

## Study Report

**Matthew C. Popkin, M.D. and James M. Blum, Ph.D.**

**November 16, 2017**

**Title:** The effects of a novel pre and probiotic in supporting improved gut health and lowering environmental toxin levels: a pilot study.

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## **RATIONALE and BACKGROUND INFORMATION**

Medical science has come to recognize that gut health is crucial to overall health, especially chronic diseases. Chronic diseases such as obesity, insulin resistance / diabetes / metabolic syndrome spectrum, ischemic heart disease, arthritis, irritable bowel and related gut syndromes, dementia/Alzheimer and associated cognitive dysfunction, peripheral and central neurological conditions (including multiple sclerosis (MS), Parkinson's, palsies), hepatic, renal, pulmonary, and many autoimmune conditions have been shown to be related to systemic inflammation and in turn, inflammation is connected to gut biome and gut health. One of the tenants of Functional Medicine, the relatively new medical science, involves these very steps of foods and environmental toxins triggering intestinal permeability, which results in

oxidative stress and inflammation, which ultimately results in a wide array of syndromes and diseases. In this mix the gut biome plays a major role and has been considered a major component because it sends signals to the brain and produces immune mediators that influence all organ systems.

Due to Fasano's work, we know that the triggers of stress, gluten and some other food proteins, (heavy) metals, and toxic chemicals that include pesticides, herbicides, and some of the 80,000 synthetic chemicals produced for industrial purposes, up-regulate the protein zonulin, which opens pores between the intestinal enterocytes producing intestinal permeability ("leaky gut"). The gut biome is central to this picture that results in the many forms of chronic diseases. In this scenario, glyphosate, the primary compound of Roundup, which enjoys widespread use as an herbicide and enters the human body through foods and water, and hence, products that contain water.

The gut biome is made up of a precise balance of commensal and probiotic intestinal bacterial strains inhabiting the fingerlike villi of the single layer of intestinal epithelial cells that separates the intestinal lumen from the rest of the body. The space between these cells is sealed by tight junctions that regulate the permeability of the intestinal barrier. These tight junctions are complex structures that maintain the integrity of the gut barrier and are one of the main sites of damage in a compromised gut. The intestinal bacteria change the expression and distribution of tight junction proteins which regulates the intestinal barrier function. Various friendly bacterial strains lead to an increase in tight junction proteins at the gap junctions between the cells and can prevent or reverse the damage caused by various pathogens and toxins. Increased intestinal permeability can cause autoimmune, inflammatory and other diseases that are expressed both locally as in inflammatory bowel disease and celiac disease and systemically which can cause a whole body inflammatory state that effect all the organs in the body.

Maintaining the integrity of the gut biome is essential for many reasons. The gut is where most of our nutrients are absorbed. The gut is the entry point for most of the body's toxins and therefore the primary site for detoxification. Seventy-to-eighty percent (70-80%) of our immune system is in our gut so even small levels of gut dysfunction can have a huge impact on our immune function which is needed to prevent infection, fight cancer and maintain overall health. The markers we chose for this study will evaluate different aspects of gut health including gut inflammation, gut permeability and gut immune function.

So, how to combat these cascades that is resulting in the epidemic growth of so many diseases? The recent surge of probiotics, antioxidants, and gut health is in response to this new understanding. As an example, the rise in sugar-related-based diseases has experienced exponential growth in the last thirty years and now, the current worldwide numbers for diabetics stands upward of 422 million and is expected to double by 2030. In 2012, 1.5 million deaths were recorded due to diabetes. Diabetes can be managed through diet and medications but the disease results in many serious, significant, and very expensive problems that include heart, eye, peripheral vascular disease, renal failure, and cognitive dysfunction. The epidemic of sugar-related conditions has grown dramatically in the youth. Presently, the rates of pre-diabetes (insulin resistance) and diabetes in children and young adults has risen sharply since 2000.

It is well documented by basic research scientists that glyphosate is toxic to humans and other animals in several ways. Glyphosate inhibit the biosynthesis of aromatic amino acids, tyrosine, tryptophan, and phenylalanine. These amino acids are paramount to numerous metabolic pathways. The German Federal Institute for Risk Assessment has concluded glyphosate is a risk for the development of non-Hodgkin lymphoma. The World Health Organization Agency for Research on Cancer has classified glyphosate 2A, probably carcinogenic in humans. However, several American organizations have not classified glyphosate as significantly toxic.

Purium has hypothesized that a novel blend of pre and probiotics will accomplish improved gut health by altering the gut biome. In turn, the levels of glyphosate and other toxins will drop. This pilot or proof-of-concept trial will measure the toxin glyphosate levels through urine assays, intestinal permeability through testing ingested large and small sugar molecules that could pass through the gut wall (mannitol and xx), several markers of gut dysbiosis (D-lactate and LPS), a well-recognized inflammatory marker (CRP), and a functional test of gut health (food sensitivity). In addition, symptoms of existing chronic conditions will be observed and recorded. Other inflammatory symptoms include mood, energy, fatigue, and sleep quality, in addition to gut symptoms that include bloating, gas, cramping, and related parameters.

We will test this intervention and outcomes in a population of adult men, aged 20 to 65, who exhibit symptoms of chronic disease, eat an typical American diet, and are patients of the medical director. Approximately twenty potential subjects will be screened for their current glyphosate levels and the highest eight readings will be selected for inclusion.

## **STUDY GOALS and OBJECTIVES**

This is a small pilot that will hopefully provide sufficient evidence to justify a full-blown randomized clinical trial with all the bells and whistles that will include independent monitors, independent biostatisticians, and other aspects required for publication.

The goals of this pilot are to assess Purium's combined pre and probiotic combination product v. a suitable control. Specifically will they have any effect on (1) clinical symptoms in individuals that present with chronic conditions, (2) gut health as indicated by bloating, cramping, pain, gas, and transit time (3) secondary clinical outcomes such as sleep quality, fatigue, peak energy, and similar parameters, and (4) laboratory measures of glyphosate, a well-known herbicide, the primary ingredient in Roundup. Inflammatory and gut markers will include C-reactive protein (CRP), intestinal permeability (lactulose-mannitol test), LPS, d-lactate, and food sensitivity.

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## **STUDY DESIGN**

### **Type of Study**

This has been designed as a randomized pilot study with the intent of assessing a number of markers and outcomes in response to six weeks on two different pre and probiotic blends (product v. control).

Even though there are only eight subjects, the trial was designed to include a control group. It was decided to split the eight between five and three subjects in the two groups (product and control groups respectively).

