KGK synergize

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Pilot Study to Investigate the Effects of Humic Acid on Symptoms of Influenza

FINAL REPORT

Confidentially Prepared For:

Laub BioChemicals Corporation

Date: September 02, 2010

By:

KGK Synergize, Inc.
255 Queens Avenue
Suite 1440
London, Ontario
Canada N6A 5R8
Telephone: 519-438-9374
Facsimile: 519-438-8314

Medical Director
Dale Wilson, MD

TITLE PAGE

TITLE:	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Pilot Study to Investigate the Effects of Humic Acid on Flu Symptoms
STUDY IDENTIFICATION NUMBER:	KGK Study Code: 10HFHL
DATES OF STUDY:	January 27, 2010 – July 19, 2010
INVESTIGATIONAL PRODUCTS:	Humic Acid
INDICATION STUDIED:	Assess the efficacy of Humic Acid on flu symptoms through assessment of alleviation of symptoms.
STUDY PHASE:	Phase I
STUDY DESIGN:	Randomized, double-blind, placebo-controlled, parallel-group pilot study
KEYWORDS:	Humic Acid, Influenza
STUDY PERSONNEL:	
Sponsor	Laub BioChemicals Corporation 1401 Quail St., Suite 121 Newport Beach, CA 92660 USA
Sponsor Representative	Dr. Richard J. Laub, PhD President/CEO Laub BioChemicals Corporation 1401 Quail St., Suite 121 Newport Beach, CA 92660 USA 949-476-9883
CRO	KGK Synergize, Inc. Suite 1440, One London Place 255 Queens Ave. London, Ontario N6A 5R8 Canada 519-438-9374
Medical Director	Dale Wilson, MD KGK Synergize Inc. 519-438-9374 ext 250
Study Sites:	Advanced Research Institute, Inc. 3633 Little Rd., Suite 102 Trinity, Florida 34655 USA Veritas Research Corp. 14600 NW 60th Ave., Unit B Miami Lakes, Florida 33014 USA
Principal Investigators:	Sivakumar Amar, MD Yavir Escovar, MD
Sub-Investigators:	Jay Chowdappa, MD; Brian Hale, MD; Daniel Rodriguez, MD; Charles Webster, PA Julio Lora, MD
Date of Report:	September 02, 2010
Total Pages:	71 + Appendices A, B, C and D

This Study was performed in compliance with ICH Guideline for Good Clinical Practices (GCP), Current Step 4 version, dated June 10, 1996, including the archiving of essential documents.

SYNOPSIS

Name of Sponsor: Laub BioChemicals Corporation

Name of Finished Product: Humic Acid

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Investigate the Effects of Humic Acid on Flu Symptoms.

Medical Director: Dale Wilson, MD

Principal Investigators:

Sivakumar Amar, MD
Advanced Research Institute, Inc.

Yavir Escovar, MD
Veritas Research Corp.

Study Sites:

Advanced Research Institute, Inc
3633 Little Rd., Suite 102
Trinity, Florida 34655
USA

Veritas Research Corp
14600 NW 60th Ave., Unit B
Miami Lakes, Florida 33014
USA

Study Period: January 27, 2010 – July 19, 2010

Phase of Development: I

Objectives:
The primary objective of this Study was to assess the efficacy of Humic Acid on flu symptoms as assessed by the alleviation of symptoms after 7 and 14 days of treatment in adults with influenza A or B.

Methodology:
This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group study with a single 14-day treatment period to assess the efficacy of Humic Acid on flu symptoms in adults. This Study was conducted at two sites in the US: Advanced Research Institute, Inc. (Trinity, FL) and Vertitas Research Corp. (Miami Lakes, FL). The Study was managed by KGK Synergize, Inc.

At Screening, a Subject Information and Consent Form was given to each potential Subject. The Subject read the information and was given the opportunity to seek more information if needed. The Subject was

also provided with the option of taking the consent form home for review prior to making his/her decision. If agreeable, the Subject signed the Consent form and received a duplicate. Once consent was obtained, screening proceeded. After the Subject had signed the Informed Consent form, a Screening Number was assigned sequentially and entered into the Screening and Enrollment Log. Screening Numbers were allocated in the chronological order of the Subject's signing the Informed Consent form. Eligibility was determined based on inclusion and exclusion criteria. Medical history and concomitant therapies were reviewed and vital signs (heart rate, blood pressure) were taken. Physical examination (excluding breast, rectal/vaginal examination), urine pregnancy test for women of childbearing potential, self-administered questionnaires (symptoms and VAS) and laboratory tests (haematology, chemistry, and immunological markers) were determined and a urine pregnancy test was performed.

Eligible Subjects were randomized on the same day to Humic Acid or Placebo via the Randomization Schedule provided to the Investigator. Subject Randomization Numbers were to be allocated in the order listed on the Randomization Schedule. After all visit assessments were performed, Subjects were dispensed the Study Product. Subjects received one of the following treatment regimens: Humic Acid as 2 tablets TID for a total of 6 tablets daily for 14 days, or Placebo as 2 tablets TID for a total of 6 tablets daily for 14 days. Subjects were instructed in detail by site personnel about the dosing regimen. The first dose of Study Product was to be taken the day after Visit 1 (Treatment Day 1). Paper diaries and electronic thermometers were provided to the Subjects. Diaries were used by Subjects to record daily symptom scores, daily oral temperature, and Investigational Product use, concomitant therapy use including treatments taken for symptoms, and changes in health status including adverse effects. Subjects were allowed to use concomitant therapies for the treatment of symptoms (i.e., antipyretics, expectorants, throat lozenges). Subjects were asked to refrain from taking acetaminophen, aspirin, ibuprofen or NSAID within 4 hours prior to temperature readings. Subjects were scheduled to return to the clinic for follow-up at Days 7 and 14.

Subjects returned to the clinic for Visit 2 on Day 7 (± 2 days). Any remaining Investigational Product and packaging were returned and a new supply of product was dispensed. Subjects returned their diaries and received a new diary. During Visit 2, each Subject's diary, concomitant therapies and adverse events were reviewed. Compliance was calculated; vital signs, self-administered VAS questionnaire and laboratory tests (haematology and immunological markers) were performed and recorded. The next visit was scheduled for Day 14 (± 2 days).

Subjects returned to the clinic for Visit 3 on Day 14 (± 2 days). Any remaining Investigational Product and packaging were returned. Subject diaries were also returned. During this visit the Subject's diary, concomitant therapies and adverse events were reviewed. Compliance was calculated; vital signs, self-administered VAS questionnaire and laboratory tests (haematology, chemistry and immunological markers) were performed and recorded during this visit.

Number of Patients Planned: 40

Number of Patients Analyzed: 37

Investigational Products, Dose and Mode of Administration:
The Investigational Product was provided by the Sponsor. The manufacturing process was performed under GMP requirements and control. The Investigational Product was carefully stored at the Study site in a lockable, limited access area, in compliance with pertinent regulations. Only authorized personnel had access to the Investigational Product. The bottles were stored at room temperature between 15-30°C and were not exposed to direct sunlight or heat.

The Investigational Product was labeled according to the requirements of ICH-GCP guidelines and applicable local regulatory guidelines. Investigational Product was randomized and coded.

Each tablet contained:

Active Ingredient:
Humic Acid 250 mg

Excipients (Inactive Ingredients):
Dextrose, sucrose fatty acid ester, silicon dioxide USP/FCC, and sodium starch glycolate USP.

Subjects were instructed to begin taking the Investigational Product the day following their randomization visit (Treatment Day 1). Subjects were instructed to take 2 tablets three times daily, preferably with meals. If a Subject missed a dose they were instructed to take that dose as soon as they remembered. Subjects were instructed not to consume more than three doses in a single day. Subjects were instructed to return all original packaging and any unused tablets at the next Study visit and were instructed to record tablet use in their Subject treatment diary.

Reference Therapy, Dose and Mode of Administration:
Placebo tablets were manufactured, stored and administered in a similar manner as the active Investigational Product.

Each Placebo tablet contained:

Dextrose, sucrose fatty acid ester, microcrystalline cellulose, and sodium starch glycolate USP.

Manufacturer of Investigational Product:
Laub BioChemicals Corporation
1401 Quail St., Ste. 121, Newport Beach, CA 92660 USA

Criteria for Evaluation:
Criteria for evaluation included the effect of Humic Acid on flu symptoms as assessed by the alleviation of symptoms after 7 and 14 days of treatment in adults with influenza A or B. Additional outcomes of interest were Visual Analogue Scale (VAS) 0-100 mm to determine Subject's ability to perform usual activities, doses of concomitant therapies for symptom treatment, immunological markers (WBC differential, CD4+, CD8+, TNF-α, IL-8), vital signs, and adverse events.

Statistical Analysis:
Subjects completing at least one post-randomization visit were included in analysis of efficacy. All Subjects known to have started treatment were included in analysis of safety. Between-group differences in the number of withdrawals were compared using Fisher's exact test. For primary and secondary outcomes, between-group comparisons of screening/baseline data and data collected as scores were made using analysis of T-tests. Within-group comparisons were made using paired T-tests. For continuous variables, including temperature, WBC differential, cytokines and CD4+ and CD8+ cell counts, analysis of covariance was performed using available screening/baseline data as a covariate. Safety data and adverse events were summarized by treatment group. The number of individuals experiencing adverse events was compared using Fisher's exact test. Between-group comparisons at screening for vital signs, haematology parameters and blood chemistry parameters were made using T-tests. For comparisons at Weeks 1 and 2, analysis of covariance was performed using available

screening/baseline data as a covariate. Compliance, defined as the number of pills taken in the two groups, was compared using a T-test.

Statistical analysis was performed using SAS Version 9.1. Probability values less than 0.05 were considered statistically-significant.

Summary and Conclusions:

Efficacy Results:
Subjects on Humic Acid reported higher scores for cough, fever, runny nose, stuffy nose, aches, chills, sneezing, earaches and fatigue on Day 1. After supplementation for 7 days with Humic Acid, symptom scores improved by a greater percentage than did those for Subjects taking Placebo for the same duration for cough (61.9% vs. 36.8%), fever (91.7% vs. 81.8%), runny nose (66.7% vs. 62.5%), stuffy nose (66.7% vs. 62.5%), aches (86.4% vs. 62.5%), chills (91.7% vs. 66.7%), sneezing (70.6% vs. 61.5%) and fatigue (80.0% vs. 54.5%). Mean scores for Subjects on Humic Acid were also lower than for those on Placebo after 7 days of treatment for cough, fever, aches, chills and fatigue in spite of being worse than Placebo on Day 1.

There were no significant statistical differences between groups with respect to Visual Analogue Scale (VAS) scores at Screening or after 1 or 2 weeks of supplementation with Humic Acid or Placebo. Within groups, significant increases in VAS scores were demonstrated from Baseline to Weeks 1 and 2 for Subjects in both the Humic Acid and Placebo groups ($p \leq 0.001$), with greater improvement found from Screening to Week 2 in Subjects on Humic Acid as compared with Placebo (44.5% vs. 38.7%). The improvement in VAS scores for Subjects on Humic Acid coincided with a greater lessening of their flu symptoms from the beginning of the Study to Day 7 in comparison with those on Placebo over the same time-span.

There were no significant statistical differences between groups with respect to mean temperatures of Subjects at Screening or after 1 or 2 weeks of supplementation with Humic Acid or Placebo. Oral temperature was significantly reduced in both Humic Acid and Placebo groups from Screening to Week 1 ($p < 0.001$ and $p = 0.037$, respectively), and from Screening to Week 2 ($p = 0.003$ and $p = 0.009$, respectively). However, the reduction in temperature was greater for Subjects taking Humic Acid within the first week of treatment as compared to Subjects taking Placebo (-0.7°C vs. -0.4°C).

There were no significant statistical differences between groups with respect to absolute CD4+ and CD8+ cell counts at Screening or after 1 or 2 weeks of supplementation with Humic Acid or Placebo. However, there was a trend toward an increase in CD4+ cell counts in Subjects on Humic Acid and a decrease in CD4+ cell counts in Subjects on Placebo after 2 weeks of supplementation. A similar shift was seen in CD8+ cell counts.

There was a trend toward Subjects randomized to Placebo having higher levels of serum TNF-α at Screening ($p = 0.088$). After 2 weeks of supplementation, serum concentrations reduced in both groups and reached statistical significance between groups ($p = 0.046$). Subjects on Humic Acid had a mean reduction from 1.5 pg/mL at screening to 1.1 pg/mL after 2 weeks of supplementation, while Subjects on Placebo had a mean reduction from 2.8 pg/mL at Screening to 2.6 pg/mL after 2 weeks of supplementation. IL-8 decreased in both groups from Screening to Week 2; however, there were no significant statistical differences between groups.

Safety Results:
A total of 18 adverse events were reported during the Study. Of these, 17 events occurred in 9 Subjects (47.4%) on Humic Acid and 18 events occurred in 6 Subjects (33.3%) on Placebo.

A total of 16 adverse events were reported during the Study having a possible or probable relationship to the Test Article as assessed by the Investigator while blinded to treatments. A greater number of Subjects reported diarrhea (3 vs. 2), dizziness (1 vs. 0), nausea (1 vs. 0), vomiting (1 vs. 0) and stomach cramps (1 vs. 0) on Humic Acid as compared to Placebo. A greater number of Subjects reported stomach aches (1 vs. 0) and stomach discomfort (1 vs. 0) in the Placebo group as compared to the Humic Acid group. It should be noted that these adverse events may also have been flu symptoms; thus, conclusions cannot be drawn regarding adverse event relationships to Test Article. Three Subjects demonstrated an elevation in ALT and AST (2 on Placebo and 1 on Humic Acid), which led to Test-Article discontinuation in two cases. Potential factors that may cause high AST and ALT levels include alcohol consumption within 24 hours of having these blood markers tested; thus, firm conclusions cannot be made regarding the relationship of these events to Test Product since a higher number of Subjects experienced the same event in the Placebo group as compared with the Humic Acid group.

There were no significant statistical differences between groups with respect to measures of blood pressure, heart rate, haematological or general chemistry parameters at any time-point assessed during the Study.

Conclusion:

In conclusion, Humic Acid demonstrated clinically-noteworthy efficacy on influenza viral infection in the 2010 flu season by improving flu-related symptoms, cytokine response, immune-system modulators CD4+ and CD8+, and VAS scores when provided as 6 x 250-mg tablets daily for 14 days within the demographic of Subjects studied.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS AND SYMBOLS

AE	Adverse event
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
CBC	Complete blood count
CD4+	T helper cells
CD8+	Cytotoxic T cells
Cl	Chloride
COPD	Chronic obstructive pulmonary disease
°C	Degrees Celsius
°F	Degrees Fahrenheit
EDTA	Ethylenediaminetetraacetic acid
e.g.	For example
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
>	Greater than
HIV	Human immunodeficiency virus
ICH	International conference of harmonization
i.e.	In other words
IL-8	Interleukin-8
K	Potassium
kg	Kilogram
mg	Milligram
mL	Milliliter
mm	Millimeter
mm Hg	Millimeters of mercury
Na	Sodium
NSAID	Non-steroidal anti-inflammatory drug
ppm	Parts per million
%	Percent
RNA	Ribonucleic acid
SAE	Serious adverse event
SST	Serum separating tube
TID	Three times daily
TNFα	Tumor necrosis factor-alpha
ULN	Upper limit of normal
VAS	Visual analogue scale
WBC	White blood cell
WHO	World Health Organization

ETHICS

This Study was reviewed by an Institutional Review Board (IRB). Unconditional approval was granted on January 19, 2010 by Institutional Review Board Services, Aurora, Ontario.

This Study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

Informed consent was obtained from each Subject at the Screening Visit prior to any Study-related activities. A copy of the Patient Information and Consent Form is provided in Appendix B.

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This clinical trial was managed by KGK Synergize Clinic, London, ON, Canada, under the supervision of its Medical Director, Dale Wilson, MD.; and was conducted at two sites in Florida, USA (Advanced Research Institute, Inc., Trinity, FL and Veritas Research Corp., Miami Lakes, FL) under the supervision of the Principal Investigators Sivakumar Amar, MD (Advanced Research Institute, Inc.) and Yavir Escovar, MD (Veritas Research Corp.). Statistical analysis was conducted by Larry Stitt, MSc and the report was authored by Malkanthi Evans, PhD.

1. INTRODUCTION

Influenza, commonly referred to as the flu, is an acute viral infection caused by RNA viruses of the family Orthomyxoviridae (the influenza viruses) (Eccles, 2005). Influenza viruses are known for high morbidity and mortality in humans and animals, and are a cause of acute respiratory diseases (WHO, 2009). Epidemics occur yearly during winter and, while most people recover from influenza, large numbers who need hospitalization, and many die from the disease. In United States, yearly on average, 5% to 20% of the population becomes infected with the influenza virus, more than 200,000 people are hospitalized from influenza-related complications, and approximately 36,000 people die from influenza-related causes (Centers for Disease Control and Prevention, 2009). Influenza causes serious public health and economic problems as a result of absence from the work force and productivity losses.

There are three types of seasonal influenza–A, B and C. These types are further classified according to different kinds and combinations of virus surface proteins. Influenza is characterized by a sudden onset of high fever, chills, cough, headache, muscle and joint pain, weakness, general discomfort, sore throat and runny nose (Brankston *et al.,* 2007); and is often confused with the common cold but is more severe and is caused by a different type of virus (Eccles, 2005).

The most effective way to prevent influenza and related health consequences of the illness is by vaccination. The drawback to the vaccine is that it is most effective when circulating viruses are well-matched with vaccine viruses (Horwood and Macfarlane, 2002). Antivirals such as Zanamivir and Oseltamivir (commonly known as Tamiflu) have been shown to inhibit both influenza A and influenza B virus replication *in vitro* (Blick *et al.*, 1998; Sidwell *et al.*, 1998; Li *et al.*, 1998). Further, Amantadine and Rimantadine have been used in the prevention and treatment of influenza viruses (Lu *et al.*, 2002). Annual epidemics are caused by antigenic shifts in influenza viruses, which results in new virus subtypes (Kilbourne, 1975). Because antigenic shifts occur unpredictably, the general population has no immunity to the new subtypes and effective vaccines cannot be prepared in advance. As influenza viruses are constantly changing, the success of the vaccines is often in question. Further limitations are related to adverse effects of vaccines in some recipients, as well as the fear of vaccine causing the flu or other severe adverse health effects. As a result, approximately 15-20% of the population refrains from vaccination. An effective alternative treatment, medicine, or combination therapy for the treatment of influenza without side effects is therefore desirable.

Previous scientific studies on Humic Acid have shown that it exhibits anti-inflammatory (Kuhnert *et al.*, 1982) and antiviral properties (Mentel *et al.*, 1983). Humic Acid is a high molecular-weight discotic molecule that is isolated *inter alia* from soil. Humates act as nutrients and media additives for soil microflora, and for the production of antibiotics in the soil (Huck *et al.*, 1991). Humic substances have been shown to exhibit antiviral properties against rhinovirus (Sydow *et al.*, 1986); recent studies have also shown that Humic Acid impairs the attachment of human immunodeficiency virus (HIV) (Laub, 2000; Laub, 1995), herpes simplex virus types 1 and 2 (Helbig, *et al*, 1987; Kloecking, 1991), influenza types A and B, and other respiratory tract infections (Laub, 2000; Sydow *et al.*, 1986). Previous studies have additionally suggested the broad antibacterial potential of natural and synthetic Humic Acids with varying degrees of sensitivity to test organisms. In one study the sensitivity ranged from 2500-1250 microorganisms/mL with natural Humic Acid, and 39 microorganisms/mL with synthetic hydroquinone Humic Acid (Ansorg and Rochus, 1978). Recent studies have additionally shown the positive effects of humus extract in Ayu fish against *Flavobacterium psychrophilum* infection (cold-water disease) (Nakagawa *et al.,* 2009).

The mechanism of action of Humic Acid responsible for the inhibition of viral infection is believed to be the prevention of attachment of virus particles onto host cells (viral fusion inhibition), which in turn limits viral replication (Laub, 1999). *In vitro* studies of Humic-like substances, for example, the oxidative polymer of protocatechuic acid (OP-PCA), have demonstrated the inhibition of replication of influenza virus A/WSN/33 (H1N1) in Madin-Darby canine kidney (MDCK) cells at concentrations of no cytotoxicity. It has also been demonstrated that Humic Acid inhibits the endonuclease activity of viral RNA polymerase (Lu *et al.*, 2001). (Influenza viral RNA polymerase plays an important role in viral RNA synthesis, which occurs after a virus has penetrated a host cell.) While Humic Acid is effective and may be added at any time after viral attachment, higher inhibitory effects are generally found when added at or prior to the stage of virus-cell fusion.

