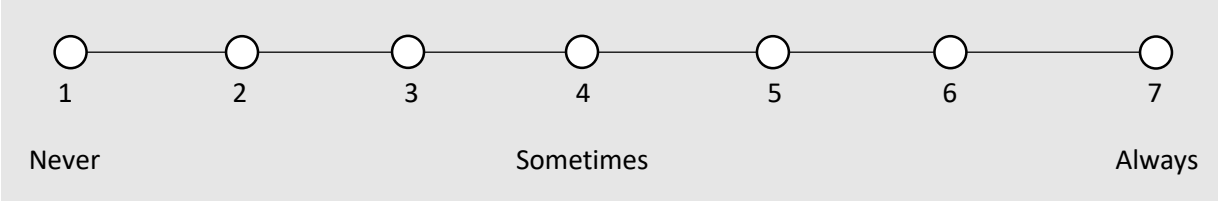
What time of day do you feel at your best?



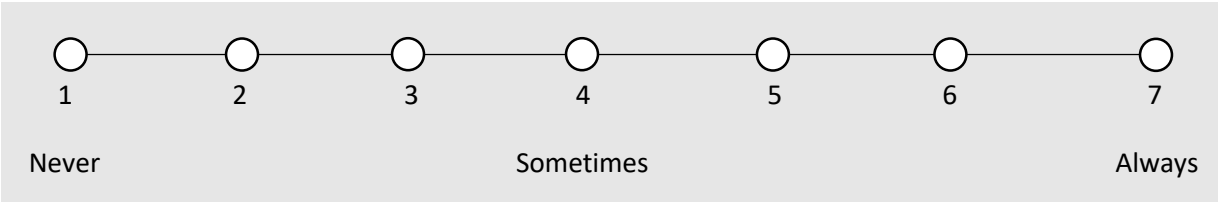
23. I feel unwell at all times of the day and night



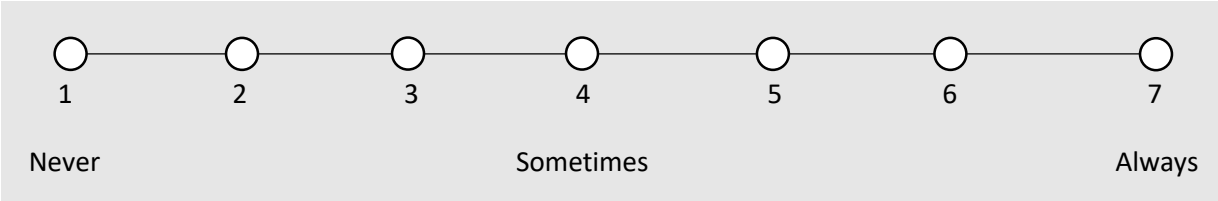
24. I wake up feeling tired



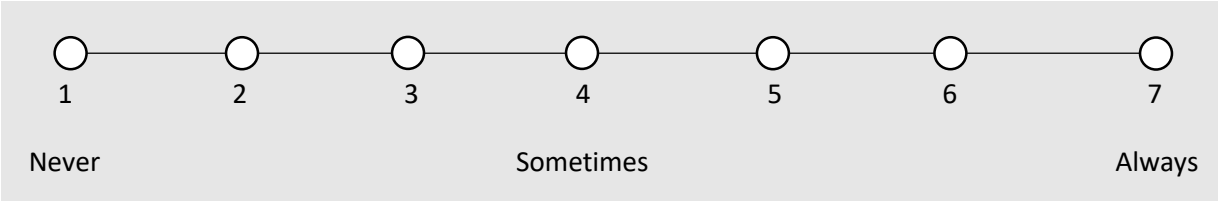
25. I have a hard time participating in vigorous activity



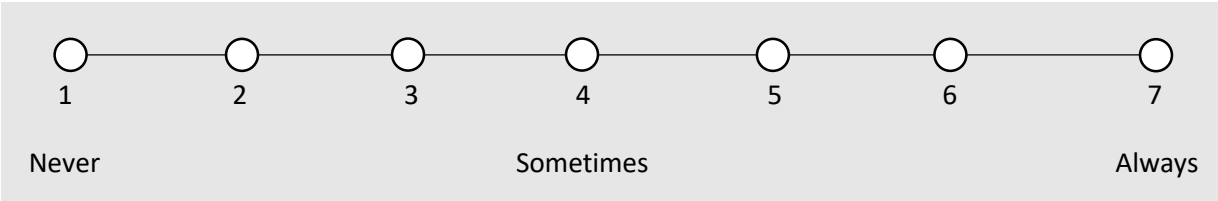
26. I don't do much during the day



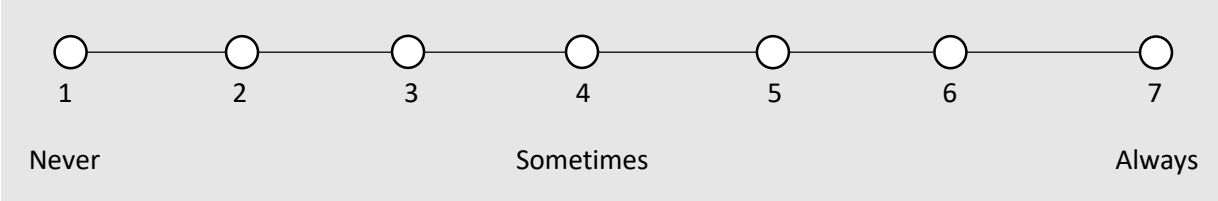
27. I have enough energy for everyday life



28. I have problems starting things



29. I feel no desire to do anything



30. When I am doing something, I can concentrate quite well