It was argued to use a negative control group but it was felt that a positive control would provide more information. A product with an excellent reputation and history was chosen as a suitable control.

### **Study Population**

All study participants will be patients of Dr. Popkin. Potential subjects are not required to use Dr. Popkin exclusively.

A total of eight (8) male subjects are needed to complete this pilot clinical trial. Hopefully the loss to follow-up following randomization will be zero or very low (one or two). We expect to screen between 16 and 24 potential subjects for elevated glyphosate levels.

In health and medical terms, we want individuals who have some level of inflammatory or chronic condition that can be measured or assessed. Conditions that could qualify would include: obesity, insulin resistance, diabetes, metabolic syndrome, arthritis or other arthritis-related conditions including joint stiffness and joint pain, pain syndromes, irritable bowel conditions and diseases, neurological conditions (TIA, MS, palsies, Parkinson's), cognitive decline, dementia, autoimmune diseases, ischemic heart disease, peripheral vascular disease, pulmonary (asthma, COPD), skin (psoriasis, eczema, acne), and others.

General consensus exists for an indirect measure of body fatness called the body mass index (BMI). BMI is defined as a person's weight in kilograms (kg) divided by the square of their height in meters (m<sup>2</sup>). The National Institute of Health has issued standard classifications of adult weight levels based on the following BMI calculations:

<b>Table B: Adult Weight Level Classifications Based on Body Mass Index (BMI) (2)</b>	
Classification	BMI (kg/m <sup>2</sup> )
Underweight	<18.5 kg/m <sup>2</sup>
Normal	18.5-24.9 kg/m <sup>2</sup>
Overweight	25.0-29.9 kg/m <sup>2</sup>
Obesity	29.9-40.0 kg/m <sup>2</sup>
Extreme obesity	>40.0 kg/m <sup>2</sup>

The acceptable levels for this trial include those falling from Normal BMI through the lower half of the obese individuals (BMI 18.5 – 35.0).

## **Inclusionary Criteria**

Potential subjects who meet the following criteria may be considered for this trial:

- Are male
- Between the ages of 20 to 65
- Having a BMI from 18.5 to 35.0
- Belong to the medical practice of Matthew C. Popkin, M.D. (they may see other physicians as well)
- Have symptoms consistent with an inflammatory or chronic condition or disease
- Generally eat a typical American diet of some prepared foods, some fast-food
- Individuals who do not eat a great percentage of organic foods or ingredients
- Wish to participate in a trial of pre and probiotics to help with any of the following
  - Decreased toxic load
  - Improved gut health
  - Improved symptoms of their chronic condition
  - Improved sleep quality, energy, and similar end-points
- Understand their responsibilities as a subjects in this trial, specifically
  - High compliance in taking their supplement on a daily basis (high compliance is defined as greater than 86% (6 out of 7 days)
  - Total compliance in making all their visits (an acceptable date range is within four days of their scheduled appointment)
  - High compliance in reporting their symptoms and observations (determined by experience of the research team based on expectations – an acceptable report will list a number of observations while a report with few notes will trigger a discussion with the subject and providing additional examples of an ‘acceptable report’)

## **Diet and shopping habits**

Individuals who eat organic –vs- those who rarely eat organic. Clearly, we do not want to choose organic as these individuals most likely will have lower levels of the target compound glyphosate.

Healthy eaters -vs- fast-food junkies. Presumably, those who eat more fast food will have higher levels of glyphosate.

## **Exclusionary Criteria**

Potential subjects who meet any of the following exclusion criteria are not eligible for participation in this proof-of-concept trial:

- Are unwilling to follow the procedures of the trial, such as making visits or taking the supplements when asked to;
- Are unable to tolerate the ingredients in any of the botanical supplements or who have a propensity to allergic reaction;

- Have unintentionally lost or gained 10 or more pounds of body weight in the last 3 months;
- Have an acute illness (such as a severe cold or flu) or have been hospitalized within the past month for certain conditions;
- Have severe co-morbid disease including cardiac, pulmonary, renal, hepatic, carotid, peripheral vascular disease, stroke, neurological, clotting disorders or active cancer;
- Abuse alcohol or illicit drugs.
- Take anticoagulants other than aspirin or take MAO inhibitors
- Are uncontrolled or insulin-dependent diabetics (IDDM)
- Have uncontrolled hypertension;
  - Systolic blood pressure (SBP) > 180 mm Hg or diastolic blood pressure (DBP) > 100 mm Hg, upon two of three repeated measures, and not on medications for hypertension.
  - Systolic blood pressure (SBP) > 150 mm Hg or diastolic blood pressure (DBP) > 90mm Hg, upon two of three repeated measures, and not on medications for hypertension;
- Have had a recent cardiovascular event (past 36 months), or a family history of sudden death or heart attacks before the age of 55;
- Have a Body Mass Index (BMI) of less than 16 or greater than 38 m/kg<sup>2</sup>;
- The anticipated need for surgery of any type during the entire study;
- Subjects who plan to donate blood or blood products during the study or for thirty (30) days following the study;
- Subjects with evidence of active peptic ulcer disease, or who have a reliable history of gastrointestinal bleeding within the past five (5) years;
- Subjects with recurrent or a history of intestinal disorders that may interfere with the absorption;
- Have any disease or condition that in the investigator's opinion compromises the integrity of the clinical trial or the safety of the subject;

Severe co-morbid disease is defined as any condition that would cause severe limitations or inability to carry out usual activities of daily living.

The exclusion criteria identified above are based upon general safety concerns identified with the condition and/or product from recommendations made by the study physician, confounders identified by the biostatistician, or information identified in product ingredients' research.

**Controls:**

This group will receive a placebo-based product. They will take this product on the same schedule as those taking the Purium product.

This will allow us appropriately compare the effects of the Purium product against a control product.

**Subject Reimbursement:**

Each subject who completes the trial will receive \$100. Since it is crucial that we have subjects in the trial for six weeks, we will pay them once complete to ensure higher compliance.

**Duration of the Study:**

Once subjects are randomized, they will take their assigned product for a period of six weeks.

Subjects will be seen again at the clinic at eight weeks but are eligible to communicate with Dr. Popkin regarding this trial for up to twelve weeks following randomization.

It is expected to take up to two-to-three months to identify, recruit, obtain informed consent, and randomize all the subjects. Recruitment will be ongoing until all eight subjects have been randomized and will reopen if there is loss-to-follow-up.