While previous *in vitro* and live-animal studies have demonstrated the therapeutic potential of Humic Acid, live-animal acute toxicity studies sponsored by Laub BioChemicals Corporation have additionally shown the material to be complete safety at levels of up to 50 mg/kg body weight. Thus, concentrations in the range of 50-2000 parts per million (ppm) are efficacious, yet not cytotoxic (Schiller *et al.*, 1979).

This Study was the first test of the effects of Humic Acid on flu symptoms in humans; the results provide valuable information on influenza prevention and treatment.

2. STUDY OBJECTIVES

The primary objective of this Study was to assess the efficacy of Humic Acid on flu symptoms as gauged by the alleviation of symptoms after 7 and 14 days of treatment in adults with influenza A or B. This was determined by the use of a daily diary to assess the following symptoms during the trial on a 4-point scale (0=absent, 1=mild, 2=moderate, 3=severe):

- cough
- fever
- runny nose
- stuffy nose
- aches and pains
- headache
- chills
- sneezing
- earaches
- fatigue

Additional endpoints included:

- Visual Analogue Scale (VAS) 0-100 mm, for ability to perform usual activities
- Doses of concomitant therapies for symptom treatment
- Immunological markers (WBC differential, CD4+, CD8+, TNFα, IL-8)

3. INVESTGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN-DESCRIPTION

The Study design is depicted in Figure 1.

Figure 1: Study Diagram

TREATMENT GROUPS

Number of Subjects	Interventions
20	Humic Acid 250 mg/tablet
20	Placebo
40	**Total**

This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group efficacy pilot Study. The Study consisted of a single 14-day treatment period. Screening and randomization occurred on the same day.

The planned sample size for the Study was 40 Subjects, with 20 Subjects randomized equally to each of the two Study arms. The Subjects were recruited over the 2010 Spring flu season.

Subjects were randomized to one of the two treatment groups: Humic Acid 250 mg or Placebo in a 1:1 ratio based on a randomization schedule.

In order to evaluate primary and secondary endpoints, Study assessments were conducted at Baseline, Day 7 and Day 14. The Study was conducted at two sites in the US.

At screening, a Patient Information and Consent Form was given to each potential Subject. The Subject read the information and was given the opportunity to seek more information if needed. The Subject was also provided with the option of taking the Consent Form home for review prior to making his/her decision. If agreeable, the Subject signed the Consent Form and received a duplicate. Once consent was obtained, screening proceeded. After the Subject had signed the Informed Consent, a Screening Number was assigned sequentially and entered into the Screening and Enrollment Log. Screening Numbers were allocated in chronological order of the Subject's signing the Informed Consent. Eligibility was determined based on inclusion and exclusion criteria. Medical history and concomitant therapies were reviewed and vital signs (heart rate, blood pressure) were taken. Physical examination (excluding breast, rectal/vaginal examination), urine pregnancy test for women of childbearing potential, self-administered questionnaires (symptoms and VAS) and laboratory tests (haematology, chemistry, and immunological markers) were determined and a urine pregnancy test was performed.

Eligible Subjects were randomized on the same day to Humic Acid or Placebo via the Randomization Schedule provided to the Investigator on the same day. Subject Randomization Numbers were allocated in the order listed on the Randomization Schedule. After all visit assessments were performed, Subjects were dispensed the Study Product. Subjects received one of the following treatment regimens:

- Humic Acid as 2 tablets TID for a total of 6 tablets daily for 14 days
- Placebo as 2 tablets TID for a total of 6 tablets daily for 14 days

Subjects were instructed in detail by site personnel about the dosing regimen. The first dose of Study Product was to be taken the day after Visit 1 (Treatment Day 1). Paper diaries and electronic thermometers were provided to the Subjects. Diaries were used by Subjects to record daily symptom scores, daily oral temperature, Investigational Product use, concomitant therapy use including treatments taken for symptoms, and changes in health status including adverse effects. Subjects were allowed to use concomitant therapies for the treatment of symptoms (i.e., antipyretics, expectorants, throat lozenges). Subjects were asked to refrain from taking acetaminophen, aspirin, ibuprofen or NSAID within 4 hours prior to temperature readings. Subjects returned to the clinic for follow-up at Days 7 and 14.

Subjects returned to the clinic for Visit 2 on Day 7 (± 2 days). Any remaining Investigational Product and packaging were returned and a new supply of product was dispensed. Subjects returned their diaries and received a new diary. During Visit 2, each Subject's diary, concomitant therapies and adverse events were reviewed. Compliance was calculated, vital signs, self-administered VAS questionnaire and laboratory tests (haematology and immunological markers) were performed. The next visit was scheduled for Day 14 (± 2 days).

Subjects returned to the clinic for Visit 3 on Day 14 (± 2 days). Any remaining Investigational Product and packaging were returned. Subject diaries were also returned. During this visit the Subject diary, concomitant therapies and adverse events were reviewed. Compliance was calculated, vital signs, self-administered VAS questionnaire and laboratory tests (haematology, chemistry and immunological markers) were performed during this visit.

Table 1: Schedule of Assessments

Procedures/Assessments	Visit 1	Visit 2	Visit 3
	Screen/Baseline		End of Study
	Week 0	Week 1	Week 2
	Day 0	Day 7 ± 2	Day 14 ± 2
Informed consent	X		
Review inclusion/exclusion criteria	X		
Review medical history	X		
Review concomitant therapies	X	X	X
Vital signs (heart rate, blood pressure, temperature)	X	X	X
Urine pregnancy test as required	X		
Physical exam	X		
Laboratory tests: General Chemistry electrolytes (Na, K, Cl), creatinine, AST, ALT, GGT, bilirubin	X		X
Laboratory tests: Hematology CBC, T lymphocyte counts	X	X	X
Laboratory tests: Cytokines TNFα, IL-8	X	X	X
Symptoms questionnaire	X		
VAS (self-administered)	X	X	X
Dispense Investigational Product	X	X	
Dispense thermometer	X		
Dispense diary	X	X	
Daily symptoms scores recorded	X	X	X
Daily oral temperature recorded	X	X	X
Return Investigational Product		X	X
Return/review Subject diary		X	X
Compliance calculated		X	X
Review adverse events		X	X

3.2 SELECTION OF STUDY POPULATION

The target population for this Study consisted of 40 adults with influenza A or B.

The Study was conducted on both male and female Subjects of any ethnicity. Each Subject had to fulfill the inclusion criteria listed in Section 3.2.1. Subjects were not included in the Study if they met any of the exclusion criteria listed in Section 3.2.2.

3.2.1 Inclusion Criteria

1. Male or female, age 18 years or older
2. If female, Subject is not of childbearing potential. Defined as females who have had a hysterectomy or oophrectomy, bilateral tubal ligation or were post-menopausal (natural or surgically with > 1 year since last menstruation)

   –OR:
   Female Subjects of childbearing potential must agree to use a medically-approved method of birth control and have a negative urine pregnancy test result. Acceptable methods of birth control included:
   - double-barrier method (condoms with spermicide or diaphragm with spermicide)
   - 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)
   - intrauterine devices
   - vasectomy of partner
   - abstinence
3. Positive diagnostic testing for influenza A or B by using rapid influenza antigen test (nasopharyngeal swabs)
4. Illness, as defined by onset or presence of respiratory symptom (cough, sore throat, nasal symptoms, sneezing) and one of the following symptoms beginning within 48 hours before Study enrolment:
   - fever ≥ 38.0°C (≥ 100.4°F) taken orally, or Subject report of fever within 24 hours prior to screening
   - constitutional symptom [headache, myalgia (muscle pain), sweats/chills, fatigue]
5. Available for all visits scheduled in the Study
6. Receipt of any vaccine against influenza (based on verbal confirmation by the Subject) for current season was allowed
7. Agreement to comply with Study procedures and Test-Article consumption
8. Gave voluntary, written, informed consent to participate in the Study

3.2.2 Exclusion Criteria

1. Women who were pregnant, breastfeeding, or planning to become pregnant during the course of the trial
2. Experienced any acute disease or infection requiring systemic antibiotic or antiviral therapy within the past 7 days
3. Cancer chemotherapy/radiation treatment within the 3 months prior to enrolment
4. Receipt of blood or blood products and/or plasma derivatives or any immunoglobulin preparation within 4 months prior to enrolment

5. Clinically-significant acute respiratory distress
6. Chronic obstructive pulmonary disease (COPD)
7. Severe asthma (at the discretion of the Principal Investigator)
8. Known or suspected impairment/alteration of the immune system or immunocompromised (in the past 5 years)
9. Disorders of coagulation
10. Surgery planned during the Study period
11. History of drug or alcohol abuse
12. Participation in a clinical research trial within 30 days prior to randomization
13. Allergy or sensitivity to Study supplement ingredients
14. Individuals who were cognitively impaired and/or who were unable to give informed consent
15. Any other condition which in the Investigator's opinion may have adversely affected the Subject's ability to complete the Study or its measures or which may have posed significant risk to the Subject

3.2.3 Removal of Patients from Therapy or Assessment

The following criteria were used for determination of Subject removal during the course of the trial:

Personal reasons

Subject discontinuation was to be considered at the discretion of the Principal Investigator. The circumstances of any discontinuation were to be documented in detail. If possible, the evaluations planned for the end of Study were to be carried out at the time when the Subject was withdrawn from the Study. Any Subject leaving the Study prematurely was not replaced by another. Criteria for removal of Subjects from the Study included:

Personal reasons

As stated in the Informed Consent Form, a Subject could withdraw from the Study for any reason at any time.

Clinical judgment of physician

A Subject could have been withdrawn from the Study if, in the opinion of the Principal Investigator, it was not in the Subject's best interest to continue. This included but was not limited to adverse events or serious adverse events related to the Investigational Product causing clinically-significant illness; the need for prohibited concomitant medication; female Subjects who became pregnant during the course of the trial.

Protocol violation

Any Subject found to have entered this Study in violation of the protocol was to be discontinued from the Study at the discretion of the Principal Investigator. This included any Subject found to have been inappropriately enrolled (did not meet eligibility criteria). Subject non-compliance included either not showing up for Study visits, not taking Investigational Product as directed, or refusing to undergo Study visit procedures. Subjects who were found to be taking prohibited medications or supplements without the knowledge of the Principal Investigator were also to be withdrawn. Any major protocol deviations (i.e., those that increased the risk to Subjects and/or compromise the integrity of the Study or its results) would also have resulted in Subject discontinuation.

3.3 TREATMENTS

3.3.1 Treatments Administered

The Investigational Product was provided by the Sponsor. The manufacturing process was done under GMP requirements and control. The Investigational Product was carefully stored at the Study site in a lockable, limited-access area, in compliance with pertinent regulations. Only authorized personnel had access to the Investigational Product. The bottles were stored at room temperature between 15-30°C and were not exposed to direct sunlight or heat.

The Investigational Product was labeled according to the requirements of ICH-GCP guidelines and applicable local regulatory guidelines. Investigational Product was randomized and coded. The Investigator was provided with a Randomization List indicating the order of randomization. Each Subject was assigned a Randomization Code according to the order of the Randomization List.

3.3.2 Identity of Investigational Products

The two treatments provided in this Study were Humic Acid 250 mg and Placebo control.

3.3.2.1 Humic Acid

The Study medication Humic Acid was provided by Laub BioChemicals Corporation. Each tablet contained:

Active Ingredient:
Humic Acid, 250 mg

Excipients (Inactive Ingredients):

Dextrose, sucrose fatty acid ester, silicon dioxide USP/FCC, and sodium starch glycolate USP.

3.3.2.2 Placebo

Placebo tablets were manufactured, stored and administered in a similar manner as the Study dietary supplement, and were provided by Laub BioChemicals Corporation. Each tablet contained: dextrose, sucrose fatty acid ester, microcrystalline cellulose, and sodium starch glycolate USP.

3.3.3 Method of Assigning Patients to Treatment Groups

Subjects were assigned to treatment groups (order of treatments) using computer-generated randomization tables (www.randomization.com). Subjects were randomized into 28 blocks of 2 for a total of 56 Randomization Numbers. The list was divided and sent with products to each site based on site performance with respect to enrolment; enrolment was competitive.

3.3.4 Blinding

Blinding was considered necessary for this Study and was feasible. No known supplement side effects were likely to reveal patient classification. In order to protect blinding, capsule bottles were labeled with individual unique Randomization Numbers and a Treatment Number, labeled according to the order to be received. The Investigator was provided with sealed envelopes for each Randomization Code. These envelopes were to remain sealed except in the event of an emergency. In the event that an AE was considered serious and related to the Investigational Product, the blind would have been broken for that individual Subject, preventing the premature unblinding of all other Subjects. Notification of unblinding was to be reported to the Study Sponsor within 24 hours.

Neither the Subject nor Investigator nor research staff were aware of which treatment sequence order the Subject was assigned. Interim analysis was not performed and there were no serious adverse events which occurred during the Study and thus no premature unblinding occurred.

3.3.5 Timing of Doses

The Study Product was supplied in the form of tablets. Subjects were instructed to take 2 tablets three times daily (TID), preferably with meals. Subjects were instructed to begin taking the Study Product on the day following their randomization visit (Treatment Day 1). If a Subject missed a dose, they were instructed to take it as soon as they remembered that day, and were also instructed not to take more than 3 doses in a single day.

3.3.6 Prior and Concomitant Therapy

The use of antibiotic or antiviral therapies within seven days of randomization was prohibited. Subjects who had received immunosuppressive therapies in the past five years or chemotherapy/radiation treatment within three months prior to screening were not enrolled into this Study. Birth control was allowed during the Study. Subjects who were currently taking prescribed birth control agreed to maintain their current method and dosing regimen during the course of the Study.

Subjects were allowed to use concomitant therapies for the treatment of symptoms (i.e., antipyretics, decongestants, expectorants, throat lozenges). Subjects were asked to refrain from taking acetaminophen, aspirin, ibuprofen or NSAID within 4 hours prior to temperature readings.

3.3.7 Treatment Compliance

Treatment compliance was assessed by counting the returned tablets at each visit. Compliance was calculated by determining the number of tablets taken divided by the number of tablets expected to have been taken per the following formula:

$$\frac{number\ of\ tablets\ taken}{number\ of\ tablets\ expected\ to\ be\ taken} \times 100\%$$

Subjects who were found to be less than 80% compliant with Test-Article usage were counseled by a Study team member and counseling was documented. Subjects who were found to be less than 70% compliant with Test-Article usage at any two consecutive Study visits were withdrawn.

3.4 EFFICACY AND SAFETY VARIABLES

3.4.1 Efficacy and Safety Measurements Assessed

Efficacy Variables:
In order to assess the efficacy of Humic Acid on flu symptoms, Subjects completed a daily diary to assess the following symptoms during the trial on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe):

- cough
- fever
- runny nose
- stuffy nose
- aches and pains
- headache
- chills
- sneezing
- earaches
- fatigue

Additionally, a Visual Analogue Scale (VAS, 0-100mm) was completed to determine the ability of Subjects to perform usual activities. Doses of concomitant therapies for symptom treatment were also recorded as a measure of efficacy. Other efficacy variables included WBC differential, CD4+ and CD8+ cell counts, and serum concentrations of TNF-α and IL-8.

Whole blood was collected into EDTA tubes for CBC (including WBC differential) and T-lymphocyte counts (CD4+, CD8+). Serum was generated from blood collected into SST tubes for analysis of TNF-α and IL-8. Laboratory tests were conducted at Granite Diagnostic Laboratories, Inc. (Palm Harbor, FL) and Allied Research International Clinical Laboratory (Miami Gardens, FL) with the exception of the cytokines TNF-α and IL-8, which were analyzed at KGK Synergize, Inc., London, ON. TNF-α (BD Biosciences, Cat. No. 555212), and IL-8 (BD Biosciences, Cat. No. 555244) were analyzed by EIA following manufacturer's instructions. Urine pregnancy tests were performed at clinic sites. All tests were conducted using standard procedures.

Safety Variables:
Systolic and diastolic blood pressure and heart rate were measured at Screening and after 1 and 2 weeks of treatment as a measure of safety. Further, haematology and general clinical chemistry tests (including liver and kidney function tests, glucose, and electrolyte balance) were performed to monitor Subject safety at Screening and after 1 and 2 weeks of treatment. Briefly, serum was generated from blood collected into SST tubes for electrolytes (Na, K, Cl), glucose, creatinine, AST, ALT, GGT and bilirubin. Laboratory tests were conducted at Granite Diagnostic Laboratories, Inc. (Palm Harbor, FL) and Allied Research International Clinical Laboratory (Miami Gardens, FL)

Adverse events were reported during the Study for assessment of the tolerability of Humic Acid. An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation Subject who had been administered an Investigational Product and which did not necessarily have a causal relationship to the treatment. An AE was 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

was considered related to that product. Pre-existing conditions that worsened during the Study were to be reported as AEs.

During the Study, Subjects recorded adverse effects in their Subject diary. At each visit the Subject was asked "Have you experienced any difficulties or problems since I saw you last"? Any adverse events (AEs) were documented and recorded in the Study Record and were classified according to description, duration, intensity, frequency, and outcome. The intensity of AEs was graded on a three-point scale (mild, moderate, severe). The causality relationship of Investigational Product to adverse event was assessed by the Investigator as:

Not related: no temporal relationship to Investigational Product administration or there is a reasonable causal relationship between non-Investigational Product, concurrent disease or circumstance and the AE.

Unlikely: there is a temporal relationship to Investigational Product administration but there is no reasonable causal relationship between the Investigational Product and the AE.

Possible: there is a reasonable relationship between the Investigational Product and AE. Dechallenge information is lacking or unclear.

Probable: there is a reasonable relationship between the Investigational Product and AE. The event responds to dechallenge.

Most probable: there is a reasonable relationship between the Investigational Product and AE. The event responds to withdrawal of Investigational Product (dechallange) and recurs with rechallenge when clinically feasible.

A serious adverse event (SAE) was defined as any experience that suggested a significant hazard, contraindication, side effect or precaution. An SAE was any AE that resulted in any of the following outcomes:

- Death
- A life-threatening adverse event
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly/birth defect in the offspring of a Subject who received the Study treatment
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the Subject 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.

3.4.2 Drug Concentration Measurements

Measurements of blood concentrations of Humic Acid were not conducted during this Study.

3.5 DATA QUALITY ASSURANCE

Electronic Case Report Forms (ECRF) were verified against source documents by KGK's Clinical Monitor to ensure accuracy of data entry. Protocol compliance, adherence to GCP guidelines, and Investigational Product accountability were also confirmed.

3.6 STATISTICAL METHODS PLANNED AND DETERMINATION OF SAMPLE SIZE

3.6.1 Statistical and Analytical Plans

The distribution of baseline characteristics in the two groups was to be compared descriptively. Analysis of efficacy was to include all Subjects completing at least one follow-up visit post randomization. For analysis of symptom scores, there was to be no imputation of missing data. The average score was to be based on the available number of days of data. Treatment-group comparisons for primary and secondary outcomes were to be made using the ANOVA (analysis of variance) model. Safety analysis was to include all Subjects randomized to treatment. Safety analysis was to include parameters of haematology, general chemistry, and adverse events. Compliance with Investigational Product usage and the usage of concomitant medications was to be compared between groups using Chi-square test. Categorical data were to be described using frequency counts and proportions; and the mean, standard deviation, minimal and maximal values, and medians were to be calculated for continuous variables.

For adverse events, a descriptive analysis was to be provided with adverse events presented in a frequency table, by body system/group and treatment. Furthermore, nature, incidence, severity, and causality were to be reported for each adverse event.

3.6.2 Determination of Sample Size

The planned sample size for this Study was 40 Subjects with 20 Subjects randomized equally to each of the two Study-arms. No formal sample size calculation was conducted for this Study. Drop-outs during the treatment period were not to be replaced.

3.7 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

The Study was conducted according to the protocol dated January 05, 2010 with the following changes:

1. On March 04, 2010, sites were informed that Subjects could be enrolled without meeting Inclusion Criterion No. 3 (positive diagnostic testing for influenza A or B by using rapid influenza antigen test) (nasopharyngeal swabs), provided that the Subject had a physician diagnosis of influenza and met the symptom criteria as described in Inclusion Criterion No. 4. The rapid influenza antigen test was to be continued to be performed and results documented.
2. The Study was terminated July 19, 2010 after enrolment of 37 Subjects due to the end of the 2010 Spring flu season

Changes to statistical methods included using Fisher's exact test for comparison of compliance and the number of Subjects experiencing an adverse event as these tests were more appropriate for the data collected and design of the trial. Further, a within-group analysis was conducted for VAS scores and oral temperature using paired T-tests.

4. STATISTICAL METHODS

4.1 DATA SETS AND STATISTICAL METHODS

Subjects completing at least one post-randomization visit were included in analysis of efficacy. All Subjects known to have started treatment were included in analysis of safety. Between-group differences in the number of withdrawals were compared using Fisher's exact test.

4.1.1 Patient Disposition and Loss-To-Follow-Up
A description of the disposition of all randomized patients is provided in Figure 2.

4.1.2 Demographic and Baseline Characteristics
The distribution of baseline characteristics in the two groups was compared descriptively, and is presented in Tables 3 and 4.

4.1.3 Primary and Secondary Endpoints
For primary and secondary outcomes, between-group comparisons of screening/baseline data and data collected as scores were made using analysis of T-tests. Within-group comparisons were made using paired T-tests. For continuous variables, including temperature, WBC differential, cytokines and CD4 and CD8 cell counts, analysis of covariance was performed using available screening/baseline data as a covariate.

4.1.4 Safety
Safety data and adverse events were summarized by treatment group. The number of individuals experiencing adverse events was compared using Fisher's exact test. Between-group comparisons at screening for vital signs, haematology parameters and blood chemistry parameters were made using T-tests. For comparisons at Weeks 1 and 2, analysis of covariance was performed using available screening/baseline data as a covariate.

4.1.5 Compliance
Compliance, defined as the number of tablets taken in the two groups, was compared using a T-test.

4.1.6 Level of Significance
Probability values less than 0.05 were considered statistically significant.

4.1.7 Statistical Software
SAS Version 9.1 was used to perform statistical analysis.

5. STUDY PATIENTS

5.1 DISPOSITION OF PATIENTS

Figure 2: Disposition of Study Patients

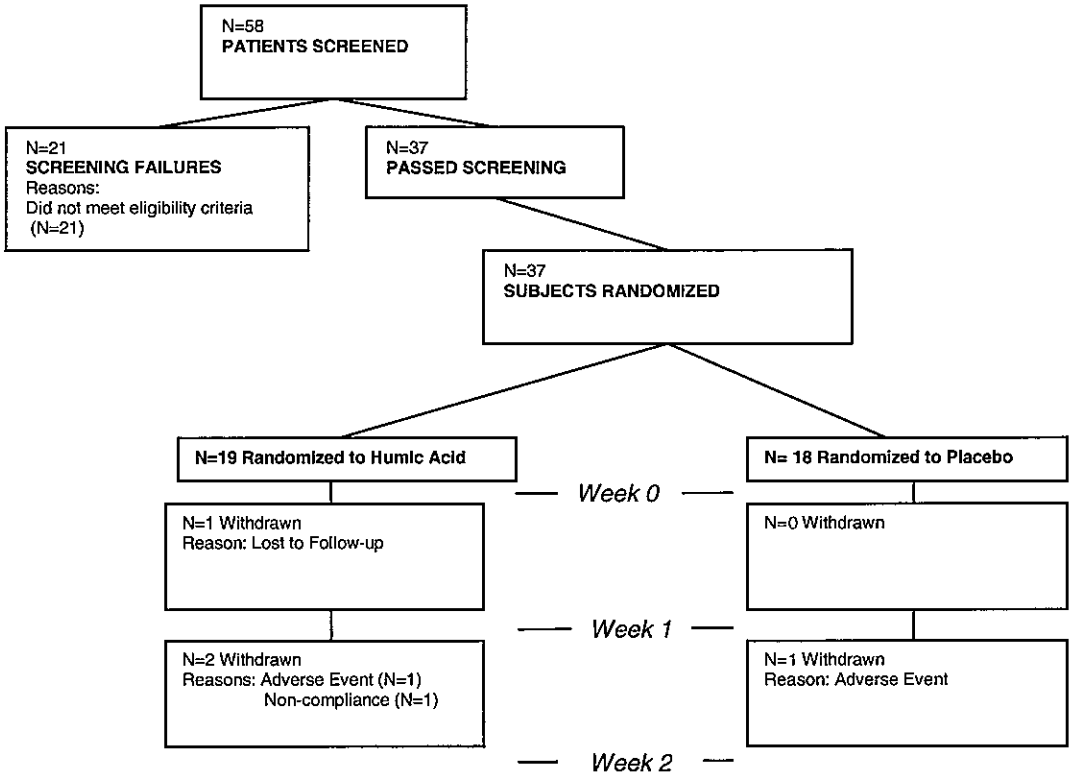


Table 2: Proportion of Withdrawals for All Subjects Randomized to Treatment

	Humic Acid (N = 19)	Placebo (N = 18)	P Value[φ]
	(n, %)	(n, %)	
No	16/19 (78.9%)	17/18 (94.4%)	0.604
Yes	3/19 (21.1%)	1/18 (5.6%)	

N is number; P is probability.

[φ] Between-group statistical comparisons were conducted using Fisher's exact test. Probability values $p < 0.05$ are significant.

A total of 37 Subjects were randomized to participate in the Study. Three Subjects randomized to Humic Acid withdrew after randomization, one in the first week and the other two in the second week of the treatment period. One Subject was lost to follow-up, the other two withdrew due to an adverse event (N=1) (elevated AST and ALT) and non-compliance (N=1). One Subject withdrew from Placebo due to an adverse event (elevated AST and ALT). The number of withdrawals was not statistically-significant between groups ($p = 0.604$).

5.2 PROTOCOL DEVIATIONS

No protocol deviations occurred during this Study.

6. EFFICACY EVALUATION

6.1 DATA SETS ANALYZED

6.1.1 Listing of Missing Observations and Observations Excluded from Analysis

CD4+ and CD8+ cell counts could not be determined at Screening for one Subject on Placebo (Randomization No. 1011918) due to the blood sample containing clots.

6.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Table 3: Screening Demographics and Characteristics of All Subjects Randomized (N=37)

	Humic Acid (N = 19)	Placebo (N = 18)	P Value
Age [N] Mean ± SD SEM Median (Min, Max)	[19] 38.4 ± 9.5 2.2 41.0 (20.0, 60.0)	[18] 37.4 ± 12.0 2.8 40.5 (19.0, 55.0)	0.772[φ]
Gender {f/n (%)}			
Female	12/19 (63.2%)	11/18 (61.1%)	0.898[ν]
Male	7/19 (36.8%)	7/18 (38.9%)	
Race/Ethnicity {f/n (%)}			
Black	0/19 (0.0%)	2/18 (11.1%)	0.400[†]
Italian	0/19 (0.0%)	1/18 (5.6%)	
Latin American	17/19 (89.5%)	14/18 (77.8%)	
White	2/19 (10.5%)	1/18 (5.6%)	
Alcohol Use {f/n (%)}			
None	14/19 (73.7%)	15/18 (83.3%)	0.578[†]
Occasional	2/19 (10.5%)	0/18 (0.0%)	
Weekly	3/19 (15.8%)	3/18 (16.7%)	
Tobacco Use {f/n (%)}			
Current	4/19 (21.1%)	1/18 (5.6%)	0.401[†]
Never	13/19 (68.4%)	13/18 (72.2%)	
Past	2/19 (10.5%)	4/18 (22.2%)	

N is number; P is probability; SD is standard deviation; SEM is standard error of the mean; Min is minimum; Max is maximum; f is frequency.
[φ] Between-group statistical comparisons were conducted using T-test. Probability values $p < 0.05$ are significant.
[ν] Between-group statistical comparisons were conducted using Chi-square test. Probability values $p < 0.05$ are significant.
[†] Between-group statistical comparisons were conducted using Fisher's exact test. Probability values $p < 0.05$ are significant.

Table 4: Frequency of Flu Symptoms Present at Screening for Subjects Randomized (N = 37)

	Humic Acid (N = 19)	Placebo (N = 18)	P Value[φ]
Cough {f/n (%)}			
No	0/19 (0.0%)	0/18 (0.0%)	---
Yes	19/19 (100.0%)	18/18 (100.0%)	
Sore Throat {f/n (%)}			
No	5/19 (26.3%)	3/18 (16.7%)	0.693
Yes	14/19 (73.7%)	15/18 (83.3%)	
Nasal Symptoms {f/n (%)}			
No	1/19 (5.3%)	4/18 (22.2%)	0.180
Yes	18/19 (94.7%)	14/18 (77.8%)	
Sneezing {f/n (%)}			
No	3/19 (15.8%)	7/18 (38.9%)	0.151
Yes	16/19 (84.2%)	11/18 (61.1%)	
Oral Temperature ≥38°C {f/n (%)}			
Yes	18/19 (94.7%)	16/18 (88.9%)	0.604
No	1/19 (5.3%)	2/18 (11.1%)	
Fever within previous 24 hours {f/n (%)}			
No	0/19 (0.0%)	0/18 (0.0%)	---
Yes	19/19 (100.0%)	18/18 (100.0%)	
Myalgia (muscle pain) {f/n (%)}			
No	1/19 (5.3%)	1/18 (5.6%)	>0.999
Yes	18/19 (94.7%)	17/18 (94.4%)	
Sweats/Chills {f/n (%)}			
No	2/19 (10.5%)	4/18 (22.2%)	0.405
Yes	17/19 (89.5%)	14/18 (77.8%)	
Fatigue {f/n (%)}			
No	7/19 (36.8%)	6/18 (33.3%)	>0.999
Yes	12/19 (63.2%)	12/18 (66.7%)	

N is number; P is probability; f is frequency; °C is degrees Celsius.

[φ] Between-group statistical comparisons were conducted using Fisher's exact test. Probability values $p < 0.05$ are significant.

6.3 MEASUREMENTS OF TREATMENT COMPLIANCE

Table 5: Mean Compliance with Respect to Treatment Regimen (Number of Dosages Consumed) for All Subjects Randomized into the Study

	Humic Acid (N = 19) [N] Mean ± SD SEM Median (Min, Max)	Placebo (N = 18) [N] Mean ± SD SEM Median (Min, Max)	P Value[φ]
Compliance			
Week 1	[18] 97.1 ± 9.9 2.3 100.0 (57.9, 100.0)	[17] 97.8 ± 5.7 1.4 100.0 (82.6, 104.0)	0.819
Week 2	[18] 87.9 ± 24.0 5.7 100.0 (15.8, 100.0)	[18] 93.6 ± 16.5 3.9 100.0 (33.3, 100.0)	0.414
Average Compliance (over available)	[18] 92.5 ± 13.4 3.2 100.0 (57.9, 100.0)	[18] 95.0 ± 11.5 2.7 100.0 (58.0, 100.0)	0.560
Average Compliance (assuming missing is zero)	[18] 92.5 ± 13.4 3.2 100.0 (57.9, 100.0)	[18] 95.0 ± 11.5 2.7 100.0 (58.0, 100.0)	0.560

[φ] Between-group statistical comparisons were conducted using a T-test. Probability values $p < 0.05$ are significant.

There were no significant differences between groups with respect to treatment compliance, which was >85% at all time-points assessed in both treatment groups.

6.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

6.4.1 Analysis of Efficacy

6.4.1.1 Influenza Symptom Scores

Table 6: Daily Influenza Symptom Scores of Subjects During the First 7 Days of Treatment with Humic Acid or Placebo

Symptoms	Humic Acid (N = 19) [N] Mean ± SD SEM Median (Min, Max)	Placebo (N = 18) [N] Mean ± SD SEM Median (Min, Max)	P Value[φ]
Cough (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Day 1	[19] 2.1 ± 1.3 0.3 3.0 (0.0, 3.0)	[18] 1.9 ± 1.0 0.2 2.0 (0.0, 3.0)	0.780
Day 2	[19] 2.1 ± 1.1 0.3 2.0 (0.0, 3.0)	[18] 1.9 ± 1.0 0.2 2.0 (0.0, 3.0)	0.639
Day 3	[19] 1.7 ± 1.2 0.3 2.0 (0.0, 3.0)	[18] 1.7 ± 1.0 0.2 2.0 (0.0, 3.0)	0.916
Day 4	[19] 1.4 ± 1.1 0.2 1.0 (0.0, 3.0)	[18] 1.6 ± 1.0 0.2 2.0 (0.0, 3.0)	0.583
Day 5	[19] 1.3 ± 1.1 0.3 1.0 (0.0, 3.0)	[18] 1.3 ± 1.0 0.2 1.5 (0.0, 3.0)	0.966
Day 6	[19] 0.9 ± 0.9 0.2 1.0 (0.0, 3.0)	[18] 1.2 ± 0.9 0.2 1.0 (0.0, 3.0)	0.264
Day 7	[19] 0.8 ± 0.8 0.2 1.0 (0.0, 2.0)	[18] 1.2 ± 0.9 0.2 1.0 (0.0, 2.0)	0.232

Table 6 Continued

	Humic Acid (N = 19)	Placebo (N = 18)	P Value[φ]
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
Fever (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Day 1	[19] 1.2 ± 1.1 0.3 1.0 (0.0, 3.0)	[18] 1.1 ± 0.9 0.2 1.0 (0.0, 3.0)	0.654
Day 2	[19] 0.7 ± 0.9 0.2 0.0 (0.0, 3.0)	[18] 0.8 ± 0.9 0.2 0.5 (0.0, 3.0)	0.895
Day 3	[19] 0.5 ± 0.8 0.2 0.0 (0.0, 3.0)	[18] 0.2 ± 0.5 0.1 0.0 (0.0, 2.0)	0.204
Day 4	[19] 0.3 ± 0.7 0.2 0.0 (0.0,3.0)	[18] 0.1 ± 0.5 0.1 0.0 (0.0, 2.0)	0.461
Day 5	[19] 0.2 ± 0.7 0.2 0.0 (0.0, 3.0)	[18] 0.1 ± 0.3 0.1 0.0 (0.0, 1.0)	0.592
Day 6	[19] 0.2 ± 0.7 0.2 0.0 (0.0, 3.0)	[18] 0.2 ± 0.7 0.2 0.0 (0.0, 3.0)	0.961
Day 7	[19] 0.1 ± 0.3 0.1 0.0 (0.0, 1.0)	[18] 0.2 ± 0.5 0.1 0.0 (0.0, 2.0)	0.662
Runny Nose (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Day 1	[19] 1.8 ± 1.1 0.2 2.0 (0.0, 3.0)	[18] 1.6 ± 1.0 0.2 2.0 (0.0,3.0)	0.497
Day 2	[19] 1.8 ± 1.0 0.2 2.0 (0.0, 3.0)	[18] 1.5 ± 1.0 0.2 2.0 (0.0, 3.0)	0.402
Day 3	[19] 1.5 ± 1.1 0.2 1.0 (0.0, 3.0)	[18] 1.4 ± 1.0 0.2 1.5 (0.0, 3.0)	0.687
Day 4	[19] 1.1 ± 1.0 0.2 1.0 (0.0, 3.0)	[18] 1.1 ± 0.9 0.2 1.0 (0.0, 3.0)	0.873
Day 5	[19] 1.1 ± 0.9 0.2 1.0 (0.0, 3.0)	[18] 1.1 ± 0.9 0.2 1.0 (0.0, 3.0)	0.864
Day 6	[19] 0.9 ± 0.8 0.2 1.0 (0.0, 3.0)	[18] 0.7 ± 1.0 0.2 0.0 (0.0, 3.0)	0.454
Day 7	[19] 0.6 ± 0.6 0.1 1.0 (0.0, 2.0)	[18] 0.6 ± 0.7 0.2 0.5 (0.0, 2.0)	0.924

Table 6 Continued

	Humic Acid (N = 19)	Placebo (N = 18)	P Value[φ]
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
Stuffy Nose (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Day 1	[19] 2.1 ± 0.9 0.2 2.0 (0.0, 3.0)	[18] 1.6 ± 1.0 0.2 2.0 (0.0, 3.0)	0.164
Day 2	[19] 1.7 ± 0.9 0.2 2.0 (0.0, 3.0)	[18] 1.6 ± 1.2 0.3 2.0 (0.0, 3.0)	0.719
Day 3	[19] 1.4 ± 1.0 0.2 1.0 (0.0, 3.0)	[18] 1.2 ± 1.1 0.3 1.0 (0.0, 3.0)	0.678
Day 4	[19] 1.2 ± 1.0 0.2 1.0 (0.0, 3.0)	[18] 1.3 ± 1.0 0.2 1.0 (0.0, 3.0)	0.706
Day 5	[19] 0.9 ± 0.8 0.2 1.0 (0.0, 3.0)	[18] 0.8 ± 0.9 0.2 1.0 (0.0, 3.0)	0.698
Day 6	[19] 0.7 ± 0.8 0.2 1.0 (0.0, 3.0)	[18] 0.7 ± 0.9 0.2 0.5 (0.0, 3.0)	0.894
Day 7	[19] 0.7 ± 0.6 0.1 1.0 (0.0, 2.0)	[19] 0.6 ± 0.9 0.2 0.0 (0.0, 3.0)	0.595
Aches (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Day 1	[19] 2.2 ± 1.0 0.2 3.0 (0.0, 3.0)	[18] 1.6 ± 1.0 0.2 2.0 (0.0, 3.0)	0.079
Day 2	[19] 1.4 ± 1.1 0.2 2.0 (0.0, 3.0)	[18] 1.3 ± 0.9 0.2 1.5 (0.0, 3.0)	0.790
Day 3	[19] 1.4 ± 1.2 0.3 1.0 (0.0, 3.0)	[18] 0.9 ± 0.9 0.2 1.0 (0.0, 3.0)	0.172
Day 4	[19] 0.8 ± 0.9 0.2 1.0 (0.0, 3.0)	[18] 0.8 ± 1.0 0.2 0.5 (0.0, 3.0)	0.978
Day 5	[19] 0.7 ± 0.9 0.2 0.0 (0.0, 3.0)	[18] 0.7 ± 0.8 0.2 0.5 (0.0, 2.0)	0.949
Day 6	[19] 0.5 ± 0.8 0.2 0.0 (0.0, 3.0)	[18] 0.6 ± 1.0 0.2 0.0 (0.0, 3.0)	0.649
Day 7	[19] 0.3 ± 0.7 0.2 0.0 (0.0, 2.0)	[18] 0.6 ± 0.9 0.2 0.0 (0.0, 3.0)	0.269

Table 6 Continued

	Humic Acid (N = 19)	Placebo (N = 18)	P Value[φ]
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
Headaches (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Day 1	[19] 1.6 ± 1.2 0.3 2.0 (0.0, 3.0)	[18] 1.6 ± 1.2 0.3 2.0 (0.0, 3.0)	0.849
Day 2	[19] 1.4 ± 1.1 0.3 1.0 (0.0, 3.0)	[18] 1.1 ± 0.9 0.2 1.0 (0.0, 3.0)	0.447
Day 3	[19] 1.6 ± 1.1 0.3 2.0 (0.0, 3.0)	[18] 1.1 ± 1.1 0.3 1.0 (0.0, 3.0)	0.163
Day 4	[19] 1.1 ± 1.1 0.3 1.0 (0.0, 3.0)	[18] 0.7 ± 0.9 0.2 0.0 (0.0, 3.0)	0.196
Day 5	[19] 0.6 ± 1.0 0.2 0.0 (0.0, 3.0)	[18] 0.3 ± 0.5 0.1 0.0 (0.0, 1.0)	0.237
Day 6	[19] 0.4 ± 0.8 0.2 0.0 (0.0, 3.0)	[18] 0.5 ± 0.8 0.2 0.0 (0.0, 2.0)	0.624
Day 7	[19] 0.5 ± 0.9 0.2 0.0 (0.0, 3.0)	[18] 0.4 ± 0.8 0.2 0.0 (0.0, 2.0)	0.771
Chills (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Day 1	[19] 1.2 ± 1.2 0.3 1.0 (0.0, 3.0)	[18] 0.6 ± 1.0 0.2 0.0 (0.0, 3.0)	0.111
Day 2	[19] 0.8 ± 1.0 0.2 1.0 (0.0, 3.0)	[18] 0.6 ± 1.0 0.2 0.0 (0.0, 3.0)	0.473
Day 3	[19] 0.6 ± 0.9 0.2 0.0 (0.0, 3.0)	[18] 0.2 ± 0.7 0.2 0.0 (0.0, 3.0)	0.197
Day 4	[19] 0.4 ± 0.8 0.2 0.0 (0.0, 3.0)	[18] 0.2 ± 0.6 0.2 0.0 (0.0, 2.0)	0.402
Day 5	[19] 0.3 ± 0.7 0.2 0.0 (0.0, 3.0)	[18] 0.2 ± 0.5 0.1 0.0 (0.0, 2.0)	0.669
Day 6	[19] 0.2 ± 0.7 0.2 0.0 (0.0, 3.0)	[18] 0.2 ± 0.5 0.1 0.0 (0.0, 2.0)	0.832
Day 7	[19] 0.1 ± 0.3 0.1 0.0 (0.0, 1.0)	[18] 0.2 ± 0.5 0.1 0.0 (0.0, 2.0)	0.662