**STUDY DESIGN**

In order to test Purium Product Biomedic for any effectiveness at reducing glyphosate levels and for improvements in gut health, and other inflammatory symptoms, compared to controls, we will need to recruit individuals with high normal levels of urine glyphosate levels and those with symptoms associated with chronic inflammatory conditions/diseases.

Slightly more than half of those will receive product (Biomedic) and the remainder will receive a similar product (controls) for a period of six weeks. After their initial assessment and randomization, follow-up visits will occur every two weeks for a total of six weeks. Blood and urine will be obtained during these visits.

Potential male subjects will be screened for higher ranges of glyphosate levels and existing inflammatory conditions. Those in the high normal range to elevated levels of glyphosate will be included, if they have inflammatory symptoms. The exact number of subjects needed to screen for eight subjects is unknown since we have no information on these levels in South Florida individuals. Presumably, those eating a fast food, non-organic food lifestyle will offer us the best chance to obtain these individuals.

Biomedic is designed to improve the gut biome by providing a prebiotic in the form of Prebiosure 350mg, a probiotic Lactospore 15mg (bacillus coagulans 15 billion cfu/gm) and Humic and Fulvic compounds (Humisure 5mg/FOS 135mg). As such, functional testing of gut health will be performed by measuring inflammation, intestinal permeability and intestinal immune function both before and after treatment. Controls will receive a placebo containing similar levels of both a pre and probiotic.

Laboratory testing will be done to assess glyphosate levels, inflammatory markers, highly specific gut biome surrogate markers of intestinal permeability and food sensitivity testing to assess gut immune function. This multi-factorial study will assess both the detection and removal of glyphosate from the body while at the same time assessing inflammation, intestinal permeability and intestinal immune

function by measuring the functional improvement of the gut as a result of repairing, re-inoculating and restoring the gut biome.

### Detailed Summary

- This is a **single-center**, prospective, randomized, double-blinded, product-controlled, parallel-group-design clinical trial of Purium Pre-and-Probiotic product™ versus control product in subjects who are experiencing symptoms of chronic conditions and wishing to determine if the product will reduce their levels of glyphosate.
- Subjects will be **recruited** from the list of Dr. Popkin's current practice. All potential subject and subject visits will take place at 2415 Hollywood Blvd., in Hollywood, FL.
- All subjects will be assessed for the initial week for baseline levels of diet and exercise; non-compliant subjects will be dropped;
- At the **Initial Visit**, subjects will read, understand, and then may sign an informed consent form prior to any clinical trial procedures. NOTE: potential subjects have several days to consider the implications of enrolling in this trial. Each potential subject is allowed one call to ask if they want to participate but only one call. After that, they are closed out.
- After **consenting**, subjects will have their weight, height, blood pressure, and pulse measured.
- **At their Initial Visit, subjects will have urine obtained for glyphosate. This is part of the screening process. Only those with the highest levels of glyphosate will be entered into the experimental phase of the trial.**
- Subjects will complete a series of baseline questions concerning their medical conditions and history, behavior, and related parameters.
- Later, as approximately fifteen potential subjects have had their glyphosate assayed, a glyphosate curve will be developed it should be clear which subjects qualify by exhibiting high levels of glyphosate. They will be enrolled.
- If the subject qualifies with high glyphosate, they will be processed by being assigned the next randomization number.
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- At the **Baseline Visit**, subjects will be **randomized** into one of two groups for a six week period, with clinic visits every two weeks.
- **Randomization will be unequal:** Using **blocks of 8**, five subjects will be assigned to the product group and three to the control group; See the Statistical Section for the randomization scheme and details.
- At their baseline visit, **blood will be drawn for various markers.**
- Following randomization, subjects will be seen again at the Clinic **every two weeks** throughout the trial. See the Flow Sheet for details.
- The primary end-point is glyphosate levels and symptoms of their inflammatory conditions. Both self reports and assessments made by the clinical team will comprise these inflammatory symptoms. All end-points will be assessed at each two-week visits.
- **Phone calls** between each Clinic Visit will be made to **reinforce compliance.**
- The **Week 7 Visit** (called the 6-Week Visit) will be the subjects' last visit marking the end of the trial. **Blood will be drawn** for various markers.
- The data will be entered into an Excel database by our data coordinator.

- **An intent-to-treat analysis** will be completed comparing the two groups.
- Subjects will be seen again at the 8 Week mark to check for any outcomes, including possible adverse events.
- Subjects will complete self-reporting questionnaires at the Initial Visit, baseline, 2, 4, and 6 weeks.
- Subjects will have laboratory testing taken after their Initial Visit and at baseline, and each subjective visit.
- The single site is a working physicians' office where qualified staff will see all subjects at each clinic visit.

#### **Placebo Subjects Taking Product**

- Subjects randomized to control will be offered the actual product for the same duration as those randomized to receive the product (6 weeks) at the conclusion of the active phase of the trial;
- The condition under which the control subjects take the product, is that they take the product under similar circumstances of the trial, in that, they may have research staff counseling and access to the study physician, if needed, during this period.
- Individual plans will be created for follow-up; these reports will be saved and available for review.
- None of this data will be analyzed or used during this phase.

#### **Blinding Aspects and Procedures**

- This trial is double-blinded;
- The identity of the specific treatment or placebo arm is not available to the clinical team, unless a medical emergency arises. The consulting physician is always able to gain access to this information.
- We use a multi-step process that assures this confidentiality. One of two study coordinators prepares the product bags that are given to each subject. Each bag is marked with a number that includes the study number and specific subject number. For example 12123 would be decoded as study number 121 and subject number 23.
- The study coordinator will keep secured records as required by the IRB that includes the randomization scheme, subject identifiers, and other pertinent information. This information is kept from the clinical staff. In cases of medical problems, Dr. Popkin will be given the identity of the randomization. The IRB and the study sponsor will be notified under these circumstances as required by IRB guidelines.

#### **Withdrawal**

#### **Subject Discontinuation and Sponsor Discontinuation**

## **Subject Discontinuation**

In the event a subject withdraws from the clinical trial prematurely, the assessments required for the 6-Week Visit will be completed whenever possible. Every effort will be made to collect the assigned product container and used and unused assigned product. If the subject is withdrawn due to an adverse event(s), the subject will be monitored until the adverse event has resolved or until the event is determined to be due to a stable or chronic condition or concurrent illness(es).

A Drop Explanation Form will be completed to document the reason for subject discontinuation.

Reasons for a subject's removal from the clinical trial may include, but are not limited to:

- Adverse event(s);
- Noncompliance;
- Withdrawal of consent;
- Disqualification;
- Death.