Table 6 Continued

	Humic Acid (N = 19)	Placebo (N = 18)	P Value[Φ]
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
Sneezing (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Day 1	[19] 1.7 ± 1.1 0.2 2.0 (0.0, 3.0)	[18] 1.3 ± 1.0 0.2 1.0 (0.0, 3.0)	0.242
Day 2	[19] 1.3 ± 1.1 0.3 1.0 (0.0, 3.0)	[18] 1.3 ± 1.1 0.3 1.0 (0.0, 3.0)	0.962
Day 3	[19] 1.1 ± 0.9 0.2 1.0 (0.0, 3.0)	[18] 1.2 ± 1.2 0.3 1.0 (0.0, 3.0)	0.863
Day 4	[19] 0.7 ± 0.8 0.2 1.0 (0.0, 3.0)	[18] 0.9 ± 1.0 0.2 1.0 (0.0, 3.0)	0.605
Day 5	[19] 0.6 ± 0.8 0.2 1.0 (0.0, 3.0)	[18] 0.7 ± 0.9 0.2 0.0 (0.0, 2.0)	0.741
Day 6	[19] 0.6 ± 0.8 0.2 0.0 (0.0, 3.0)	[18] 0.8 ± 0.8 0.2 1.0 (0.0, 2.0)	0.448
Day 7	[19] 0.5 ± 0.6 0.1 0.0 (0.0, 2.0)	[18] 0.5 ± 0.7 0.2 0.0 (0.0, 2.0)	0.904
Earaches (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Day 1	[19] 0.6 ± 1.0 0.2 0.0 (0.0, 3.0)	[18] 0.2 ± 0.5 0.1 0.0 (0.0, 2.0)	0.197
Day 2	[19] 0.6 ± 1.1 0.2 0.0 (0.0, 3.0)	[18] 0.2 ± 0.5 0.1 0.0 (0.0, 2.0)	0.214
Day 3	[19] 0.5 ± 0.9 0.2 0.0 (0.0, 3.0)	[18] 0.1 ± 0.3 0.1 0.0 (0.0, 1.0)	0.075
Day 4	[19] 0.3 ± 0.7 0.2 0.0 (0.0, 3.0)	[17] 0.1 ± 0.2 0.1 0.0 (0.0, 1.0)	0.186
Day 5	[19] 0.3 ± 0.7 0.2 0.0 (0.0, 3.0)	[18] 0.1 ± 0.2 0.1 0.0 (0.0, 1.0)	0.260
Day 6	[19] 0.2 ± 0.7 0.2 0.0 (0.0, 3.0)	[18] 0.1 ± 0.3 0.1 0.0 (0.0, 1.0)	0.592
Day 7	[19] 0.2 ± 0.5 0.1 0.0 (0.0, 2.0)	[18] 0.0 ± 0.0 0.0 0.0 (0.0, 0.0)	0.191

Table 6 Continued

	Humic Acid (N = 19)	Placebo (N = 18)	P Value[φ]
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
Fatigue (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Day 1	[19] 1.5 ± 1.2 0.3 2.0 (0.0, 3.0)	[18] 1.1 ± 1.1 0.3 1.0 (0.0, 3.0)	0.346
Day 2	[19] 1.0 ±1.0 0.2 1.0 (0.0, 3.0)	[18] 0.7 ± 0.8 0.2 1.0 (0.0, 2.0)	0.348
Day 3	[19] 1.0 ± 1.1 0.3 1.0 (0.0, 3.0)	[18] 0.7 ± 0.8 0.2 0.5 (0.0, 2.0)	0.395
Day 4	[19] 0.6 ± 0.9 0.2 0.0 (0.0, 3.0)	[18] 0.6 ± 0.7 0.2 0.0 (0.0, 2.0)	0.777
Day 5	[19] 0.4 ± 0.9 0.2 0.0 (0.0, 3.0)	[18] 0.5 ± 0.7 0.2 0.0 (0.0, 2.0)	0.770
Day 6	[19] 0.5 ± 0.9 0.2 0.0 (0.0, 3.0)	[18] 0.7 ± 0.8 0.2 0.0 (0.0, 2.0)	0.506
Day 7	[19] 0.3 ± 0.7 0.1 0.0 (0.0, 2.0)	[18] 0.5 ± 0.7 0.2 0.0 (0.0, 2.0)	0.297

N is number; P is probability; SD is standard deviation; SEM is standard error of the mean; Min is minimum; Max is maximum.
[φ] Between-group statistical comparisons were conducted using Wilcoxon non-parametric two sample T-test. Probability values $p < 0.05$ are significant.

Although there were no statistically-significant differences with respect to symptom scores between treatment groups, Subjects on Humic Acid reported higher scores at the beginning of the Study for cough, fever, runny nose, stuffy nose, aches, chills, sneezing, earaches and fatigue as compared with those on Placebo. However, after supplementation for 7 days with Humic Acid, symptom scores reduced by greater percentages than did those for Subjects taking Placebo for the same duration for cough (61.9% vs. 36.8%), fever (91.7% vs. 81.8%), runny nose (66.7% vs. 62.5%), stuffy nose (66.7% vs. 62.5%), aches (86.4% vs. 62.5%), chills (91.7% vs. 66.7%), sneezing (70.6% vs. 61.5%) and fatigue (80.0% vs. 54.5%). Mean scores for Subjects on Humic Acid were also lower than for those on Placebo after 7 days of treatment for cough, fever, aches, chills and fatigue in spite of being worse than Placebo on Day 1.

Table 7: Average Weekly Influenza Symptom Scores of Subjects over the 14-Day Treatment Period with Humic Acid or Placebo

	Humic Acid (N = 19) [N] Mean ± SD SEM Median (Min, Max)	Placebo (N = 18) [N] Mean ± SD SEM Median (Min, Max)	P Value[φ]
Cough (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Average (Day 0-7)	[19] 1.5 ± 0.9 0.2 1.6 (0.0, 2.9)	[18] 1.5 ± 0.7 0.2 1.8 (0.0, 2.6)	0.749
Average (Day 8-14)	[18] 0.7 ± 0.8 0.2 0.6 (0.0, 3.0)	[18] 0.8 ± 0.7 0.2 0.6 (0.0, 2.1)	0.485
Average (Day 1-14)	[19] 1.1 ± 0.8 0.2 1.2 (0.0, 2.9)	[18] 1.2 ± 0.7 0.2 1.1 (0.0, 2.1)	0.820
Fever (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Average (Day 0-7)	[19] 0.5 ± 0.6 0.1 0.3 (0.0, 2.7)	[18] 0.4 ± 0.4 0.1 0.3 (0.0, 1.1)	0.951
Average (Day 8-14)	[18] 0.1 ± 0.2 0.1 0.0 (0.0, 0.9)	[18] 0.1 ± 0.4 0.1 0.0 (0.0, 1.7)	0.749
Average (Day 1-14)	[19] 0.3 ± 0.4 0.1 0.2 (0.0, 1.8)	[18] 0.3 ± 0.3 0.1 0.2 (0.0, 1.4)	0.902
Runny Nose (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Average (Day 0-7)	[19] 1.3 ± 0.8 0.2 1.3 (0.0, 2.9)	[18] 1.1 ± 0.8 0.2 1.1 (0.0, 2.7)	0.484
Average (Day 8-14)	[18] 0.3 ± 0.5 0.1 0.1 (0.0, 1.7)	[18] 0.6 ± 0.7 0.2 0.2 (0.0, 2.0)	0.312
Average (Day 1-14)	[19] 0.9 ± 0.6 0.1 0.8 (0.0, 2.3)	[18] 0.8 ± 0.6 0.1 0.6 (0.0, 1.9)	0.927
Stuffy Nose (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Average (Day 0-7)	[19] 1.2 ± 0.7 0.2 1.3 (0.0, 2.9)	[18] 1.1 ± 0.9 0.2 1.1 (0.0, 3.0)	0.542
Average (Day 8-14)	[18] 0.4 ± 0.5 0.1 0.2 (0.0, 1.7)	[18] 0.5 ± 0.7 0.2 0.1 (0.0, 2.0)	0.804
Average (Day 1-14)	[19] 0.9 ± 0.6 0.1 0.9 (0.0, 2.3)	[18] 0.8 ± 0.6 0.2 0.6 (0.0, 1.9)	0.808

Table 7 Continued

	Humic Acid (N = 19)	Placebo (N = 18)	P Value[φ]
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
Aches (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Average (Day 0-7)	[19] 1.0 ± 0.8 0.2 1.1 (0.1, 2.9)	[18] 0.9 ± 0.7 0.2 0.9 (0.0, 2.0)	0.692
Average (Day 8-14)	[18] 0.3 ± 0.6 0.1 0.0 (0.0, 1.9)	[18] 0.4 ± 0.7 0.2 0.0 (0.0, 2.3)	0.713
Average (Day 1-14)	[19] 0.7 ± 0.6 0.1 0.6 (0.1, 2.4)	[18] 0.7 ± 0.7 0.2 0.4 (0.0, 2.1)	0.616
Headaches (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Average (Day 0-7)	[19] 1.0 ± 0.8 0.2 1.0 (0.0, 2.9)	[18] 0.8 ± 0.7 0.2 0.8 (0.0, 2.0)	0.437
Average (Day 8-14)	[18] 0.4 ± 0.6 0.2 0.1 (0.0, 2.1)	[18] 0.5 ± 0.7 0.2 0.0 (0.0, 2.0)	0.973
Average (Day 1-14)	[19] 0.8 ± 0.7 0.2 0.6 (0.0, 2.4)	[18] 0.6 ± 0.6 0.1 0.5 (0.0, 1.8)	0.420
Chills (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Average (Day 0-7)	[19] 0.5 ± 0.7 0.2 0.3 (0.0, 2.7)	[18] 0.3 ± 0.5 0.1 0.0 (0.0, 1.4)	0.238
Average (Day 8-14)	[18] 0.1 ± 0.3 0.1 0.0 (0.0, 1.1)	[18] 0.2 ± 0.5 0.1 0.0 (0.0, 2.3)	>0.999
Average (Day 1-14)	[19] 0.4 ± 0.5 0.1 0.2 (0.0, 1.9)	[18] 0.2 ± 0.5 0.1 0.0 (0.0, 1.9)	0.137
Sneezing (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Average (Day 0-7)	[19] 0.9 ± 0.7 0.2 1.0 (0.0, 2.9)	[18] 1.0 ± 0.8 0.2 0.8 (0.0, 2.1)	0.760
Average (Day 8-14)	[18] 0.3 ± 0.5 0.1 0.0 (0.0, 1.9)	[18] 0.3 ± 0.5 0.1 0.1 (0.0, 1.7)	0.702
Average (Day 1-14)	[19] 0.6 ± 0.6 0.1 0.5 (0.0, 2.4)	[18] 0.6 ± 0.6 0.1 0.6 (0.0, 1.7)	0.867

Table 7 Continued

	Humic Acid (N = 19)	Placebo (N = 18)	P Value[φ]
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
Earaches (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Average (Day 0-7)	[19] 0.4 ± 0.8 0.2 0.0 (0.0, 2.9)	[18] 0.1 ± 0.3 0.1 0.0 (0.0, 1.2)	0.207
Average (Day 8-14)	[18] 0.1 ± 0.4 0.1 0.0 (0.0, 1.7)	[18] 0.0 ± 0.1 0.0 0.0 (0.0, 0.3)	>0.999
Average (Day 1-14)	[19] 0.3 ± 0.6 0.1 0.0 (0.0, 2.3)	[18] 0.1 ± 0.1 0.0 0.0 (0.0, 0.5)	0.345
Fatigue (Scale: 0 = absent, 1 = mild, 2 = moderate, 3 = severe)			
Average (Day 0-7)	[19] 0.8 ± 0.8 0.2 0.6 (0.0, 2.9)	[18] 0.7 ± 0.7 0.2 0.5 (0.0, 1.9)	0.975
Average (Day 8-14)	[18] 0.2 ± 0.5 0.1 0.0 (0.0, 1.9)	[18] 0.2 ± 0.4 0.1 0.0 (0.0, 1.1)	0.200
Average (Day 1-14)	[19] 0.5 ± 0.7 0.2 0.3 (0.0, 2.4)	[18] 0.5 ± 0.5 0.1 0.3 (0.0, 1.4)	0.890

N is number; P is probability; SD is standard deviation; SEM is standard error of the mean; Min is minimum; Max is maximum.
[φ] Between-group statistical comparisons were conducted using Wilcoxon non-parametric two-sample T-test. Probability values $p < 0.05$ are significant.

6.4.1.2 Concomitant Medication for Symptoms

Table 8: Proportion of Subjects Using at Least One Concomitant Medication for Possible Flu Symptoms

	Humic Acid (N = 19)	Placebo (N = 18)	P Value[φ]
	(n, %)	(n, %)	
No	15/19 (78.9%)	14/18 (77.8%)	>0.999
Yes	4/19 (21.1%)	4/18 (22.2%)	

N is number; P is probability.
[φ] Between-group statistical comparisons were conducted using Fisher's exact test. Probability values $p < 0.05$ are significant.

A total of 29 Subjects (78.4%) used at least one concomitant medication for possible flu symptoms (fever, headache, nasal congestion, sore throat, body ache, cough, diarrhea, etc.). The number of Subjects using concomitant medication to alleviate possible flu symptoms was similar between treatment groups ($p > 0.999$).

6.4.1.3 Visual Analogue Scale (VAS)

Table 9a: Visual Analogue Scale Scores for Ability to Perform Usual Activities of Subjects at Screening and After 1 and 2 Weeks of Supplementation with Humic Acid or Placebo

	Humic Acid (N = 19)	Placebo (N = 18)	P Value[φ]
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
Visual Analogue Scale (Ability to perform usual activities; 0=not at all, 100 = extremely able)			
Screening	[19] 41.4 ± 16.6 3.8 41.0 (13.0, 71.0)	[18] 50.6 ± 25.6 6.7 50.0 (4.0, 93.0)	0.239
Week 1	[18] 68.0 ± 20.2 4.7 71.0 (19.0, 98.0)	[18] 78.1 ± 25.8 6.1 87.5 (19.0, 100.0)	0.199
Week 2	[18] 85.7 ± 17.3 4.1 92.0 (36.0, 100.0)	[18] 89.2 ± 17.9 4.0 96.5 (29.0, 100.0)	0.555

N is number; P is probability; SD is standard deviation; SEM is standard error of the mean; Min is minimum; Max is maximum.
[φ] Between-group statistical comparisons were conducted using a T-test. Probability values $p < 0.05$ are significant.

There were no statistically-significant differences between groups with respect to VAS scores at Screening or after 1 or 2 weeks of supplementation with Humic Acid or Placebo.

Table 9b: Within-Group Differences in Visual Analogue Scale Scores for Ability to Perform Usual Activities for Subjects from Screening to Week 1 and Week 2 of Supplementation with Humic Acid or Placebo

	Humic Acid (N = 19)		Placebo (N = 18)	
	[N] Mean ± SD SEM Median (Min, Max)	P Value[φ]	[N] Mean ± SD SEM Median (Min, Max)	P Value[φ]
Visual Analogue Scale (Ability to perform usual activities; 0=not at all, 100 = extremely able)				
Difference between week 1 and Screening	[18] 26.8 ± 25.4 6.0 33.5 (-20.0, 79.0)	<0.001	[18] 27.6 ± 30.1 7.1 22.5 (-18.0, 91.0)	0.001
Difference between week 2 and Screening	[18] 44.5 ± 26.4 6.2 49.5 (-35.0, 81.0)	<0.001	[18] 38.7 ± 32.4 7.6 45.0 (-28.0, 90.0)	<0.001

N is number; P is probability; SD is standard deviation; SEM is standard error of the mean; Min is minimum; Max is maximum.
[φ] Within-group statistical comparisons were conducted using a paired T-test. Probability values $p < 0.05$ are significant.

Statistically-significant increases in VAS scores were demonstrated from Baseline to Weeks 1 and 2 for Subjects in both the Humic Acid and Placebo groups ($p \leq 0.001$), with greater increases found from Screening to Week 2 in Subjects on Humic Acid as compared with Placebo (44.5% vs. 38.7%).

6.4.1.4 Oral Temperature

Table 10a: Mean Oral Temperature Measurements of Subjects at Screening and After 1 and 2 Weeks of Supplementation with Humic Acid or Placebo

	Humic Acid (N = 19)	Placebo (N = 18)	P Value
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
Temperature (°C)			
Screening	[19] 37.1 ± 0.5 0.1 37.1 (36.2, 38.0)	[18] 37.1 ± 0.7 0.2 37.2 (35.5, 38.1)	0.879 [φ]
Week 1	[18] 36.5 ± 0.4 0.1 36.5 (35.8, 37.0)	[18] 36.7 ± 0.3 0.1 36.7 (36.0, 37.4)	0.089 [γ]
Week 2	[18] 36.7 ± 0.3 0.1 36.7 (36.1, 37.4)	[18[36.4 ± 0.6 0.1 36.5 (34.7, 37.3)	0.135 [γ]

N is number; P is probability; SD is standard deviation; SEM is standard error of the mean; Min is minimum; Max is maximum; °C is degrees Celsius.
[φ] Between-group statistical comparisons were conducted using a T-test. Probability values $p < 0.05$ are significant.
[γ] Between-group statistical comparisons were conducted using analysis of covariance (ANCOVA). Probability values $p < 0.05$ are significant.

There were no statistically-significant differences between groups with respect to mean temperatures of Subjects at Screening or after 1 or 2 weeks of supplementation with Humic Acid or Placebo. However, there was a trend toward lower body temperature scores after 1 week of supplementation with Humic Acid in comparison with Placebo (36.5°C vs. 36.7°C, $p = 0.089$).

Table 10b: Within-Group Differences In Oral Temperature of Subjects from Screening to Week 1 and Week 2 of Supplementation with Humic Acid or Placebo

	Humic Acid (N = 19)		Placebo (N = 18)	
	[N] Mean ± SD SEM Median (Min, Max)	P Value [φ]	[N] Mean ± SD SEM Median (Min, Max)	P Value [φ]
Temperature (°C)				
Difference Between Screening and Week 1	[18] -0.7 ± 0.6 0.1 -0.6 (-1.6, 0.3)	<0.001	[18] -0.4 ± 0.8 0.2 -0.4 (-1.7, 1.1)	0.037
Difference Between Screening and Week 2	[18] -0.5 ± 0.6 0.1 -0.4 (-1.5, 0.4)	0.003	[18] -0.7 ± 1.0 0.2 -0.7 (-3.0, 1.0)	0.009

N is number; P is probability; SD is standard deviation; SEM is standard error of the mean; Min is minimum; Max is maximum; °C is degrees Celsius.
[φ] Within-group statistical comparisons were conducted using a paired T-test. Probability values $p < 0.05$ are significant.

Oral temperature was significantly reduced in both Humic Acid and Placebo groups from Screening to Week 1 ($p < 0.001$ and $p = 0.037$, respectively), and from Screening to Week 2 ($p = 0.003$ and $p = 0.009$, respectively). The reduction in temperature was greatest for Humic Acid within the first week of treatment as compared to Placebo (-0.7°C vs. -0.4°C).