Compliance is defined as subjects who use 85% or more of the assigned product and complete 85% or more of the clinical trial forms and logs.

If a subject withdraws from the clinical trial, the subject's identification number will not be reassigned.

## **Adverse Events**

### **Assessment of Adverse Events**

An adverse event (AE) is any reaction, side effect or other undesirable experience that occurs in conjunction with the use of Diet Product, whether or not the event is considered related to Diet Product. New and worsening signs and symptoms of underlying or emerging disease will be recorded as an adverse event. Any subject complaint reported will be recorded as an adverse event.

### **Serious Adverse Events**

A serious adverse event (SAE) is any adverse event occurring that results in the following:

- Death
- A life-threatening event;
- Requires in-patient hospitalization;
- A persistent or significant disability/incapacity.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

The IRB and Purium will be notified of all serious and unexpected adverse events using a Drop Explanation Form and forms specified by the IRB within a time frame specified by the IRB.

#### **Adverse Event Severity Definitions**

- Mild – The adverse event, taken as an isolated event, would cause no limitations of usual activities.
- Moderate – The adverse event, taken as an isolated event, would cause some limitation of usual activities.
- Severe – The adverse event, taken as an isolated event, would cause severe limitations or inability to carry out usual activities.

#### **CONFIDENTIALITY**

In order to maintain subject privacy, all subject records will identify subjects by their subject identification number only. Drs. Blum and Popkin will grant monitor(s) and auditor(s) from the United States Department of Health and Human Services (DHHS), the United States Food and Drug Administration (FDA), and other federal or state governmental agencies, the IRB, Purium access to subject records to verify data and to audit the data collection process. Subject confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

#### **Intervention**

The intervention is a daily capsule of a pre and a probiotic. The two products are described in this section.

#### **Product and Control Administration**

Capsules will be taken twice daily, morning and evening.

Product will be taken for six weeks

#### **Purium Study Product**

Capsule Amounts: As the formula stands it consists of the following (per capsule)

350mg Digestive Wheat Germ Extract

15mg LactoSpore 15B cfu/gram

50mg HumicSure 60/40

135mg Fruitafit IQ

## Purium Study Product

A short paragraph describing how the given ingredients in the Biomedic study product might produce the desired effects and why the ingredients of the placebo will act as an appropriate placebo will also be included.

### Biomedic active ingredients:

- 1) Prebiotic in the form of Prebiosure 350mg
- 2) Probiotic Lactospore 15mg (bacillus coagulans 15 billion cfu/gm)
- 3) Humic and Fulvic compounds (Humisure 5mg/FOS 135mg)

### FulvicSure and HumicSure

Humic acid is molecularly larger than fulvic acid but has similar structure and biological properties. It is soluble between the pH range of 7 to 14. It cannot be absorbed by the GI tract. It acts like a buffer in modulating blood pH. It helps prevent the absorption of toxins and bacteria in the gut and helps in absorption of nutrients. Overall, it helps cleanse the colon and helps block the absorption of toxins.

Fulvic acid is the smallest fraction of the humic substances, soluble in both acidic and alkali liquids (pH 2-14). Fulvic acid is an extremely active biological substance, because it is an electron-transfer catalyst and known for its antiviral properties. It can detoxify the cell through chelation, and can amplify the actions of substances such as Coenzyme Q10.

### Frutafit® IQ Version: 02.2005 R7,07

#### Compositional Specifications

All values expressed on dry matter.

Dry matter content	95-99%
Carbohydrate content	
Inulin	> 90%
Fiber	> 90%
Fructose, glucose, sucrose	< 10%
Average chain length	8-13 monomers
Ash	< 0.2%
Heavy metals	complies with legal requirements

#### Description Microbiological Specifications

Frutafita IQ is an all-natural inulin. It is a powdered food ingredient based on chicory root extract, developed for applications that require instant dispersion, flow, and porosity. This product has excellent dispersability. It is a mixture of non-digestible (dietary fiber) fructose units linked

together by 13(2-1) linkages, terminated by a glucose unit.

### Nutritional Information

All values are expressed per 100 g product.

#### Carbohydrates

Digestible (fructose, glucose, sucrose)	7 grams
Non digestible (dietary fiber, inulin)	90 grams
Proteins	0 grams
Fats	0 grams
Moisture	3 grams
Dietary fibers (AOAC 997.08)	90 grams
Sodium	40 mg
Calcium	11.5 mg
Potassium	7.5 mg
Iron	0.4 mg
Other Minerals	negligible
Vitamins	negligible
Gluten	absent
Lactose	absent
Folate	absent
Insecticides, pesticides	absent
Enzymatic activity	absent
Color, flavors, preservatives	absent
Caloric Value	1.6 kcal/gm
Glycemic Index (GI) value	14

NOTE: Caloric value - calculated value based on 1.5 kcal/gram pure inulin that has been established in scientific studies. Please check local legislation and adapt if necessary

- Packaging 44.09 lb. / 20 kg white multi paper bag with colored PE inner liner.
- Labeling Chicory root fiber, Chicory root extract, Inulin, Oligofructose.
- Safety GRAS (notification number 000118), USDA approved.
- Storage Product should be stored under dry conditions in the original unopened bag.
- Min. 5 years from production date, in unopened bags. Best before date is printed on each bag.
- For the production of this product, Sensus only uses raw materials from conventionally cultivated chicory varieties.
- Therefore, no labeling as GMO derived ingredient is needed for application of this product according to the regulations EC(2001/18), EC(1892/2003), EC(1830/2003).
- Neither the raw chicory root nor the process additives used in its production of Frutafit® IQ contain the following allergens: gluten, milk components, soy, nuts, fruit, eggs, meat or fish.
- Fructans (inulin/oligofructose) in food products can be analyzed by the following methods: (AOAC 997.08), (AACC 32-31), (AOAC 999.03) (AACC 32-32).