6.4.1.5 WBC Differential

Table 11: White Blood Cell Count and White Blood Cell Differential of Subjects at Screening and After 1 and 2 Weeks of Supplementation with Humic Acid or Placebo

	Humic Acid (N = 19)	Placebo (N = 18)	P Value
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
White Blood Cell (10^9/L)			
Screening	[19] 8.6 ± 2.2 0.5 8.2 (5.5, 13.8)	[18] 7.4 ± 2.7 0.6 6.8 (3.8, 14.6)	0.173 [φ]
Week 1	[18] 8.0 ± 2.2 0.5 8.4 (4.6, 13.4)	[18] 7.0 ± 2.4 0.6 6.4 (3.9, 12.1)	0.577 [Y]
Week 2	[18] 7.9 ± 1.8 0.4 7.8 (4.9, 10.9)	[18] 6.7 ± 2.3 0.5 6.3 (4.0, 11.6)	0.258 [Y]
Neutrophils (%)			
Screening	[19] 62.9 ± 8.2 1.9 64.2 (44.6, 76.4)	[18] 62.0 ± 8.5 2.0 62.4 (46.7, 74.4)	0.732 [φ]
Week 1	[18] 60.8 ± 8.9 2.1 60.8 (43.4, 78.4)	[18] 62.6 ± 7.5 1.8 62.6 (51.9, 77.0)	0.505 [Y]
Week 2	[18] 61.2 ± 6.0 1.4 60.2 (52.8, 73.1)	[18] 60.2 ± 8.2 1.9 61.9 (39.5, 70.4)	0.734 [Y]
Monocyte (%)			
Screening	[19] 5.1 ± 1.5 0.3 4.8 (2.7, 7.8)	[18] 5.4 ± 1.6 0.4 5.4 (2.9, 7.8)	0.595 [φ]
Week 1	[18] 4.5 ± 1.0 0.2 4.5 (3.2, 6.8)	[18] 4.2 ± 1.0 0.2 4.2 (2.1, 5.9)	0.273 [Y]
Week 2	[18] 4.3 ± 1.4 0.3 4.2 (1.9, 6.7)	[18] 4.2 ± 1.1 0.3 4.1 (2.6, 7.1)	0.514 [Y]
Eosinophil (%)			
Screening	[19] 2.4 ± 2.0 0.5 1.9 (0.8, 9.1)	[18] 2.6 ± 1.7 0.4 2.2 (0.4, 6.3)	0.754 [φ]
Week 1	[18] 2.6 ± 1.9 0.4 2.0 (0.7, 8.2)	[18] 2.3 ± 1.0 0.2 2.0 (1.1, 4.1)	0.240 [Y]
Week 2	[18] 2.8 ± 2.0 0.5 2.1 (1.0, 8.5)	[18] 2.4 ± 1.1 0.3 2.1 (0.9, 4.7)	0.109 [Y]
Basophil (%)			
Screening	[19] 0.7 ± 0.3 0.1 0.6 (0.3, 1.3)	[18] 0.5 ± 0.3 0.1 0.5 (0.0, 1.0)	0.086 [φ]
Week 1	[18] 0.6 ± 0.4 0.1 0.5 (0.1, 1.8)	[18] 0.4 ± 0.2 0.1 0.4 (0.2, 1.0)	0.505 [Y]
Week 2	[18] 0.5 ± 0.2 0.0 0.6 (0.2, 0.8)	[18] 0.5 ± 0.2 0.0 0.4 (0.2, 0.9)	0.898 [Y]

Table 11 Continued

	Humic Acid (N = 19)	Placebo (N = 18)	P Value
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
Absolute Neutrophil ($x10^3$/uL)			
Screening	[19] 5.5 ± 2.0 0.5 5.0 (2.5, 10.3)	[18] 4.7 ± 2.1 0.5 3.8 (1.9, 10.4)	0.257 [φ]
Week 1	[18] 5.0 ± 2.1 0.5 4.6 (2.2, 11.1)	[18] 4.5 ± 1.8 0.4 4.0 (2.1, 8.2)	0.742 [Y]
Week 2	[18] 4.9 ± 1.3 0.3 4.8 (2.7, 7.5)	[18] 4.1 ± 1.8 0.4 3.7 (1.7, 8.1)	0.367 [Y]
Absolute Lymphocyte ($x10^3$/uL)			
Screening	[19] 2.3 ± 0.5 0.1 2.2 (1.4, 3.5)	[18] 2.0 ± 0.7 0.2 1.8 (1.1, 3.4)	0.193 [φ]
Week 1	[18] 2.3 ± 0.7 0.2 2.2 1.5, 4.0)	[18] 2.0 ± 0.6 0.1 1.9 (1.0, 3.4)	0.299 [Y]
Week 2	[18] 2.3 ± 0.6 0.1 2.4 (1.3, 3.9)	[18] 2.0 ± 0.5 0.1 1.8 (1.3, 3.0)	0.288 [Y]
Absolute Monocyte ($x10^3$/uL)			
Screening	[19] 0.4 ± 0.1 0.0 0.4 (0.3, 0.7)	[18] 0.4 ± 0.1 0.0 0.4 (0.2, 0.6)	0.253 [φ]
Week 1	[18] 0.4 ± 0.1 0.0 0.4 (0.3, 0.5)	[18] 0.3 ± 0.1 0.0 0.3 (0.1, 0.5)	0.019 [Y]
Week 2	[18] 0.3 ± 0.1 0.0 0.3 (0.2, 0.6)	[18] 0.3 ± 0.1 0.0 0.2 (0.2, 0.5)	0.275 [Y]
Absolute Eosinophil ($x10^3$/uL)			
Screening	[19] 0.2 ± 0.2 0.0 0.2 (0.1, 0.9)	[18] 0.2 ± 0.1 0.0 0.2 (0.0, 0.4)	0.383 [φ]
Week 1	[18] 0.2 ± 0.1 0.0 0.2(0.1, 0.7)	[18] 0.2 ± 0.1 0.0 0.1(0.0, 0.3)	0.238 [Y]
Week 2	[18] 0.2 ± 0.2 0.0 0.2 (0.1, 0.8)	[18] 0.2 ± 0.1 0.0 0.1 (0.0, 0.3)	0.127 [Y]

Table 11 Continued

	Humic Acid (N = 19)	Placebo (N = 18)	P Value
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
Absolute Basophil ($x10^3$/uL)			
Screening	[19] 0.1 ± 0.1 0.0 0.1 (0.0, 0.1)	[18] 0.0 ± 0.1 0.0 0.0 (0.0, 0.2)	0.090 [φ]
Week 1	[18] 0.0 ± 0.0 0.0 0.0 (0.0, 0.1)	[18] 0.0 ± 0.0 0.0 0.0 (0.0, 0.1)	0.893 [Y]
Week 2	[18] 0.0 ± 0.1 0.0 0.0 (0.0, 0.1)	[18] 0.0 ± 0.0 0.0 0.0 (0.0, 0.1)	0.101 [Y]

N is number; P is probability; SD is standard deviation; SEM is standard error of the mean; Min is minimum; Max is maximum; uL is microliter; % is percent.

[φ] Between-group statistical comparisons were conducted using a T-test. Probability values $p < 0.05$ are significant.

[Y] Between-group statistical comparisons were conducted using analysis of covariance (ANCOVA). Probability values $p < 0.05$ are significant.

After one week of treatment there was a significant difference between groups in the number of monocytes, Subjects on Placebo exhibiting a reduction ($p = 0.011$). By Week 2, both treatment groups had a reduction in monocyte counts to 0.3 x 10^3/uL ($p = 0.275$). There were no other significant changes between groups in the white blood cell differential.

6.4.1.6 CD4+ and CD8+ Cell Counts

Table 12: CD4+ and CD8+ Cell Counts of Subjects at Screening and After 1 and 2 Weeks of Supplementation with Humic Acid or Placebo

	Humic Acid (N = 19)	Placebo (N = 18)	P Value
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
CD4+ Absolute Count (Cells/uL)			
Screening	[19] 1136.6 ± 274.0 62.9 1159.0 (566.0, 1626.0)	[17] 1002.8 ± 339.2 82.3 932.0 (436.0, 1719.0)	0.200 [φ]
Week 1	[18] 1130.1 ± 336.0 79.2 1029.0 (745.0, 1949.0)	[18] 978.3 ± 321.8 75.9 887.0 (491.0, 1755.0)	0.645 [γ]
Week 2	[18] 1169.8 ± 315.3 74.3 1094.5 (638.0, 2041.0)	[18] 973.1 ± 290.5 68.5 934.5 (402.0, 1498.0)	0.308 [γ]
CD8+ Absolute Count (Cells/uL)			
Screening	[19] 611.7 ± 232.8 53.4 541.0 (320.0, 1073.0)	[17] 552.9 ± 241.2 58.5 498.0 (167.0, 1140.0)	0.463 [φ]
Week 1	[18] 653.6 ± 369.3 87.1 533.5 (301.0, 1742.0)	[18] 560.4 ± 299.7 70.6 570.5 (173.0, 1365.0)	0.968 [γ]
Week 2	[18] 620.7 ± 217.7 51.3 573.5 (361.0, 1102.0)	[18] 546.7 ± 229.4 54.1 582.5 (191.0, 1091.0)	0.882 [γ]

N is number; P is probability; SD is standard deviation; SEM is standard error of the mean; Min is minimum; Max is maximum; uL is microliter.

[φ] Between-group statistical comparisons were conducted using a T-test. Probability values $p < 0.05$ are significant.

[γ] Between-group statistical comparisons were conducted using analysis of covariance (ANCOVA). Probability values $p < 0.05$ are significant.

There were no statistically-significant differences between groups with respect to absolute CD4+ and CD8+ cell counts at Screening or after 1 or 2 weeks of supplementation with Humic Acid or Placebo. However, there was a trend toward an increase in CD4+ cell counts in Subjects on Humic Acid and a decrease in CD4+ cell counts in Subjects on Placebo after 2 weeks of supplementation. A similar shift was seen in CD8+ cell counts.

6.4.1.7 TNF-α and IL-8

Table 13a: Serum TNF-α and IL-8 Concentrations of Subjects at Screening and After 1 and 2 Weeks of Supplementation with Humic Acid or Placebo

	Humic Acid (N = 19)	Placebo (N = 18)	P Value
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
TNF-α (pg/mL)			
Screening	[19] 1.5 ± 1.9 0.4 0.7 (0.3, 7.1)	[18] 16.4 ± 52.3 12.3 2.5 (0.6, 224.7)	0.222 [φ]
Week 1	[18] 1.6 ± 2.2 0.5 0.9 (0.3, 8.6)	[18] 16.1 ± 51.4 12.1 2.0 (0.6, 220.5)	0.755 [γ]
Week 2	[18] 1.1 ± 1.0 0.2 0.7 (0.3, 4.3)	[18] 16.0 ± 51.5 12.1 1.7 (0.6, 220.8)	0.274 [γ]
IL-8 (pg/mL)			
Week 0	[19] 15.6 ± 15.4 3.5 10.6 (4.4, 75.2)	[18] 14.9 ± 9.5 2.2 12.3 (4.3, 37.0)	0.863 [φ]
Week 1	[18] 14.5 ± 7.2 1.7 13.1 (3.9, 29.8)	[18] 13.7 ± 12.3 2.9 9.2 (3.7, 47.6)	0.880 [γ]
Week 2	[18] 15.1 ±10.2 2.4 11.9 (3.9, 46.1)	[18] 13.6 ± 8.1 1.9 11.8 (4.1, 37.2)	0.686 [γ]

N is number; P is probability; SD is standard deviation; SEM is standard error of the mean; Min is minimum; Max is maximum; TNF-α is tumor necrosis factor alpha; IL-8 is interleukin 8; pg is picogram; mL is milliliter.

[φ] Between-group statistical comparisons were conducted using a T-test. Probability values $p < 0.05$ are significant.

[γ] Between-group statistical comparisons were conducted using analysis of covariance (ANCOVA). Probability values $p < 0.05$ are significant.

There were no statistically-significant differences between groups with respect to TNF-α when time-point assessed. A high standard deviation was found for the results as two Subjects demonstrated high levels at all time-points, indicating the possibility of an underlying inflammatory response (approximately 220 pg/mL for one Subject and approximately 26 pg/mL for the other Subject). On review of medical history, there were no indications of any known medical conditions that might have been responsible for these values. An analysis was performed removing these two Subjects and the results are presented in Table 13b. IL-8 decreased in both groups from Screening to Week 2; however, there were no significant differences between groups.

Table 13b: Serum TNF-α Concentrations of Subjects at Screening and After 1 and 2 Weeks of Supplementation with Humic Acid or Placebo after Removal of Two Outliers

	Humic Acid (N = 19)	Placebo (N = 18)	P Value
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
TNF-α (pg/mL)			
Screening	[19] 1.5 ± 1.9 0.4 0.7 (0.3, 7.1)	[16] 2.8 ± 2.4 0.6 2.4 (0.6, 9.4)	0.088 [φ]
Week 1	[18] 1.6 ± 2.2 0.5 0.9 (0.3, 8.6)	[16] 2.8 ± 3.3 0.8 1.7 (0.6, 13.4)	0.440 [Y]
Week 2	[18] 1.1 ± 1.0 0.2 0.7 (0.3, 4.3)	[16] 2.6 ± 2.5 0.6 1.7 (0.6, 9.4)	0.046 [Y]

N is number; P is probability; SD is standard deviation; SEM is standard error of the mean; Min is minimum; Max is maximum; TNF-α is tumor necrosis factor alpha; IL-8 is interleukin 8; pg is picogram; mL is milliliter.

[φ] Between-group statistical comparisons were conducted using a T-test. Probability values $p < 0.05$ are significant.

[Y] Between-group statistical comparisons were conducted using analysis of covariance (ANCOVA). Probability values $p < 0.05$ are significant.

There was a trend toward Subjects randomized to Placebo having higher levels of serum TNF-α at Screening ($p = 0.088$). After 2 weeks of supplementation, serum concentrations reduced in both groups and reached statistical significance between groups ($p = 0.046$). Subjects on Humic Acid had a mean reduction from 1.5 pg/mL at screening to 1.1 pg/mL after 2 weeks of supplementation, while Subjects on Placebo had a mean reduction from 2.8 pg/mL at Screening to 2.6 pg/mL after 2 weeks of supplementation.

6.4.2 Statistical/Analytical Issues

Two Subjects demonstrated high levels of serum TNF-α. Analysis was conducted with and without including these data, and the results are presented in Tables 13a and 13b, respectively. There were no other statistical or analytical issues encountered.

6.4.3 Handling of Dropouts or Missing Data

Available data were included in all analyses of efficacy variables. No data were imputed where missing.

6.4.4 Tabulation of Individual Response Data

Individual response data are included in an electronic file in Appendix D.

6.5 EFFICACY CONCLUSIONS

Although there were no significant statistical differences with respect to symptom scores between treatment groups, Subjects on Humic Acid reported higher initial scores for cough, fever, runny nose, stuffy nose, aches, chills, sneezing, earaches and fatigue. However, after supplementation for 7 days with Humic Acid, symptom scores were improved by greater percentages than were those for Subjects taking Placebo for the same duration, for cough (61.9% vs. 36.8%), fever (91.7% vs. 81.8%), runny nose (66.7% vs. 62.5%), stuffy nose (66.7% vs. 62.5%), aches (86.4% vs. 62.5%), chills (91.7% vs. 66.7%), sneezing (70.6% vs. 61.5%) and fatigue (80.0% vs. 54.5%). Mean scores for Subjects on Humic Acid were also lower than for those on Placebo after 7 days of treatment for cough, fever, aches, chills and fatigue in spite of being worse than Placebo on day 1.

There were no significant statistical differences between groups with respect to VAS scores at Screening or after 1 or 2 weeks of supplementation with Humic Acid or Placebo. Within groups, significant increases in VAS scores were found from Baseline to Weeks 1 and 2 for Subjects in both the Humic Acid and Placebo groups ($p \leq 0.001$), with greater improvement found from Screening to Week 2 in Subjects on Humic Acid as compared with Placebo (44.5% vs. 38.7%). The improvement in VAS scores for Subjects on Humic Acid coincided with a greater lessening of their flu symptoms from the beginning of the Study to Day 7, in comparison with those on Placebo over the same time-span.

There were no significant statistical differences between groups with respect to mean temperatures of Subjects at Screening or after 1 or 2 weeks of supplementation with Humic Acid or Placebo. Oral temperature was significantly reduced in both Humic Acid and Placebo groups from Screening to Week 1 ($p < 0.001$ and $p = 0.037$, respectively), and from Screening to Week 2 ($p = 0.003$ and $p = 0.009$, respectively). However, the reduction in temperature was greater for Subjects taking Humic Acid within the first week of treatment as compared to Subjects taking Placebo (-0.7°C vs. -0.4°C).

There were no significant statistical differences between groups with respect to absolute CD4+ and CD8+ cell counts at Screening or after 1 or 2 weeks of supplementation with Humic Acid or Placebo. However, there was a trend toward an increase in CD4+ cell counts in Subjects on Humic Acid and a decrease in CD4+ cell counts in Subjects on Placebo after 2 weeks of supplementation. A similar shift was seen in CD8+ cell counts.

There was a trend toward Subjects randomized to Placebo having higher levels of serum TNF-α at Screening ($p = 0.088$). After 2 weeks of supplementation, serum concentrations reduced in both groups and reached statistical significance between groups ($p = 0.046$). Subjects on Humic Acid had a mean reduction from 1.5 pg/mL at Screening to 1.1 pg/mL after 2 weeks of supplementation, and Subjects on Placebo had a mean reduction from 2.8 pg/mL at Screening to 2.6 pg/mL after 2 weeks of

supplementation. IL-8 decreased in both groups from Screening to Week 2; however, there were no significant statistical differences between groups.

7. SAFETY EVALUATION

7.1 EXTENT OF EXPOSURE

Duration: Duration of exposure was 2 weeks for each product

Dose: Subjects randomized to receive Humic Acid took 2 tablets three times daily for the 2-week treatment period. Each tablet contained 250 mg of Humic Acid.

Subjects randomized to receive Placebo took 2 tablets three times daily for the 2-week treatment period.

7.2 ADVERSE EVENTS

7.2.1 Brief Summary of Adverse Events

A total of 35 adverse events were reported during the Study. Of these, 17 events occurred in 9 Subjects (47.4%) on Humic Acid and 18 events occurred in 6 Subjects (33.3%) on Placebo. Nine of the 17 events reported by Subjects on Humic Acid and 7 of the 18 events reported by Subjects on Placebo were categorized by the Investigator as possibly or probably related to Test Article. Test Article was discontinued in 2 cases, one Subject on Humic Acid and one Subject on Placebo. Both Subjects had an elevation in the liver function markers AST and ALT.

7.2.2 Display of Adverse Events

Table 14: Listing of Adverse Events Reported by Subjects Taking Humic Acid

Randomization Code Assigned at Baseline	AE-CRF Term	Category	Intensity	Date of Onset	Relationship to test article	Action Taken	Date of Resolution
1011951	Nausea	Gastrointestinal disorders	Mild	3/28/2010	Unlikely	None	3/29/2010
1011951	Dizziness	Nervous system disorders	Mild	3/29/2010	Unlikely	None	3/31/2010
1011951	Shortness of breath	Respiratory, thoracic and mediastinal disorders	Mild	3/28/2010	Unlikely	None	3/30/2010
1011951	Diarrhea	Gastrointestinal disorders	Mild	3/28/2010	Unlikely	None	4/2/2010
1011952	Vomiting	Gastrointestinal disorders	Mild	3/7/2010	Possible	None	3/7/2010
1011952	Constipation	Gastrointestinal disorders	Mild	3/7/2010	Not Related	None	3/8/2010
1011934	Laceration on Right Leg	Injury, poisoning and procedural complications	Moderate	4/2/2010	Not Related	Con Med Required	2/4/2010
1011930	Dizziness	Nervous system disorders	Mild	4/3/2010	Possible	None	4/5/2010
1011942	Diarrhea	Gastrointestinal disorders	Mild	4/22/2010	Possible	None	4/23/2010
1011942	Stomach Cramps	Gastrointestinal disorders	Mild	4/23/2010	Possible	None	4/27/2010
1011942	Diarrhea	Gastrointestinal disorders	Mild	4/25/2010	Possible	None	4/28/2010
1011949	Elevated ALT and AST	Investigations	Moderate	5/1/2010	Probable	Test Article Discontinued	Ongoing*
1011938	Diarrhea	Gastrointestinal disorders	Mild	4/27/2010	Possible	None	4/27/2010
1011938	Nausea	Gastrointestinal disorders	Mild	4/28/2010	Possible	None	4/28/2010
1011938	Dizziness	Nervous system disorders	Mild	5/5/2010	Unlikely	None	5/6/2010
1011936	Heartburn	Gastrointestinal disorders	Mild	5/8/2010	Possible	Con Med Required	5/9/2010
1011943	Neck Pain	Musculoskeletal and connective tissue disorders	Mild	5/12/2010	Unlikely	Con Med Required	5/12/2010

* Decreased upon repeat at early termination visit after test article discontinuation but still higher than baseline; no further follow-up was done

Table 15: Listing of Adverse Events Reported by Subjects Taking Placebo

Randomization Code Assigned at Baseline	AE-CRF Term	Category	Intensity	Date of Onset	Relationship to test article	Action Taken	Date of Resolution
1011925	Elevated ALT and AST	Investigations	Moderate	3/17/2010	Possible	Test Article Discontinued	3/24/2010
1011925	Headache	Nervous system disorders	Mild	3/21/2010	Unlikely	Con Med Required	3/21/2010
1011907	Stomach Cramps	Gastrointestinal disorders	Mild	3/21/2010	Not Related	None	3/21/2010
1011907	Diarrhea	Gastrointestinal disorders	Mild	3/21/2010	Possible	Con Med Required	3/24/2010
1011907	Back Pain	Musculoskeletal and connective tissue disorders	Mild	3/22/2010	Unlikely	Con Med Required	3/27/2010
1011907	Premenstrual Syndrome	Reproductive system and breast disorders	Mild	3/22/2010	Not Related	Con Med Required	3/27/2010
1011907	Stomach Cramps	Gastrointestinal disorders	Mild	3/28/2010	Not Related	None	3/28/2010
1011907	Body aches	Injury, poisoning and procedural complications	Mild	3/29/2010	Not Related	Con Med Required	3/29/2010
1011924	Elevated ALT and AST	Investigations	Moderate	4/16/2010	Possible	None	Ongoing*
1011909	Joint Pain	Musculoskeletal and connective tissue disorders	Mild	4/22/2010	Unlikely	Con Med Required	4/22/2010
1011909	Chest Pain	Musculoskeletal and connective tissue disorders	Mild	4/22/2010	Unlikely	None	4/22/2010
1011909	Heartburn	Gastrointestinal disorders	Mild	4/23/2010	Unlikely	None	4/23/2010
1011909	Joint Pain	Musculoskeletal and connective tissue disorders	Mild	4/24/2010	Not Related	None	4/25/2010
1011909	Stomach Ache	Gastrointestinal disorders	Mild	4/24/2010	Possible	None	4/24/2010
1011909	Diarrhea	Gastrointestinal disorders	Mild	4/25/2010	Possible	None	4/26/2010
1011909	Heartburn	Gastrointestinal disorders	Mild	4/25/2010	Possible	None	4/25/2010
1011926	Dizziness	Nervous system disorders	Mild	4/22/2010	Unlikely	None	4/22/2010
1011914	Stomach Discomfort	Gastrointestinal disorders	Mild	4/30/2010	Possible	None	5/1/2010

* Subject did not show for repeat blood test appointment. When contacted, Subject refused to come back to clinic.

7.2.3 Analysis of Adverse Events

Table 16: Proportion of Subjects Reporting an Adverse Event During the Study for All Subjects Randomized

	Study Group		P Value
	Humic Acid (N = 19)	Placebo (N = 18)	
Adverse Events {f/n (%)}			
No	9/19 (47.4%)	6/18 (33.3%)	0.508[φ]
Yes	10/19 (52.6%)	12/18 (66.7%)	

N is number; P is probability; f is frequency

[φ] Between-group statistical comparisons were conducted using Fisher's exact test. Probability values $p < 0.05$ are significant. One Subject having an adverse event during the washout period (after Placebo, before Reduce) was excluded from the statistical analysis.

There were no significant differences between groups with respect to the number of Subjects reporting an adverse event ($p = 0.508$).

Table 17: Frequency of Adverse Events Occurring During the Treatment Period for All Subjects Randomized to Humic Acid

Body System Event	Mild					Moderate					Severe					Total					Total
	Not Related	Unlikely Related	Possibly Related	Probably Related	Most Probably Related	Not Related	Unlikely Related	Possibly Related	Probably Related	Most Probably Related	Not Related	Unlikely Related	Possibly Related	Probably Related	Most Probably Related	Not Related	Unlikely Related	Possibly Related	Probably Related	Most Probably Related	All Adverse Events
Gastrointestinal disorder																					
Nausea		1/19 (5.3%)	1/19 (5.3%)														1/19 (5.3%)	1/19 (5.3%)			2/19 (10.5%)
Diarrhea		1/19 (5.3%)	3/19 (15.8%)														1/19 (5.3%)	3/19 (15.8%)			4/19 (21.1%)
Vomiting			1/19 (5.3%)															1/19 (5.3%)			1/19 (5.3%)
Constipation	1/19 (5.3%)															1/19 (5.3%)					1/19 (5.3%)
Stomach Cramps			1/19 (5.3%)															1/19 (5.3%)			1/19 (5.3%)
Heart Burn			1/19 (5.3%)															1/19 (5.3%)			1/19 (5.3%)
Nervous system disorders																					
Dizziness		2/19 (10.5%)	1/19 (5.3%)														2/19 (10.5%)	1/19 (5.3%)			3/19 (15.8%)
Respiratory, thoracic and mediastinal disorders																					
Shortness of breath		1/19 (5.3%)															1/19 (5.3%)				1/19 (5.3%)
Injury, poisoning and procedural complications																					
Laceration on Right Leg						1/19 (5.3%)										1/19 (5.3%)					1/19 (5.3%)
Investigations																					
Elevated ALT and AST									1/19 (5.3%)										1/19 (5.3%)		1/19 (5.3%)
Musculoskeletal and connective tissue disorders																					
Neck Pain		1/19 (5.3%)															1/19 (5.3%)				1/19 (5.3%)

Table 18: Frequency of Adverse Events Occurring During the Treatment Period for All Subjects Randomized to Placebo

Body System Event	Mild					Moderate					Severe					Total					Total
	Not Related	Unlikely Related	Possibly Related	Probably Related	Most Probably Related	Not Related	Unlikely Related	Possibly Related	Probably Related	Most Probably Related	Not Related	Unlikely Related	Possibly Related	Probably Related	Most Probably Related	Not Related	Unlikely Related	Possibly Related	Probably Related	Most Probably Related	All Adverse Events
Gastrointestinal disorder																					
Stomach Cramps	2/18 (11.1%)															2/18 (11.1%)					2/18 (11.1%)
Diarrhea			2/18 (11.1%)															2/18 (11.1%)			2/18 (11.1%)
Heart Burn		1/18 (5.6%)	1/18 (5.6%)														1/18 (5.6%)	1/18 (5.6%)			2/18 (11.1%)
Stomach Ache			1/18 (5.6%)															1/18 (5.6%)			1/18 (5.6%)
Stomach Discomfort			1/18 (5.6%)															1/18 (5.6%)			1/18 (5.6%)
Investigations																					
Elevated ALT and AST								2/18 (11.1%)										2/18 (11.1%)			2/18 (11.1%)
Nervous system disorders																					
Headache		1/18 (5.6%)															1/18 (5.6%)				1/18 (5.6%)
Dizziness		1/18 (5.6%)															1/18 (5.6%)				1/18 (5.6%)
Musculoskeletal and connective tissue disorders																					
Back Pain		1/18 (5.6%)															1/18 (5.6%)				1/18 (5.6%)
Joint Pain	1/18 (5.6%)	1/18 (5.6%)														1/18 (5.6%)	1/18 (5.6%)				2/18 (11.1%)
Chest Pain		1/18 (5.6%)															1/18 (5.6%)				1/18 (5.6%)
Reproductive system and breast disorders																					
Premenstrual Syndrome	1/18 (5.6%)															1/18 (5.6%)					1/18 (5.6%)
Injury, poisoning and procedural complications																					
Body Aches	1/18 (5.6%)															1/18 (5.6%)					1/18 (5.6%)

Table 19: Listing of Adverse Events and the Number of Subjects Reporting an Adverse Event Assessed by the Investigator as Having a Possible or Probable Relationship to the Test Article

Adverse Event	Humic Acid (N = 19)	Placebo (N = 18)
Diarrhea	3	2
Dizziness	1	0
Elevated ALT and AST	1	2
Heartburn	1	1
Nausea	1	0
Vomiting	1	0
Stomach Ache	0	1
Stomach Cramps	1	0
Stomach Discomfort	0	1

A total of 16 adverse events were reported during the Study having a possible or probable relationship to the Test Article as assessed by the Investigator while blinded to treatments. A greater number of Subjects reported diarrhea (3 vs. 2), dizziness (1 vs. 0), nausea (1 vs. 0), vomiting (1 vs. 0) and stomach cramps (1 vs. 0) on Humic Acid as compared to Placebo. A greater number of Subjects reported stomach aches (1 vs. 0 and stomach cramps (1 vs. 0) in the Placebo group as compared to the Humic Acid group. It should be noted that these adverse events may also have been flu symptoms; thus, conclusions cannot be drawn regarding adverse event relationships to Test Article. It is noteworthy that 3 Subjects demonstrated an elevation in ALT and AST (2 on Placebo and 1 on Humic Acid), which led to Test-Article discontinuation in two cases. The Subject on Humic Acid did not report taking any other concomitant medications during the Study, and AST and ALT levels decreased upon repeat at early termination visit after Test-Article discontinuation. Of the 2 Subjects on Placebo, 1 Subject also used Advil, Tylenol and Pseudoephedine and the other Subject used Tylenol, Theraflu and Advil during the Study. Firm conclusions cannot be made regarding the relationship of these events to Test Product since a higher number of Subjects experienced the same event in the Placebo group as compared with the Humic Acid group.

7.2.4 Listing of Adverse Events by Patient

Listing of adverse events by Patient is attached in Appendix D.

7.3 SERIOUS ADVERSE EVENTS AND SIGNIFICANT ADVERSE EVENTS

7.3.1 Listing of Deaths, other Serious Adverse Events and Significant Adverse Events

7.3.1.1 Deaths
No deaths occurred during the course of the Study.

7.3.1.2 Other Serious Adverse Events of All Subjects
There were no serious adverse events that occurred during the course of the Study.

7.3.1.3 Significant Adverse Events of All Subjects
Significant adverse events were defined as those requiring an intervention, such as Test-Article interruption, discontinuation, withdrawal or reduction, or concomitant therapy; and are detailed in Tables 20 and 21 by treatment. Following this classification, there were a total of 7 significant adverse events experienced by 3 Subjects taking Placebo, and 4 significant adverse events experienced by 4 Subjects taking Humic Acid. Test Article was discontinued in one instance for an adverse event classified as probably related to Humic Acid and in one instance for an adverse event classified as possibly related to Placebo. In both cases the event was elevation of liver function markers AST and ALT. Concomitant medication was required in 3 cases in the Humic Acid group for a laceration on the leg (N = 1, not related), heartburn (N = 1, possibly related) and neck pain (N = 1, unlikely related). Concomitant medication was used in 6 cases for Subjects on Placebo for headache (N = 1, unlikely related), diarrhea (N = 1, possibly related), back pain (N = 1, unlikely related), premenstrual syndrome (N = 1, not related), body aches (N = 1, not related) and joint pain (N = 1, unlikely related). The relationship of these events to Test Article was assigned by the Investigator while blinded to the treatments.

Table 20: Listing of Adverse Events Requiring Concomitant Medication, Test-Article Interruption, Test-Article Discontinuation or Other Action for All Subjects Randomized to Humic Acid

Randomization Code Assigned at Baseline	AE-CRF Term	Category	Intensity	Date of Onset	Relationship to Test Article	Action Taken	Date of Resolution
1011934	Laceration on Right Leg	Injury, poisoning and procedural complications	Moderate	4/2/2010	Not Related	Con Med Required	2/4/2010
1011949	Elevated ALT and AST	Investigations	Moderate	5/1/2010	Probable	Test Article Discontinued	Ongoing*
1011936	Heartburn	Gastrointestinal disorders	Mild	5/8/2010	Possible	Con Med Required	5/9/2010
1011943	Neck Pain	Musculoskeletal and connective tissue disorders	Mild	5/12/2010	Unlikely	Con Med Required	5/12/2010

* Decreased upon repeat at early termination visit after test article discontinuation but still higher than baseline, no further follow-up was done

Table 21: Listing of Adverse Events Requiring Concomitant Medication, Test-Article Interruption, Test-Article Discontinuation or Other Action for All Subjects Randomized to Placebo

Randomization Code Assigned at Baseline	AE-CRF Term	Category	Intensity	Date of Onset	Relationship to Test Article	Action Taken	Date of Resolution
1011925	Elevated ALT and AST	Investigations	Moderate	3/17/2010	Possible	Test Article Discontinued	3/24/2010
1011925	Headache	Nervous system disorders	Mild	3/21/2010	Unlikely	Con Med Required	3/21/2010
1011907	Diarrhea	Gastrointestinal disorders	Mild	3/21/2010	Possible	Con Med Required	3/24/2010
1011907	Back Pain	Musculoskeletal and connective tissue disorders	Mild	3/22/2010	Unlikely	Con Med Required	3/27/2010
1011907	Premenstrual Syndrome	Reproductive system and breast disorders	Mild	3/22/2010	Not Related	Con Med Required	3/27/2010
1011907	Body aches	Injury, poisoning and procedural complications	Mild	3/29/2010	Not Related	Con Med Required	3/29/2010
1011909	Joint Pain	Musculoskeletal and connective tissue disorders	Mild	4/22/2010	Unlikely	Con Med Required	4/22/2010

7.4 CLINICAL SAFETY PARAMETERS

Table 22: Systolic Blood Pressure, Diastolic Blood Pressure and Heart Rate of All Subjects Randomized to the Study at Screening and After 1 and 2 Weeks of Supplementation with Humic Acid or Placebo

	Humic Acid (N = 19)	Placebo (N = 18)	P Value
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
Mean Systolic Blood Pressure (mm Hg)			
Screening	[19] 114.2 ± 11.7 2.7 113.0 (90.0, 138.3)	[18] 112.1 ± 10.3 2.4 115.5 (90.0, 123.0)	0.575 [φ]
Week 1	[18] 114.6 ± 13.3 3.1 117.5 (91.0, 136.0)	[18] 110.8 ± 11.2 2.6 113.5 (91.0, 128.0)	0.166 [Y]
Week 2	[18] 117.4 ± 15.9 3.8 118.0 (93.0, 159.0)	[18] 111.9 ± 11.1 2.6 117.5 (92.0, 125.0)	0.159 [Y]
Mean Diastolic Blood Pressure (mm Hg)			
Screening	[19] 76.4 ± 8.4 1.9 78.0 (60.0, 98.0)	[18] 72.3 ± 8.2 1.9 75.5 (60.0, 87.0)	0.140 [φ]
Week 1	[18] 75.1 ± 6.5 1.5 77.2 (60.0, 84.0)	[18] 71.7 ± 6.7 1.6 73.0 (60.0, 80.0)	0.351 [Y]
Week 2	[18] 74.3 ± 7.9 1.9 78.5 (60.0, 84.0)	[18] 71.1 ± 8.3 1.9 73.0 (59.0, 81.0)	0.633 [Y]
Mean Heart Rate (BPM)			
Screening	[19] 72.4 ±7.7 1.8 73.0 (59.0, 86.0)	[18] 68.4 ± 8.3 2.0 65.0 (59.0, 87.0)	0.145 [φ]
Week 1	[18] 76.0 ± 10.3 2.4 75.0 (62.0, 108.0)	[18] 72.2 ± 12.4 2.9 72.0 (57.0, 102.0)	0.925 [Y]
Week 2	[18] 76.7 ± 5.6 1.3 76.0 (68.0, 87.0)	[18] 71.6 ± 10.1 2.4 72.0 (54.0, 91.0)	0.300 [Y]

N is number; P is probability; SD is standard deviation; SEM is standard error of the mean; Min is minimum; Max is maximum; mm Hg is millimeters mercury; BPM is beats per minute.

[φ] Between-group statistical comparisons were conducted using a T test. Probability values $p < 0.05$ are significant.

[Y] Between-group statistical comparisons were conducted using analysis of covariance (ANCOVA). Probability values $p < 0.05$ are significant.

There were no significant differences between groups with respect to systolic blood pressure, diastolic blood pressure or heart rate after supplementation with Humic Acid or Placebo over the 2-week course of the Study.

Table 23: Clinical Chemistry and Hematology Parameters of All Subjects Randomized to the Study at Screening and After 1 and 2 Weeks of Supplementation with Humic Acid or Placebo

	Humic Acid (N = 19)	Placebo (N = 18)	P Value
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
ALT (IU/L)			
Screening	[19] 35.1 ± 24.9 5.7 24.0 (13.0, 105.0)	[18] 30.8 ± 19.2 4.5 24.5 (13.0, 76.0)	0.569 [φ]
Week 1	[18] 36.0 ± 27.4 6.5 29.0 (11.0, 131.0)	[18] 31.0 ± 22.4 5.3 26.5 (11.0, 91.0)	0.892 [γ]
Week 2	[18] 34.7 ± 27.1 6.4 27.5 (7.0, 122.0)	[18] 29.9 ± 23.1 5.5 26.0 (13.0, 113.0)	0.974 [γ]
AST (IU/L)			
Screening	[19] 28.6 ± 8.1 1.8 28.0 (16.0, 47.0)	[18] 28.8 ± 12.9 3.0 23.5 (17.0, 65.0)	0.943 [φ]
Week 1	[18] 27.3 ± 9.0 2.1 26.5 (17.0, 57.0)	[18] 32.7 ± 34.4 8.1 25.5 (19.0, 169.0)	0.535 [γ]
Week 2	[18] 27.6 ± 9.1 2.1 27.0 (15.0, 50.0)	[18] 27.5 ± 8.0 1.9 27.0 (16.0, 55.0)	0.978 [γ]
Bilirubin (mg/dL)			
Screening	[19] 0.5 ± 0.2 0.0 0.4 (0.2, 0.9)	[18] 0.4 ± 0.2 0.1 0.4 (0.2, 1.1)	0.525 [φ]
Week 1	[18] 0.4 ± 0.2 0.0 0.45 (0.2, 0.7)	[18] 0.4 ± 0.3 0.1 0.4 (0.2, 1.4)	0.412 [γ]
Week 2	[18] 0.5 ± 0.2 0.0 0.4 (0.3, 0.9)	[18] 0.5 ± 0.2 0.1 0.4 (0.2, 1.2)	0.828 [γ]
GGT (IU/L)			
Screening	[19] 27.8 ± 18.3 4.2 21.0 (9.0, 77.0)	[18] 26.7 ± 18.6 4.4 23.0 (7.0, 77.0)	0.848 [φ]
Week 1	[18] 28.3 ± 16.9 4.0 23.5 (11.0, 68.0)	[18] 23.6 ± 17.0 4.0 19.0 (8.0, 81.0)	0.129 [γ]
Week 2	[18] 29.9 ± 19.3 4.5 22.0 (8.0, 73.0)	[18] 23.9 ± 17.0 4.0 21.0 (7.0, 78.0)	0.118 [γ]
Creatinine (mg/dL)			
Screening	[19] 0.8 ± 0.2 0.0 0.8 (0.5, 1.2)	[18] 0.9 ± 0.2 0.0 0.9 (0.4, 1.2)	0.245 [φ]
Week 1	[18] 0.8 ± 0.2 0.0 0.7 (0.6, 1.1)	[18] 0.8 ± 0.2 0.0 0.8 (0.4, 1.3)	0.823 [γ]
Week 2	[18] 0.8 ± 0.1 0.0 0.8 (0.6, 1.0)	[18] 0.8 ± 0.2 0.0 0.8 (0.4, 1.1)	0.739 [γ]