**Control Product**

**Nature City's TrueLife PB**

**Probiotic Blend (1 capsule) 30 billion CFU**

Lactobacillus acidophilus La-14

Bifiobacterium lactis BI-04

Lactobacillus salivarius Ls-33

Lactobacillus planetarium Lp-115

Lactobacillus casei Lc-11

Lactobacillus rhamnosus Lr-32

ACTAZIN: kiwifruit standardized extract 125 mg

FloraFit (pre-biotic) (inulin)

**Table A: Clinical Trial Flow sheet**

Clinical Trial Procedures	Call	Initial Visit	Baseline Visit	2-Wk Visit	4-Wk Visit	6-Wk Visit
Actual Weeks		0	1	3	5	7
Phone conversation about the study	X					
Make a decision about being in the study	X	X				
Consider eligibility: Medical history and in-depth eligibility, measure height and blood glucose	X	X				
Diet and Exercise Baselines; Take Placebo		X	X			
Randomization			X			
Physiological markers (blood pressure and pulse);		X	X	X	X	X
Self-reporting questions		X	X	X	X	X
Physical examination		X	X	X	X	X
Review of prescription and non-prescription product use	X	X	X	X	X	X
Dispense assigned product			X	X	X	X
Take Assigned Treatment (either placebo or product)			X	X	X	X
Assess subject compliance			X	X	X	X
Assess adverse events			X	X	X	X
Blood draws		X	X	X	X	X

**There will be one addition visit at the 8-week mark to check outcomes.**

## Procedures

### Blood Pressure:

- Subject sitting down; legs not crossed;
- Measurements taken on right arm (unless noted), approximately halfway between elbow and shoulder;
- Place cuff snugly around arm, but not too tight;
- For normal BP, pump it up to approximately 150 torr;
- For those documented hypertension, pump the cuff between 175 and 200 torr;
- Place stethoscope inside the elbow over the artery;
- Slowly release cuff valve;
- As the pressure drops, listen for the first pulse (systolic pressure)
- Last pulse is the diastolic; then release completely
- Record these numbers  
Repeat 5 minutes; Average the two

If the two readings are more than 10% difference, repeat in ten minutes, once the subject has had time to relax and adjust to the interview.

### Pulse

- Arm facing down;
- Place the index finger and the middle finger on their radial pulse;
- Measure pulse for 30 seconds; multiply by two;
- Repeat in five-to-ten minutes;
- If the two readings are more than 10% difference, repeat in five minutes.

### Venous Draw

- Phlebotomist should confer with the protocol sheet and confirm with Dr. Popkin or Blum as to which bloods are to be drawn;
  - It is possible no blood work is required at this visit, especially in Follow-up Week 2 or 4;
- Go over the process of a venous draw with the subject;
- At this point, ask the individual (subject) to exercise for approx. one minute to allow the vessels to fill with blood; the clinic has a full-equipment P.T. (physical therapy) room. There are numerous ways/equipment to choose from to allow the subject their choice for this purpose;
- Meanwhile prepare your workspace for the draw (requisition form, gloves, alcohol pads, tourniquet, rubber ball, band-aid(s), draw apparatus; collection tube(s) and anything else needed;
- Ask the subject to sit in the phlebotomy chair and ask the patient to place their arm in the correct position;
- Locate their best vessel for the draw;
- Have the subject pump their fist and give them the ball;
- Apply the tourniquet;

- Inset the need with a tube leading to the holder;
- Once blood is flowing, place the collection tube to the holder;
- If two different tubes are needed, take out the first tube, and apply the second tube;
- Gently rotate the first tube to mix the blood; Place in a holder;
- Remove the second tube once filled; tip the tube back and forth and place in the holder;
- Place a cotton swab over the insert area and press gently;
- Clearly make sure the tube(s) is/are properly labeled;
- Making sure the blood has stopped flowing and apply a band-aid.
- Clean up and thank the subject;
- Place the blood in the area for the Biotrinetix pick-up.

### **Urine Collection**

- Explain how to collect a urine sample and what and to collect a 'clean-catch' is;
  - The name of the subject and study number will have been written in magic marker on it;
- Provide a urine collection jar; (small plastic cup, marked with lines);
- Show the subject to the in-clinic bathroom (after their initial use of this bathroom, they will know where it is located);
  - Instruct the subject to thoroughly tighten the lid on the cup;
- Following delivery of the capped urine collection cup from the subject, wipe the cup clean and make sure it is dry;
  - Take a subject label (with the study identification on it) and place on the cup;
- Place in the pick-up area for either Biotrinetix or Genova;
  - Biotrinetix will pick up urines daily
  - Geneva will be readied for transport to Genova;

### **Measurements: End Points**

1. Laboratory Measures
2. Clinical Observations
3. Adverse Event

### **Measurement 1: Laboratory Testing**

#### **Laboratory Testing Summary**

- Glyphosate levels (determined by ELISA)
- CRP levels (C-Reactive Protein)
- Food Sensitivity Testing – IgG antibody testing

## Measurement 2: Clinical Observation Assessment

### Observation Summary

- Changes in physiological parameters, i.e., blood pressure, weight, etc.
- Disease state parameters, i.e., IBS, arthritis, diabetes, obesity, etc.
- Overall Well-being: i.e., mood, energy levels, sleep quality, bowel elimination, etc.

## Measurement 3: Adverse Events

### MEASUREMNT DETAILS

#### 1. LABORATORY TESTING

- **Glyphosate Levels (Quantitative Levels - ELISA); Biotrinetix Laboratories**

This assay is an immunoassay for the quantitative levels of glyphosate in water-based solutions ranging from environmental samples to biological samples. It yields validatable sensitive quantitative levels that will compare favorably with HPLC (high pressure liquid chromatography) and GCMS (gas chromatography mass spectrometry).

The ELISA-based test is based on the recognition of glyphosate by polyclonal antibodies. The sample is derivatized and added to the plate wells, which have been coated with rabbit anti-rabbit antibodies. An enzyme catalyzes the reaction between the derivatized antigen and the antibodies. After an incubation period, a color reaction ensues. The reaction is washed and stopped and read in a reader.

The test has some limitations that should not occur in human urine. The normal errors from mishandling pipettes also could influence results or proper laboratory techniques will be followed.

All 8 subjects will get glyphosate tests at each baseline and each follow-up visit.

- **C-Reactive Protein (CRP) Levels; Biotrinetix Laboratories**

CRP is a highly sensitive, non-specific inflammatory marker. The High Sensitivity (hs) component is used as a cardiac marker. This serum marker is well recognized as an inflammatory marker.

All 8 subjects will receive CRP levels and will be tested at baseline, and again at four (4) and six (6) weeks.

- **Food Sensitivity Testing – IgG antibody testing; Biotrinetix Laboratories**

Food sensitivity is different than testing for an allergic reaction. Food allergy is the result of activating the IgE pathway mediated by mast cells and basophils are considered part of the adaptive immune system. Results are generally fast with physiological changes in the ten to a couple of hours. Food sensitivity on the other hand, is called a delayed onset because the onset of symptoms is experienced up

to several days. The white blood cells that are activated are part of the innate immune system and leads to a state of inflammation. It is this inflammation over time that leads to chronic disease.