Table 23 Continued

	Humic Acid (N = 19)	Placebo (N = 18)	P Value
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
Glucose (mg/dL)			
Screening	[19] 104.4 ± 43.6 10.0 92.0 (72.0, 271.0)	[18] 93.3 ± 13.7 3.2 95.0 (67.0, 115.0)	0.310 [φ]
Week 1	[18] 110.7 ± 40.3 9.5 98.0 (76.0, 251.0)	[18] 101.7 ± 15.6 3.7 97.0 (81.0, 133.0)	0.954 [Y]
Week 2	[18] 118.3 ± 44.1 10.4 101.0 (69.0, 231.0)	[18] 97.7 ± 17.8 4.2 95.0 (69.0, 134.0)	0.144 [Y]
Sodium (mmol/L)			
Screening	[19] 140.7 ± 2.7 0.6 141.0 (133.0, 144.0)	[18] 141.9 ± 1.8 0.4 141.5 (139.0, 145.0)	0.125 [φ]
Week 1	[18] 141.6 ± 2.3 0.5 142.0 (137.0, 146.0)	[18] 141.8 ± 2.3 0.5 142.0 (138.0, 146.0)	0.804 [Y]
Week 2	[18] 140.0 ± 2.0 0.5 140.0 (137.0, 144.0)	[18] 141.8 ± 2.9 0.7 141.5 (137.0, 147.0)	0.076 [Y]
Potassium (mmol/L)			
Screening	[19] 4.4 ± 0.3 0.1 4.4 (4.0, 5.2)	[18] 4.4 ± 0.5 0.1 4.4 (3.5, 5.2)	0.842 [φ]
Week 1	[18] 4.5 ± 0.3 0.1 4.5 (3.9, 4.9)	[18] 4.4 ± 0.3 0.1 4.4 (4.0, 5.3)	0.771 [Y]
Week 2	[18] 4.4 ± 0.4 0.1 4.3 (3.9, 5.8)	[18] 4.3 ± 0.4 0.1 4.2 (3.7, 5.4)	0.478 [Y]
Chloride (mmol/L)			
Screening	[19] 103.6 ± 3.0 0.7 104.0 (98.0, 110.0)	[18] 105.2 ± 2.7 0.6 105.5 (99.0, 108.0)	0.112 [φ]
Week 1	[18] 104.3 ± 3.4 0.8 104.5 (98.0, 110.0)	[18] 105.4 ± 3.1 0.7 106.0 (96.0, 111.0)	0.907 [Y]
Week 2	[18] 104.0 ± 3.3 0.8 104.5 (96.0, 108.0)	[18] 105.6 ± 2.8 0.7 106.0 (99.0, 109.0)	0.357 [Y]
Platelet Count (10^9/L)			
Screening	[19] 300.4 ± 77.0 17.7 309.0 (169.0, 420.0)	[18] 297.1 ± 76.8 18.1 289.0 (200.0, 448.0)	0.898 [φ]
Week 1	[18] 299.2 ± 54.9 13.0 291.0 (209.0, 431.0)	[18] 298.6 ± 76.2 18.0 303.5 (172.0, 438.0)	0.916 [Y]
Week 2	[18] 302.9 ± 69.6 16.4 297.5 (214.0, 463.0)	[18] 307.9 ± 88.2 20.8 282.0 (198.0, 510.0)	0.641 [Y]

Table 23 Continued

	Humic Acid (N = 19)	Placebo (N = 18)	P Value
	[N] Mean ± SD SEM Median (Min, Max)	[N] Mean ± SD SEM Median (Min, Max)	
Red Blood Cell (10^{12}/L)			
Screening	[19] 4.8 ± 0.5 0.1 4.7 (3.9, 5.5)	[18] 4.7 ± 0.5 0.1 4.7 (3.9, 5.8)	0.450 [φ]
Week 1	[18] 4.8 ± 0.5 0.1 4.8 (3.8, 5.6)	[18] 4.6 ± 0.4 0.1 4.6 (3.5, 5.6)	0.199 [Y]
Week 2	[18] 4.6 ± 0.5 0.1 4.5 (4.0, 5.4)	[18] 4.6 ± 0.4 0.1 4.7 (4.1, 5.5)	0.347 [Y]
Hemoglobin (g/dL)			
Screening	[19] 14.2 ± 1.5 0.3 13.6 (11.4, 16.5)	[18] 13.5 ± 1.4 0.3 13.2 (10.8, 16.0)	0.158 [φ]
Week 1	[18] 14.2 ± 1.5 0.4 14.2 (11.3, 16.8)	[18] 13.3 ± 1.2 0.3 13.3 (10.9, 15.9)	0.208 [Y]
Week 2	[18] 13.7 ± 1.4 0.3 13.7 (11.3, 15.8)	[18] 13.4 ± 1.1 0.3 13.1 (11.4, 15.5)	0.251 [Y]
Hematocrit (%)			
Screening	[19] 43.2 ± 4.0 0.9 42.1 (35.9, 51.0)	[18] 41.5 ± 3.8 0.9 41.0 (33.8, 47.4)	0.190 [φ]
Week 1	[18] 42.8 ± 4.2 1.0 43.3 (34.7, 49.1)	[18] 40.2 ± 3.3 0.8 40.0 (35.5, 48.8)	0.163 [Y]
Week 2	[18] 41.9 ± 4.0 0.9 42.0 (34.7, 47.4)	[18] 40.9 ± 2.6 0.6 40.8 (35.6, 46.0)	0.635 [Y]

N is number; P is probability; SD is standard deviation; SEM is standard error of the mean; Min is minimum; Max is maximum; ALT is alanine transaminase; AST is aspartate aminotransferase; GGT is gamma-glutamyltransferase; IU is international unit; L is liter, mg is milligram, dL is decilitre; g is gram; % is percent.

[φ] Between-group statistical comparisons were conducted using a T-test. Probability values $p < 0.05$ are significant.

[Y] Between-group statistical comparisons were conducted using analysis of covariance (ANCOVA). Probability values $p < 0.05$ are significant.

There were no significant differences between groups with respect to any of the general clinical or hematological parameters assessed as a measure of safety at any time-point.

7.5 SAFETY CONCLUSIONS

A total of 18 adverse events were reported during the Study. Of these, 17 events occurred in 9 Subjects (47.4%) on Humic Acid and 18 events occurred in 6 Subjects (33.3%) on Placebo.

A total of 16 adverse events were reported during the Study having a possible or probable relationship to Test Article as assessed by the Investigator while blinded to treatments. A greater number of Subjects reported diarrhea (3 vs. 2), dizziness (1 vs. 0), nausea (1 vs. 0), vomiting (1 vs. 0) and stomach cramps (1 vs. 0) on Humic Acid as compared to Placebo. A greater number of Subjects reported stomach aches (1 vs. 0) and stomach discomfort (1 vs. 0) in the Placebo group as compared to the Humic Acid group. It is possible that these adverse events may also have been flu symptoms; thus, conclusions cannot be drawn regarding adverse-event relationships to Test Article. It is noteworthy that 3 Subjects demonstrated an elevation in ALT and AST (2 on Placebo and 1 on Humic Acid), which led to Test-Article discontinuation in 2 cases. Potential factors that may influence high AST and ALT levels include alcohol consumption within 24 hours of having these blood markers tested; thus, firm conclusions cannot be made regarding the relationship of these events to Test-Product since a higher number of Subjects experienced the same event in the Placebo group as compared to the Humic Acid group.

There were no significant statistical differences between groups with respect to measures of blood pressure, heart rate, haematological or general chemistry parameters at any time-point assessed during the Study.

8. DISCUSSION AND OVERALL CONCLUSIONS

Human influenza or "the flu" is a respiratory infection caused by the influenza virus. Every year new strains of viruses appear, causing seasonal outbreaks that result in serious health consequences in immunocompromised populations. The symptoms of influenza start with a headache, chills and cough; and are followed rapidly by fever, loss of appetite, muscle aches and fatigue, running nose, watery eyes and throat irritation. Most people usually recover from influenza within a week, but people over 65 years with chronic conditions such as diabetes or cancer, and infants, are at greater risk of severe complications such as pneumonia (http://www.phac-aspc.gc.ca/influenza/index-eng.php).

Throughout recorded history, influenza pandemics have resulted in devastating mortality and disease. Three influenza pandemics occurred in the 20th Century, each resulting from new strains of influenza virus. According to the World Health Organization (WHO), each year between 250,000 and 500,000 people die worldwide due to seasonal influenza outbreaks. However, during a pandemic year, these numbers reach into the millions (WHO, 2009). In the United States, on average, 41,400 people succumbed to "the flu" each year between 1979 and 2001 (Dushoff *et al.*, 2006). Depending on the severity of the virus and associated complications, on average 20,000 Canadians are hospitalized and around 2,000 to 4,000 die every year of the flu (http://www.phac-aspc.gc.ca/influenza/index-eng.php). Due to the interconnected nature of the world and the high level of global travel, the influenza virus spreads rapidly in the event of a flu pandemic. The most recent H1N1 flu pandemic resulted in 2 to 7.4 million deaths worldwide (http://www.who.int/csr/disease/influenza/pandemic/en/).

Humic Acid, which is a product of the biodegradation of composted organic matter, is a principal component of humic substances and it is also the major organic constituent of soil (humus), peat, coal, many upland streams, dystrophic lakes, and ocean water (Stevenson *et al.*, 1994). Previous scientific research has shown that Humic Acid exhibits anti-inflammatory properties (Kuhnert *et al.*, 1982). Researchers have also observed that Humic Acid blocks virus particles from attaching to healthy host cells, thereby preventing viral replication and subsequent infection. Researchers have found in addition that Humic Acid impedes virulent influenza such as H1N1, as well as more exotic diseases caused e.g., by West Nile virus, hemorrhagic fever, and Coxsackie virus (http://humicacidforhuman consumption.webs.com).

The current Study investigated the efficacy of Humic Acid on influenza A and B symptoms after 2 weeks of treatment in adults. Flu symptoms were assessed with a scoring system based on the severity of cough, fever, runny nose, stuffy nose, aches and pains, headache, chills, sneezing, earaches, and fatigue on a 4-point scale. Of the 37 Subjects that were randomized, 33 Subjects completed the Study. The demographics of the Subjects randomized showed that the Humic Acid and Placebo groups were well-matched for gender and age. The Study design was a single-phase 14-day treatment. With regard to ethnicity, a higher percentage of Subjects recruited was Latin American, but they were equally distributed between groups. A higher percentage of Black and Italian Americans was randomized into the Placebo group (11% and 5.6% Placebo, respectively, vs. 0% in the Humic Acid group). Further, a higher percentage of Subjects in the Humic Acid group (21%) were current smokers as opposed to 5.6% in the Placebo group. Both groups were well-matched in weekly alcohol intake.

Subjects in the Humic Acid group presented with greater severity of nasal symptoms, sneezing, and sweats and chills when compared with those in the Placebo group at the beginning of the Study. Compliance was similar in both groups at Week 1 but decreased in the Humic Acid group by Week 2 due to one withdrawal.

Though there were no statistically-significant changes observed in symptomatic recovery from flu when Subjects were treated with Humic Acid for 2 weeks as compared with those on Placebo, a higher percentage of the Humic Acid Subjects showed notably-better resolution of certain of their flu symptoms. During the first week of supplementation, Subjects on Humic Acid demonstrated a 62% decrease in cough symptoms, a 92% decrease in fever, a 68% decrease in runny and stuffy nose, an 86% decrease in myalgia, a 92% decrease in chills and sneezing, and an 80% decrease in flu-associated fatigue as compared with Placebo (36.8%, 81.8%, 63%, 63%, and 70% and 55%, respectively). It is evident from the results of the Subjects on Placebo that there was a normal resolution of the symptoms over a 7-day period. However, those on Humic Acid experienced greater relief from symptoms than expected from the normal course of the infection. Mean scores for Subjects on Humic Acid were lower than those on Placebo after 7 days of treatment for cough, fever, aches, chills and fatigue in spite of having higher scores than Placebo on Day 1.

These results are clinically noteworthy since the cohort of Subjects undergoing Humic Acid treatment also reported greater severity of symptoms at Baseline, and were also more immune-susceptible since this group had a higher number of current smokers. Previous research has shown that there is an increase in influenza infections among smokers compared with nonsmokers due to higher susceptibility of their immune systems (Robbins *et al.*, 2006; Kark *et al.*, 1982).

Subjects on both Humic Acid and Placebo treatments reported similar use of concomitant medication to control symptoms associated with the flu. Further, the number of Subjects using these medications was similar in both groups.

A visual analogue scale (VAS) is a psychometric response scale that can be used to measure subjective characteristics or attitudes that cannot otherwise be directly measured (Wewers *et al.*, 1994). In the current Study, Subjects were given a self-administered VAS questionnaire to score their ability to perform usual activity on a scale from 0 (not able at all) to 100 (extremely able) after Days 7 and 14 of treatment. There was a statistically-significant increase in VAS scores observed in Subjects on Humic Acid from Screening to Weeks 1 and 2 ($p < 0.001$). However, Subjects on Placebo also demonstrated a statistically-significant increase ($p < 0.001$) in VAS scores from Screening to Weeks 1 and 2. These results are not surprising, since Subjects on Placebo would in any event be expected to show a resolution of their VAS scores with time.

Subjects on Humic Acid treatment presented with greater severity of symptoms at the beginning of the Study, which corresponded to lower scores on their VAS. However, their VAS scores showed a greater percentage improvement (64%) when compared with the scores of Subjects on Placebo (54%) after 7 days of treatment. Subjects on Humic Acid also showed a 107.0% increase in VAS scores from the beginning of the Study to Week 2. (During the normal course of a typical viral episode, resolution would have been expected to provide only a 76% increase in the VAS scores, as reflected by the scores of Subjects in the Placebo group in this Study.)

On further consideration of the effects of age on the results, the VAS scores of Subjects aged between 40 and 60 years increased by 164% when on Humic Acid compared with those on Placebo (70.3%). This finding is of clinical significance since, with any disease or infection, age is associated with a decrease in immune function.

Cytokines are polypeptides produced by immune-system cells. Cytokines play a vital role in the regulation of immune responses. The major cellular sources of TNF-α are activated macrophages, natural killer cells, and antigen-stimulated T-cells. Previous research has shown that the function of TNF-α is pleiotropic, and influences the inflammatory response as well as host resistance to pathogens

(Seo *et al.*, 2001). At low concentrations TNF-α upregulates the expression of adhesion molecules on neutrophills, lymphocytes and macrophages. At moderate concentrations it promotes fever response and increased concentrations of IL-1 and IL-6.

The current Study therefore also investigated the effects of Humic Acid on the expression of TNF-α in serum with influenza A or B on Days 7 and 14. There was statistically-significant difference observed in the expression of TNF-α in Subjects on Humic Acid treatment by Week 2, in comparison with Subjects on Placebo ($p = 0.027$). Further, Subjects on Humic Acid supplementation suppressed TNF-α expression by 26.7% from Screening to Week 2 of treatment, whereas Subjects on Placebo exhibited a 7.1% decrease. Lower levels of TNF-α were found in Subjects on Humic Acid throughout the treatment period in comparison with Subjects on Placebo.

Interleukin-8 (IL-8) is a potent chemoattractant for neutrophils and eosinophils, and has been implicated in a number of inflammatory airway diseases such as cystic fibrosis, respiratory distress syndrome, and chronic bronchitis (Shute *et al.*, 1997). Patients with asthma or other respiratory problems had increased levels of IL-8 in the blood and bronchial mucosa (Pang *et al.*, 1998). IL-8 is released by most immune cells that encounter TNF-α. The primary cellular sources of IL-8 are fibroblasts, phagocytes and endothelial cells. *In vitro*, IL-8 stimulates the activation of eosinophils, T-cells, basophils, and monocytes (Rao, 2005). In this Study there was a higher percentage decrease of IL-8 production within the Placebo group in comparison with the Humic Acid group. (An increase or a sustained level of this cytokine can lead to a better immune response.) There was no statistically-significant change observed in IL-8 expression between Subjects on Humic Acid supplementation and Subjects on Placebo after 2 weeks of treatment. However, there was only a 3.2% decrease in production of IL-8 observed in Subjects on Humic Acid, whereas Subjects on Placebo demonstrated a greater decrease of 10.2% in IL-8 production from Day 1 to Week 2. These results indicate that Humic Acid may have contributed to advantageous immune modulation in these Subjects. Further, there were lower levels of TNF-α seen throughout the Study in the Humic Acid group in comparison with the Placebo group.

CD4+ and CD8+ T-cells are useful biological markers for compromised immunocompetence and also for identifying insufficient antibody responses in the body (Goronzy *et al.*, 2001). Richter *et al.* (2007) found that many individuals have heterosubtype-specific CD4+ and CD8+ T-cells that help recognize conserved internal epitopes common to different serotypes; and, in the presence of such heretosubtypic T-cells, immunity, severity of disease, and duration of infection are reduced in individuals with flu. In the current Study the CD4+ and CD8+ lymphocyte T-cell counts in serum in Subjects treated either with Humic Acid or Placebo were measured after two weeks of treatment. Although there were no statistically-significant differences, Subjects on Humic Acid supplementation showed a 3% *increase* in absolute CD4+ cell counts from Screening to Week 2, whereas Subjects on Placebo showed a 3% *decrease* in CD4+ cell count. The finding that Humic Acid treatment in fact increased both CD4+ and CD8+ cells in this Study suggests that it may play a role in modulating the human immune system response.

This Study was conducted during the Spring 2010 flu season in the United States. The normal course of a typical viral influenza infection is reflected in the results found for the Subjects in the Placebo group. As documented in this Study, Subjects in the Placebo group showed a 76% improvement in their VAS scores by Week 2. These Subjects also had a reasonable resolution of their symptoms by that time, as would be expected from the natural progression of the flu. However, Subjects treated with Humic Acid showed a 107% improvement in their flu-related symptoms scores, a clinically-noteworthy improvement over Placebo.

Vaccination strategies are in place in most countries to combat the deleterious effects of seasonal viral outbreaks. However, controversy associated with the concept of vaccination, as well as their side

effects, limit participation in these programs. The success of immunization programs depends upon public confidence in their safety. As a consequence, a certain percentage of the population refrains from participation, thereby resulting in increased risk of viral-related complications, incapacitation, and lost wages during flu season each year. These consequences are of even greater concern to high-risk individuals, such as the elderly, and those who are already immunocompromised.

The situation strongly compels the argument to provide preventative and treatment measures to combat viral flu epidemics, such as Humic Acid, which has the ability to impede and prevent the adhesion of viruses to healthy cells as well as combat detrimental inflammatory responses to infection.

In conclusion, although the results of this Study precluded drawing firm statistical-based conclusions, it can be said that Humic Acid demonstrated pronounced clinical efficacy on flu-related symptoms, cytokine response, the immune-system modulators CD4+ and CD8+, and VAS scores when administered as 6 x 250-mg tablets daily for 14 days within the demographic of the Subjects studied.

9. RECOMMENDATIONS

1. Future studies should investigate the efficacy of Humic Acid on a larger sample of Subjects; which should also include assessment of actual viral load.
2. Stratification of Subjects based on age during randomization may provide more conclusive results on the effect of Humic Acid on the immune response.
3. Seasonal flu prevention requires at least 6 weeks of treatment; further study is therefore required on the efficacy of using Humic Acid prior to flu season and evaluating its impact as a prophylactic.
4. A combination of immunoglobulins IgG and IgE should also be covered in flu cases.
5. Since immune response decreases with age, further study should be designed with focus on the elderly.
6. Further study may be of value in examining combination therapies of Humic Acid with other flu treatments.

10. REFERENCE LIST

1. Ansorg R, Rochus W (1978). Studies on the antimicrobial effect of natural and synthetic humic acids. Arzneimittelforschung 28(12):2195-2198.

2. Blick TJ, Sahasrabudhe A, McDonald M, Owens IJ, Morley PJ, Fenton RJ, McKimm Breschkin JL (1998). The interaction of neuraminidase and hemagglutinin mutations in influenza virus in resistance to 4-guanidino-Neu5 Ac2en. Virology 246:95-103.

3. Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M (2007). Transmission of influenza A in human beings. Lancet Infect Dis 7(4):257-265.

4. Centers for Disease Control and Prevention (2009). http://www.cdc.gov/Other/about_cdcgov.html.

5. Colombo GL, Ferro A, Vinci M, Zordan M, Serra G (2006). Cost benefit analysis of influenza vaccination in a public health care unit. Therap Clin Risk Manag 2(2):219-226.

6. Dushoff J, Plotkin JB, Viboud C, Earn DJ, Simonsen L (2006). Mortality due to influenza in the United States — an annualized regression approach using multiple-cause mortality data. Amer J Epidem 163(2):181-187.

7. Eccles R (2005). Understanding the symptoms of the common cold and influenza. Lancet Infect Dis 5(11):718–25.

8. Goronzy JJ, Fulbright JW, Crowson CS (2001). Value of immunological markers in predicting responsiveness to influenza vaccination in elderly individuals. Amer Soc Microbiol 12182-12187.

9. Helbig B *et al.* (1987). Therapeutic effect of E-5-2-bromovinyl 2-deoxyuridine, caffeic acid oxidation product, and trisodiumphosphonoformate on cutaneous *herpes simplex virus type 1* infected guinea pigs. Med Viral 23(3):303-309.

10. Horwood F, Macfarlane J (2002). Pneumococcal and influenza vaccination: current situation and future prospects. Thorax 57(Suppl 2):II24–II30.

11. Huck TA, Porter N, Bushell, ME (1991). Effects of humates on microbial activity. J Gen Microbiol 137(10):2321-2329.

12. Influenza (Seasonal), World Heath Organization. 2009.

13. Kark JD, Lebiush M, Rannon L (1982). Cigarette smoking as a risk factor for epidemic (H1N1) influenza in young men. N Engl J Med 307:1042-1046.