Food sensitivity is generally reported in terms of no reactivity, mild, moderate, and severe. The number of foods and severity that are reactive will comprise the assessment for this series. Normally the results comprise the basis of an elimination diet. In our pilot, subjects will not be given their baseline test results as this might affect the study if they eliminate the reactive foods. These changes might affect the glyphosate levels as well as the inflammatory and gut biome surrogate markers. If the gut is helped by the pre and probiotics, the number and severity of the reactive foods should decrease. This will serve as yet another functional marker to assess the improvement in the gut biome as a result of removing glyphosate from the body and repairing, re-inoculating and restoring the gut biome.

Only two subjects from each group will be randomized to undergo this test.

## **2. OBSERVATIONAL**

In addition to the laboratory testing, the other primary end-points will be self-reports and clinical observations involving health and lifestyle parameters. In addition to numerous clinical parameters, we will be asking each subject to report on sleep, fatigue, energy, activity changes, and similar parameters.

The questionnaires to be used both by the clinical team and the self-reports are included in the appendixes.

## **3. ADVERSE EVENTS**

### **Assessment of Adverse Events**

An adverse event (AE) is any reaction, side effect or other undesirable experience that occurs in conjunction with the use of Diet Product, whether or not the event is considered related to Diet Product.

New and worsening signs and symptoms of underlying or emerging disease will be recorded as an adverse event. Any subject complaint reported will be recorded as an adverse event.

Serious Adverse Events: A serious adverse event (SAE) is any adverse event occurring that results in the following:

- Death
- A life-threatening event;
- Requires in-patient hospitalization;
- A persistent or significant disability/incapacity.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

The IRB and Purium will be notified of all serious and unexpected adverse events using a Drop Explanation Form and forms specified by the IRB within a time frame specified by the IRB.

#### Adverse Event Severity Definitions

- Mild – The adverse event, taken as an isolated event, would cause no limitations of usual activities.
- Moderate – The adverse event, taken as an isolated event, would cause some limitation of usual activities.
- Severe – The adverse event, taken as an isolated event, would cause severe limitations or inability to carry out usual activities.

#### VISIT SUMMARIES and DETAILS

##### Initial Screening

Dr. Popkin will review his patient records (LAST NAMES) in a systematic and alphabetical manner to review for eligible candidates. Those that qualify will be called by the office staff and invite them in for an interview.

The criteria for this review will be random in the following schema:

Numerical Order	Letter	Numerical Order	Letter	Numerical Order	Letter
1	T	2	G	3	L
4	R	5	B	6	N
7	E	8	C	9	Y
10	M	11	A	12	S
13	P	14	W	15	H
16	J	17	D	18	F
19	K	20	Z	21	O

This process serves as the **Initial Screen**. We briefly describe the trial and ask if the individual is interested. If they are, we then ask a series of questions to determine potential eligibility, using the **Intake Call Script** and the **Intake Form** that cover basic inclusion and exclusion criteria. These questions inquire about their weight condition, limitations, ability to get to the Clinic, medications, general health (co-morbid conditions), and other related issues. Specific exclusions are discussed that will include age, active diseases like diabetes or cancer, as well as other issues. This screening call takes between 10 and 15 minutes and may occur over two separate calls.

If the potential subject passes this initial screen, an appointment is scheduled for the **Initial Visit** at Dr. Popkin's Clinic at 2415 Hollywood Blvd. Hollywood, FL 33020

### ***Initial Visit***

Volunteers will be asked to participate in this clinical trial and sign an Institutional Review Board (IRB) approved Informed Consent Form (ICF). The principal investigator (PI) or Dr. Popkin will review the entire Informed Consent Form with each potential study participant prior to any signing. All questions concerning the study, their role, or their rights are answered at this time.

#### **Time must be provided for each potential subject to sign their Informed Consent.**

Sometimes individuals choose to sign their Informed Consent during this initial interview, while others require a day or two to consider it, or to talk with family members or their health care provider. We are available by phone to answer questions to family members or health care providers.

After potential subjects consent to trial participation (now considered 'subjects'), baseline assessments will be taken for:

- general medical history,
- medical questions concerning their weight and functional limitations,
- prescription and non-prescription product use, and
- demographics and background;

Subjects will:

- Be asked to complete an Initial Visit Form;
- Be asked to complete a Demographic Form;
- Have their height, weight, blood pressure, and pulse measured;
- Have their blood glucose measured;
  - If the fasting glucose levels are greater than 126 mg/dL, the subject will be dismissed from further participation;
  - If the fasting glucose is between 120 and 126 mg/dL, the subject may try again on a different day;
- Receive instructions on how and when to comply with the laboratory testing requirements;

- Receive instructions on how and when to report any medical changes, new prescription or non-prescription product use, or adverse events;
- Receive a Lab Testing Request Form and Information Sheet;
- Be scheduled to return to the Research Clinic in 2 weeks;

If a subject is not compliant at this or any other time, the research staff will discontinue the subject's participation at the principal investigator's discretion.

### ***Baseline Visit***

Subjects will:

- Be asked to complete a Baseline Visit Form;
- Have their weight, blood pressure, and pulse measured;
- Be randomized through assignment to the next available identification number from the randomization list;
- Receive instructions on how and when to use their assigned product;
- Receive instructions on how and when to report any medical changes, new prescription or non-prescription product use, or adverse events;
- Review the Information Sheet;
- Have their blood and urine collected;
- Receive a 2-week supply of their assigned product;
- Be asked to bring their assigned product containers to their 2-Week Visit;
- Be scheduled to return to Dr. Popkin's office in 2 weeks for their 2-Week Visit;

If a subject is not compliant at this or any other time, the research staff will discontinue the subject's participation at the principal investigator's discretion.

### ***2-Week Visit***

Subjects will:

- Be asked to turn in their assigned product containers, symptom log, and activity log;
- Be asked to complete a Subject Evaluation Form;
- Have their weight, blood pressure, and pulse measured;
- Review any medical changes, new prescription or non-prescription product use, or adverse events;
- Review the instructions on using their assigned product;
- Receive additional logs;
- Receive a 2-week supply of their assigned product;
- Have their blood drawn and urine sample obtained;
- Be asked to bring their assigned product containers to their 4-Week Visit;
- Be scheduled to return to Dr. Popkin's Clinic in 2 weeks within 1 hour of their scheduled Baseline Visit time for their 4-Week Visit;

#### **4-Week Visit**

Subjects will:

- Be asked to turn in their assigned product containers, symptom log, and activity log;
- Be asked to complete a Subject Evaluation Form;
- Have their weight, blood pressure, and pulse measured;
- Review any medical changes, new prescription or non-prescription product use, or adverse events;
- Review the instructions on using their assigned product;
- Receive additional logs;
- Receive a 2-week supply of their assigned product;
- Have their blood drawn and urine sample obtained;
- Be asked to bring their assigned product containers to their 6-Week Visit;
- Be scheduled to return to Dr. Popkin's Clinic in 2 weeks for their 6-Week Visit;

#### **6-Week Visit**

Subjects will:

- Be asked to turn in their assigned product containers, symptom log, and activity log;
- Be asked to complete a Subject Evaluation Form;
- Have their weight, blood pressure, and pulse measured;
- Review any medical changes, new prescription or non-prescription product use, or adverse events;
  
- Have their blood drawn and urine sample obtained;
- Be asked to complete an End-of-Study Form;
- Be scheduled to return to Dr. Popkin's Clinic in 2-3 weeks for their last follow-up visit;

The 6-Week Visit is the last STUDY visit. Subjects will not be required to take any more assigned product. Subjects' participation will end at this time. There will be one more visit for the purpose of follow-up and to ensure the safety of the assigned product.

Each subject will receive a total compensation of \$100.00 upon successful study completion. If a given subject has not met their compliance responsibility, payment may not be made.

## DATA MANAGEMENT and STATISTICAL ANALYSIS

For the most part, due to the extremely small sample size, basic descriptive statistics and corresponding graphs and t-tests will only be required. Comparisons between product and controls will be made using non-parametric t-tests. Significance will be set at 0.10.

SAS, University version, will be used for analysis.

### Randomization

The randomization list will be generated from a randomization scheme by a standard statistical method as defined by Meinert in blocks of 8 (20) with a ratio of 5:3 (product: controls). Blocks of 8 were the smallest size possible. Two sets of 8 were run.

After consenting to trial participation, subjects will be assigned at the Initial Visit to the next available identification number from the randomization list.

Subject #	Assignment	Subject #	Assignment	Subject #	Assignment
1	1	2	1	3	0
4	0	5	1	6	0
7	1	8	1	9	1
10	0	11	0	12	1
13	1	14	0	15	1
16	1				

## QUALITY ASSURANCE (k)

### Good Clinical Practices (GCP) Compliance

This clinical trial will be conducted in accordance with Good Clinical Practices (GCP) and the appropriate regulatory requirements. The principal investigator is thoroughly familiar with the appropriate use of the clinical trial procedures as described in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the clinical trial and the integrity of the data collected. Master files will be established at the beginning of the clinical trial, maintained for the duration of the clinical trial and retained according to the appropriate regulations.

A few of the QC and QA protocols and methodology will not be employed in this pilot as would be utilized in a full-blown trial with the goal of peer-reviewed publication. The stated purpose of this pilot is to demonstrate the need for the larger trial and as such, expenses for independent monitors and independent biostatisticians and a data and safety monitor group. That being stated, we are committed to having the best data we can.

We will employ one independent (Dr. Lynn Disney) experienced epidemiologist to review our procedures and protocols, the data, the statistics, and interpretation.

We will put into place a number of activities to ensure top quality and to limit errors, omissions and to keep our biases low.

Level 1: At least two of the three individuals listed in the protocol (Drs. Popkin and Blum, and Sebastian Viana) will be available for all subject interactions at the Clinic. Having at least two researchers will increase the likelihood of collecting full and complete information and minimizing errors.

Level 2: Informed Consent (IC); Dr. Blum will be the person in charge of providing IC to each potential person. However, either Dr. Popkin or Sebastian Viana will sit as co-pilot in the room to provide backup and witness. This will help to ensure that each statement made to the potential subject is accurate and full and complete. Dr. Blum will work from a checklist to help ensure that he covers all pertinent points.

Level 3: Dr. Blum will create the subject database using Excel and will enter the data. Sebastian will take a number of random forms and enter it into a duplicate database. These two databases will be compared for differences. Each difference found will be investigated. If the difference rate is greater than 0.5%, more forms will be re-entered and compared.

Level 4: Laboratory Duplicates. Several labs will be run in duplication. This will include the glyphosate levels, D-lactate, and CRP measures. This will increase the accuracy of these data points and avoid potential incorrect conclusions. Since the sample size is small, an error could lead to an incorrect conclusion.

Level 5: Clinical observations. While Dr. Popkin has been a practicing physician for almost twenty-five years and has direct knowledge of each subject's medical history and conditions, we will use QC methods. First, we plan using several clinical outcome tools that have either been published or used in previous clinical trials. These tools or questionnaires will provide an excellent method for obtaining an excellent and thorough clinical picture. This will add to Dr. Popkin's observations. Secondly, Dr. Blum has extensive clinical experience and will be present at many of the interview sessions. This will add another mechanism for collecting clinical data.

Other levels of improving the Quality of the study will be added and documented as we progress.

#### **EXPECTED OUTCOMES of the STUDY and USE of RESULTS**

As a pilot, no strong conclusions can be made from eight subjects. Hopefully, the data will indicate there is enough rationale to mount a larger trial that will have enough robustness to be published and used scientifically. These trial data will be used for internal use only and no outside use is anticipated.

No publication of this data is expected.

The study was limited and can only be used for internal purposes within the company and cannot be relied upon or referred to in any manner to support claims of performance for marketing or other purposes. Further, our contract specifically provides **“any statements as to the performance of this study product, written, oral, or otherwise, must be approved by Dr. Popkin. This study is too small in**

**terms of numbers to make any general conclusions, even if the results are extremely positive.”** Therefore, we recommend that any reference to the study should only state the following:

**“In an effort to prove the efficacy of our Biome Medic product which is a compound of 4 individual ingredients, the company undertook a limited supervised study in the form of a double blind, placebo controlled clinical trial following IRB guidelines and supervised by respected clinicians. While the results were promising, the study results are only an indicator that further, broader, more in depth and longer-term studies are warranted. The limitations of the study include the small number (8) of subjects and the limited time (6 weeks). The company plans to conduct further more in-depth studies to confirm the results. “**

Any other references to the study are not authorized. We of course remain willing to work with you if you would like to make other references to the study to ensure they are consistent with the study's limitations.

This language has been forwarded to the IRB and FDA.

## Actual Results

### Glyphosate Testing

A priori levels of significance

- P value for significance was set at 0.10 due to the small sample size.

Subjects were screened for glyphosate.

- Twenty-two subjects were screened. The top eight screening values were selected for inclusion in the study.
- Subjects were randomized according to a randomization schedule based on Meinert.
- Appropriate product was issued to each subject.
- They were tested again at BASELINE, since several weeks had lapsed since their screening lab work in most cases.
- They were tested again and the six-week lab was used for analysis. Not all subjects had six-week data, so in two cases, four week data was used as their end-point.
- One control failed to participate to the level of minimum compliance and was subsequently dropped. The ninth highest screening level was used for inclusion. His six-week data point delayed the study by more than a month.

Active Product	Baseline	End-of-Study	Difference
1	1.13	0.72	0.41
2	2.32	0.16	2.16
3	2.25	0.71	1.54
4	2.14	0.55	1.59
5	1.71	0.43	1.28
Subtotal	9.55	2.57	6.98 / 5 = 1.40 73.1%
Control Product			
1	1.18	1.15	0.03
2	0.46	0.45	0.01
3	0.88	1.80	- 0.92
Subtotal	2.52	3.40	-0.88 / 3 = -0.29 -0.13
			P < 0.07 Non-parametric

### Interpretation

Those on product dropped their glyphosate an average of 1.40 ppb over the course of the study while those on an active control product actually had their glyphosate levels rise an average of 0.29 ppb. Non-parametric statistics for the difference of means produced a  $p < 0.07$  value.

This p value would not have been significant if the one control subject hadn't had their levels rise.

### C-Reactive Protein (CRP) Testing

Only those with clinically elevated levels of CRP were eligible for this arm of the testing, since moving within normal ranges is not clinically relevant.

Only two individuals on product and one control product subject met these criteria.

Product	Baseline	End-of-Study	Difference
1	4.7 mg/dl	1.3	3.4
2	3.4	0.7	2.7
Subtotal	8.1	2.0	6.1 = 75%
Control Product			
1	4.1 mg/dl	3.5	0.6 = 15%
			Significance cannot be assessed since one group was comprised of one subject

### Interpretation

Those on product dropped their CRP levels an average of 6.1 mg/dl over the course of the study while those on an active control product had their glyphosate level fall by 0.6 mg/dl. Non-parametric statistics cannot be run with sample sizes of one.

## Food Sensitivity Testing

We measured IgG levels against 90 different food antigens. Food sensitivity testing is a broad measure involving gut biome health, gut wall integrity, overall gut health, liver health, and immune system responses. This type of testing identifies those foods responsible for causing systemic inflammation, and we now recognize that inflammation is a major factor in the development of most chronic diseases, that include obesity, glucose metabolic conditions, gut conditions, arthritis, pain syndromes, vascular health including ischemic heart disease, cognitive decline including early dementia and Alzheimer disease, and many more. We felt this would be an excellent marker for broad-spectrum disease prevention and treatment.

Results were determined to be '0' meaning there was no reactivity or safe for consumption. In the reactivity range, there was '1' (mild), '2' (moderate), and '3' (severe).

Assessment was made in the following manner. Each food added to the subtotal, by adding the corresponding score.

For example, in the following result

<b>Food</b>	<b>Results</b>	<b>Points</b>
Apple	Safe	0
Brewer's yeast	Moderate	2
Carrot	Safe	0
Egg White	Severe	3
Salmon	Mild	1
Turkey	Safe	0
Watermelon	Mild	1
<b>Subtotal</b>		<b>7 points</b>

Points were calculated for the 90 foods at Baseline and again, at the end of the study. The aggregate are as follows:

Product				
	Baseline		End-of-Study	
Subject 1	Mild = 16	16 pts	Mild = 17	17
	Moderate = 6	12	Moderate = 6	12
	Severe = 1	3	Severe = 0	0
Subtotal		31 Pts		29 Pts
Difference				2 or 6.5%
Subject 2	Mild = 13	13	Mild = 10	10
	Moderate = 15	30	Moderate = 9	18
	Severe = 8	24	Severe = 5	15
Subtotal		67 Pts		43 Pts
Difference				24 or 35.8%
Totals for Product		98 Pts		26 Pts or 26.5%

Active Control				
	Baseline		End-of-Study	
Subject 1	Mild = 12	12	Mild = 14	14
	Moderate = 10	20	Moderate = 10	20
	Severe = 3	9	Severe = 2	6
Subtotal		41 Pts		40 Pts
Difference				1 or 2.4%
Subject 2	Mild = 16	16	Mild = 12	12
	Moderate = 12	24	Moderate = 13	26
	Severe = 3	9	Severe = 1	3
		49 Pts		41 or 16.3%
Totals for Controls		90 Pts		81 or 10%

Not Significant

**Interpretation:**

There were decreases for both sets of subjects, with the active product having a decrease by 16.5% over those taking the active control. While trending towards significance, it was not nearly enough given the four subjects.

**Adverse Events:**

Three individuals on active product reported significant gastrointestinal discomfort with the dosing regimen. Doses were cut in half for those subjects which alleviated these issues. These were classified as moderate reactions and reported to the IRB. There were no complaints made from those on the control product.

**Study Conclusions:**

In each of the three tests, those taking the Product outperformed those taking an active control product. The biggest gains were found with the CRP and with the glyphosate levels. Since the CRP data was comprised from only three subjects, it is difficult to make generalizations. The data for the glyphosate levels were very encouraging but again, there were only eight reporting subjects. These showed a non-parametric significance. The data for the food sensitivity testing, which implies both gut and immune health were also encouraging and with larger numbers, would be statistically significant given that the pattern holds.

The dosing clearly was a major concern since sixty percent of the subjects could not tolerate the intended dosing of 2 pills twice daily as a loading dose or even the maintenance dose of 1 pill twice daily. Even with reduced dosing, the results were positive.

**Study Disclaimer:**

**“In an effort to prove the efficacy of our Biome Medic product which is a compound of 4 individual ingredients, the company undertook a limited supervised study in the form of a double blind, placebo controlled clinical trial following IRB guidelines and supervised by respected clinicians. While the results were promising, the study results are only an indicator that further, broader, more in depth and longer-term studies are warranted. The limitations of the study include the small number (8) of subjects and the limited time (6 weeks). The company plans to conduct further more in-depth studies to confirm the results. “**

**Researchers:**

**Principal Investigator: James M. Blum, PhD**

**Chief Medical Director: Matthew C. Popkin, M.D.**