14. Kilbourne ED (1975). "The Influenza Virus and Influenza". New York: Academic Press.

15. Kloecking R (1991). Interaction of humic acids and humic acid like polymers with *herpes simplex virus type 1*. In "Humic Substances in the Aquatic and Terrestrial Environment", Berlin: 408-412.

16. Kuhnert M *et al.* (1982). Humates and inflammation. Arch E-p. Veterinarmed 36:169-77.

17. Laub R (1995). The chemically induced inhibition of HIV-1 replication. Laub BioChemicals Corp. www.laubbiochem.com.

18. Laub R (1999). Process for preparing synthetic soil-extract materials and medicaments based thereon. US 5,945,446.

19. Laub R (2000). Laub developing humate with anti-HIV, HSV, HPV and other antiviral activity. Biotechnology Information Institute, Antiviral Drug and Vaccine Development Information 12(2).

20. Li Y, Yamakita Y, Krug RM (1998). Regulation of a nuclear export signal by an adjacent inhibitory sequence: the effector domain of the influenza virus NS1 protein. Proc Natl Acad Sci USA 95:4864-4869.

21. Lu F-J, Tseng S-N, Li M-L, Shih S-R (2002). In vitro anti-influenza virus activity of synthetic humate analogues derived from protocatechuic acid. Arch Virol 147(2):273-284.

22. Mentel R *et al.* (1983). Effectiveness of phenol body polymers (humic acids) against influenza virus. Biochim Acta 42(10):1353-1356.

23. Pang L, Knox AJ (1998). Bradykinin stimulates IL-8 production in cultured human airway smooth muscle cells: role of cyclooxygenase products. J Immunol 161:2509-2515.

24. Public Health Agency of Canada http://www.phac-aspc.gc.ca/influenza/index-eng.php.

25. Richter M, Ray SJ, Chapman TJ, Austin SJ, Rebhahn J, Mosmann TR, Gardner H, Kotelianski V, deFougerolles AR (2007). Collagen distribution and expression of collagen-binding 11 (VLA-1) and 21 (VLA-2) integrins on CD4 and CD8 T Cells during influenza infection 1. J Immunol 178:4506-4516.

26. Robbins C, Bauer C, Vujicic N, Gaschler G, Lichty BD, Brown EG, Stampfli MR (2006). Cigarette smoke impacts immune inflammatory responses to influenza in mice. Amer J Respir Crit Care Med 174:1342-1351.

27. Seo H, Webster RG (2002). The tumor necrosis factor alpha exerts powerful anti-influenza virus effects in lung epithelial cells. J Virol 1071-1076.

28. Shute JK, Vrugh IJD, Lindley ST, *et al.* (1997). Free and complexed interleukin-8 in blood and bronchial mucosa in asthama. Amer J Respir Crit Care Med 155:1877-1880.

29. Sidwell RW, Huffman JH, Barnard DL, Bailey KW, Wong MH, Morrison A, Syndergaard T, Kim CU (1998). Inhibition of influenza virus infections in mice by GS4104, an orally effective influenza virus neuraminidase inhibitor. Antiviral Res 37:107-120.

30. Stevenson FJ (1994). "Humus Chemistry: Genesis, Composition, Reactions". New York: Wiley.

31. Sydow G *et al.* (1986). The effects of phenolic polymers on retroviruses. Pharmazie 41(12):865-868.

32. Thiel KD, Heibig B, Kloecking R, Vutzler P, Sprossig M, Schweizer H (1981). Comparison of the in vitro activities of ammonium humate and of enzymically oxidized chlorogenic and caffeic acids against type 1 and type 2 human herpes virus. Pharmazie 36(1):50-53.

33. Wewers M.E, Lowe N.K (1990). A critical review of visual analogue scales in the measurement of clinical phenomena. Res Nurs Health 13:227-237.

34. World Health Organization. Global alert and response (GAR). http://www.who.int/csr/disease/influenza/pandemic/en/ .

35. World Health Organization. World now at the start of 2009 influenza pandemic. http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/index.html .

11. SIGNATURES

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the Study.

PRINCIPAL INVESTIGATOR / MEDICAL DIRECTOR:

Dale Wilson, MD
Medical Director
KGK Synergize Clinic

Sept. 7, 2010
Date

AUTHOR:

Malkanthi Evans, PhD
Scientific Director
KGK Synergize Clinic

Sept 08, 2010
Date

SITE MANAGEMENT:

Robert A. Guthrie
Vice President,
Contract Research Services
KGK Synergize, Inc.

Sept 08, 2010
Date

12. APPENDICES

Appendices submitted with the report include:

A. Protocol
B. Patient Information and Consent Form
C. CVs.
D. Regulatory and Ethics Approval
E. Electronic Data Files Including Individual Adverse Event Listing, Medical History of Patients, Concomitant Medications, and Individual Response Data

APPENDIX A

CLINICAL PROTOCOL COVER PAGE

Protocol Title:	A Pilot Study to Investigate the Effects of Humic Acid on Flu Symptoms
Protocol Number:	10HFHL
Protocol Date:	January 05, 2010
Amendment(s):	
Study Phase:	Phase I
Study Design:	Randomized, double-blind, placebo-controlled, parallel-group, pilot study
Sponsor:	Laub BioChemicals Corporation 1401 Quail St., Ste. 121 Newport Beach, CA 92660
Sponsor Contact:	Dr. Richard J. Laub, PhD President/CEO Laub BioChemicals Corporation 1401 Quail St., Ste. 121 Newport Beach, CA 92660 USA 949-476-9883
CRO:	KGK Synergize Inc. Suite 1440, "One London Place" Bldg. 255 Queens Ave. London Ontario N6A 5R8 CANADA 519-438-9374
Medical Director:	Dr. Dale Wilson, MD KGK Synergize Inc. 519-438-9374 ext. 250

LIST OF ABBREVIATIONS AND SYMBOLS

AE	Adverse event
ALT	Alanine transaminase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
CBC	Complete blood count
CD4+	T helper cells
CD8+	Cytotoxic T cells
Cl	Chloride
COPD	Chronic obstructive pulmonary disease
°C	Degrees Celsius
°F	Degrees Fahrenheit
EDTA	Ethylenediaminetetraacetic acid
e.g.	For example
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
>	Greater than
HIV	Human immunodeficiency virus
ICH	International conference of harmonization
i.e.	For example
IL-8	Interleukin-8
K	Potassium
kg	Kilogram
mg	Milligram
mL	Milliliter
mm	Millimeter
mm Hg	Millimeters of mercury
Na	Sodium
NSAID	Non-steroidal anti-inflammatory drug
ppm	Parts per million
%	Percent
RNA	Ribonucleic acid
SAE	Serious adverse event
SST	Serum separating tube
TID	Three times daily
TNFα	Tumor necrosis factor-alpha
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell
WHO	World Health Organization

TABLE OF CONTENTS

1. INTRODUCTION

Influenza, commonly referred to as the flu, is an acute viral infection caused by RNA viruses of the family Orthomyxoviridae (the influenza viruses) (Eccles, 2005). Influenza viruses are known for high morbidity and mortality in humans and animals, and are a cause of acute respiratory diseases (WHO, 2009). Epidemics occur yearly during winter and, while most people recover from influenza, there are large numbers of people who need hospitalization and many who die from the disease. In United States, yearly on average, 5% to 20% of the population becomes infected with the influenza virus, more than 200,000 people are hospitalized from influenza-related complications, and approximately 36,000 people die from influenza-related causes (Centers for Disease Control and Prevention, 2009). Influenza causes serious public health and economic problems as a result of absence in the work force and productivity losses.

There are three types of seasonal influenza – types A, B and C. These types are further classified according to different kinds and combinations of virus surface proteins. Influenza is characterized by a sudden onset of high fever, chills, cough, headache, muscle and joint pain, weakness, general discomfort, sore throat and runny nose (Brankston *et al.,* 2007) and is often confused with the common cold, but is more severe and is caused by a different type of virus (Eccles, 2005).

The most effective way to prevent influenza or severe health outcomes from illness is by vaccination. The drawback to the vaccine is that it is most effective when circulating viruses are well-matched with vaccine viruses (Horwood and Macfarlane 2002). Antivirals such as Zanamivir and Oseltamivir (commonly known as Tamiflu) have been shown to inhibit both influenza A and influenza B virus replication *in vitro* (Blick *et al.*, 1998; Sidwell *et al.*, 1998; Li *et al.*, 1998). Further, Amantadine and Rimantadine have been used in the prevention and treatment of influenza viruses (Lu *et al.*, 2002). Annual epidemics are caused by antigenic shifts in influenza viruses, which results in modification of the virus, resulting in new virus subtypes (Kilbourne, 1975). Because antigenic shifts occur unpredictably, the general population has no immunity to the new subtypes and effective vaccines cannot be prepared in advance. As influenza viruses are constantly changing, the success of the vaccines is often in question. Further limitations are related to adverse effects of vaccines in some recipients, as well as the fear ofvaccine causing the flu or other severe adverse health effects. As a result, approximately 15-20% of the population refrains from vaccination. An effective alternative treatment, medicine, or combination therapy for the treatment of influenza without side effects is therefore desirable.

Previous scientific studies on humic acid have shown that it exhibits anti-inflammatory (Kuhnert *et al.*, 1982) and antiviral properties (Mentel *et al.*, 1983). Humic acid is a high moloecular-weight discotic molecule that is isolated from soil. Humates act as nutrients and media additives for soil microflora, and for the production of antibiotics in the soil (Huck *et al.*, 1991). Humic substances have been shown to exhibit antiviral properties against rhinovirus (Sydow *et al.*, 1986); recent studies have shown that humic acid impairs the attachment of human immunodeficiency virus (HIV) (Laub, 2000; Laub, 1995), herpes simplex virus types 1 and 2 (Helbig, *et al*, 1987; Kloecking, 1991), influenza types A and B, and other respiratory tract infections (Laub, 2000; Sydow *et al.*, 1986). Previous studies have also suggested the broad antibacterial potential of natural and synthetic humic acids with varying degrees of sensitivity to test organisms. In one study the sensitivity ranged from 2500-1250 microorganisms/mL with natural humic acid, and 39 microorganism/mL with synthetic hydroquinone humic acid (Ansorg and Rochus, 1978). Recent studies have additionally shown the positive effects of humus

extract in Ayu fish against *Flavobacterium psychrophilum* infection (cold water disease) (Nakagawa *et al.,* 2009).

The mechanism of action of humic acid responsible for the inhibition of viral infection is believed to be the prevention of attachment of virus particles onto host cells (viral fusion inhibition), which in turn limits viral replication (Laub, 1999). *In vitro* studies of humic-like substances, for example, the oxidative polymer of protocatechuic acid (OP-PCA), have demonstrated the inhibition of replication of influenza virus A/WSN/33 (H1N1) in Madin-Darby canine kidney (MDCK) cells at concentrations of no cytotoxicity. It has also been demonstrated that humic acid inhibits the endonuclease activity of viral RNA polymerase (Lu *et al.*, 2001). (Influenza viral RNA polymerase plays an important role in viral RNA synthesis, which occurs after a virus has penetrated a host cell.) While humic acid is effective and may be added at any time after viral attachment, higher inhibitory effects are generally found when added at or prior to the stage of virus-cell fusion.

While previous *in vitro* and live-animal studies have demonstrated the therapeutic potential of humic acid, live-animal acute toxicity studies sponsored by Laub BioChemicals Corporation have additionally shown the material to be complete safety at levels of up to 50 mg/kg body weight. Thus, concentrations in the range of 50-2000 parts per million (ppm) are efficacious, yet not cytotoxic (Schiller *et al.*, 1979).

This study will be the first test of the effects of humic acid on flu symptoms in humans; the results will provide valuable information on influenza prevention and treatment.

2. STUDY OBJECTIVES

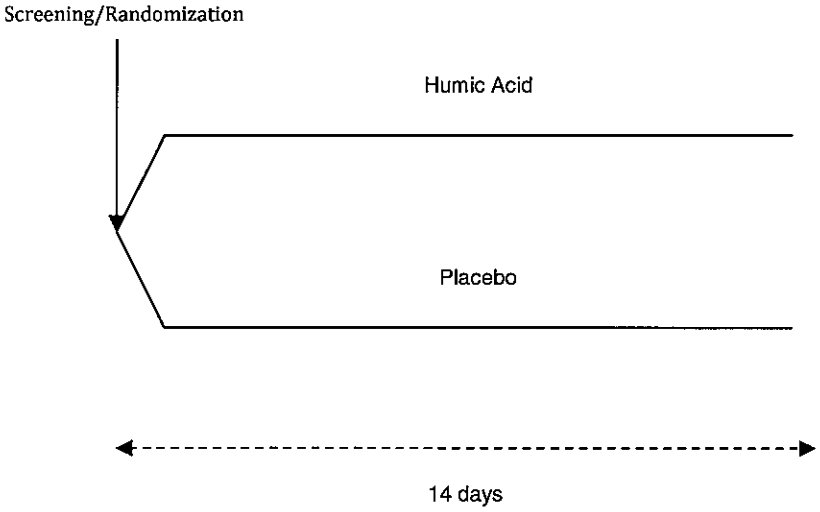
The primary objective of this study is to assess the efficacy of humic acid on flu symptoms as assessed by the alleviation of symptoms after 7 and 14 days of treatment in adults with influenza A or B. This will be determined by the use of a daily diary to assess the following symptoms during the trial on a 4-point scale (0=absent, 1=mild, 2=moderate, 3=severe):

- cough
- fever
- runny nose
- stuffy nose
- aches and pains
- headache
- chills
- sneezing
- ear aches
- fatigue

Additional endpoints will include:

- Visual analog scale (VAS) 0-100 mm, for ability to perform usual activities
- Doses of concomitant therapies for symptom treatment
- Immunological markers (WBC differential, CD4+, CD8+, TNFα, IL-8)

3. STUDY DESIGN



This is a multi-center, randomized, double-blind, placebo-controlled, parallel-group efficacy pilot study.

The study will consist of a single 14-day treatment period. Screening and randomization will occur on the same day.

The planned sample size for the study is 40 subjects, with 20 subjects randomized equally to each of the two study arms. The subjects will be recruited over the flu season.

Subjects will be randomized to one of the two treatment groups: Humic Acid or Placebo.

In order to evaluate primary and secondary endpoints, study assessments will be conducted at baseline, Day 7 and Day 14.

The study will be conducted at two sites in the US.

4. SELECTION OF STUDY POPULATION

The target population for this study consists of 40 adults with influenza A or B.

The study will be conducted in both male and female subjects of any ethnicity. Each subject will have to fulfill the inclusion criteria listed in Section 4.1. Subjects will not be included in the study if they meet any of the exclusion criteria listed in Section 4.2.

4.1 Inclusion Criteria

1. Male or female age 18 years or older
2. If female, subject is not of child bearing potential. Defined as females who have had a hysterectomy or oophrectomy, bilateral tubal ligation or are post-menopausal (natural or surgically with > 1 year since last menstruation)

   –OR:

Female subjects of childbearing potential must agree to use a medically approved method of birth control and have a negative urine pregnancy test result. Acceptable methods of birth control include:

- double-barrier method (condoms with spermicide or diaphragm with spermicide)
- 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)
- intrauterine devices
- vasectomy of partner
- abstinence

3. Positive diagnostic testing for influenza A or B by using rapid influenza antigen test (nasopharyngeal swabs)
4. Illness as defined by onset or presence of respiratory symptom (cough, sore throat, nasal symptoms, sneezing) and one the following symptoms beginning within 48 hours before study enrollment:
   - fever ≥38.0 °C (≥100.4 °F) taken orally or subject report of fever within 24 hours prior to screening.
   - constitutional symptom [headache, myalgia (muscle pain), sweats/chills, fatigue]
5. Available for all the visits scheduled in the study
6. Receipt of any vaccine against influenza (based on verbal confirmation by the subject) for current season will be allowed
7. Agreement to comply with study procedures and test article consumption
8. Has given voluntary, written, informed consent to participate in the study

4.2 Exclusion Criteria

1. Women who are pregnant, breastfeeding, or planning to become pregnant during the course of the trial
2. Experienced any acute disease or infection requiring systemic antibiotic or antiviral therapy within the past 7 days
3. Cancer chemotherapy/radiation treatment within the 3 months prior to enrollment
4. Receipt of blood or blood products and/or plasma derivatives or any immunoglobulin preparation within 4 months prior to enrollment
5. Clinically significant acute respiratory distress
6. Chronic obstructive pulmonary disease (COPD)
7. Severe asthma (at the discretion of the Principal Investigator)
8. Known or suspected impairment/alteration of the immune system or immuno-compromised (in the past 5 years)
9. Disorders of coagulation
10. Surgery planned during the study period
11. History of drug or alcohol abuse
12. Participation in a clinical research trial within 30 days prior to randomization
13. Allergy or sensitivity to study supplement ingredients
14. Individuals who are cognitively impaired and/or who are unable to give informed consent

15. Any other condition which in the Investigator's opinion may adversely affect the subject's ability to complete the study or its measures or which may pose significant risk to the subject

4.3 Concomitant Medications

The use of antibiotic or antiviral therapies within seven days of randomization is prohibited. Subjects who have received immunosuppressive therapies in the past 5 years or chemotherapy / radiation treatment within the 3 months prior to screening will not be enrolled into this study. Birth control is allowed during the study. Subjects who are currently taking prescribed birth control must agree to maintain their current method and dosing regimen during the course of the study.

Subjects will be allowed to use concomitant therapies for the treatment of symptoms (i.e., antipyretics, decongestants, expectorants, throat lozenges). Subjects will be asked to refrain from taking acetaminophen, aspirin, ibuprofen or NSAID within 4 hours prior to temperature readings.

4.4 Early Withdrawal

Subject discontinuation should be considered at the discretion of the Principal Investigator. The circumstances of any discontinuation must be documented in detail. If possible, the evaluations planned for the end of the study will be carried out at the time when the subject is withdrawn from the study. A subject leaving the study prematurely will NOT be replaced by another. Criteria for removal of subjects from the study will include:

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

Clinical Judgment of Physician. A subject may be withdrawn from the study if, in the opinion of the Principal Investigator, it is not in the subject's best interest to continue. This includes but is not limited to adverse events or serious adverse events related to the investigational product causing clinically significant illness; the need for prohibited concomitant medication; female subject who becomes pregnant during the course of the trial.

Protocol Violation. Any subject found to have entered this study in violation of the protocol will be discontinued from the study at the discretion of the Principal Investigator. This will include any subject found to have been inappropriately enrolled (did not meet eligibility criteria). Subject non-compliance includes either not showing up for study visits, not taking investigational product as directed, or refusing to undergo study visit procedures. Subjects who are found to be taking prohibited medications or supplements without the knowledge of the Principal Investigator will also be withdrawn. Any major protocol deviations (i.e., those that increase the risk to subjects and/or compromise the integrity of the study or its results) will result in subject discontinuation.

5. INVESTIGATIONAL PRODUCT

5.1 Manufacturing and Storage

The investigational product as well as placebo product to be used in this study were both manufactured under GMP conditions by an FDA-approved manufacturing facility. Both products should be stored in a cool, dry place at a maximum temperature of 85°F and 70% relative humidity.

5.2 Labeling and Coding

The humic acid and placebo investigational products will be labeled according to the requirements of ICH-GCP guidelines as well as applicable local regulatory guidelines. Investigational products will be randomized and coded by the sponsor. Each investigator will be provided with a randomization list indicating the order of randomization. Each subject will be assigned a randomization code according to the order of the randomization list. The investigator will be provided with sealed envelopes for each randomization code. These envelopes are to remain sealed except in the event of an emergency. In the event that it is necessary to unblind a subject's treatment, the envelope labeled with the subject's randomization code will be opened. Notification of unblinding must be reported to the study sponsor within 24 hours.

Sample Label

Randomization Code: ****** Protocol No.: 10HFHL
Humic Acid Lot No. 072604 or Placebo
Expiry date: December 2016
Investigational Natural Health Product
To be used under the supervision of a qualified investigator.
Sponsor & Manufacturer: Laub Biochemicals Corporation
1401 Quail St., Ste. 121, Newport Beach, CA USA
For investigational use only. Keep out of reach of children. Store at room temperature.
Contains: 60 tablets

Investigator Name: _____ Phone:_____
Subject No.: _____ Subject Initials:_____
Date dispensed:_____ Date returned:_____

5.3 Humic Acid

The active ingredient in the humic acid investigational product is humic acid, 250 mg/tablet. The remaining (inactive) ingredients are: dextrose, sucrose fatty acid ester, silicon dioxide USP/FCC, and sodium starch glycolate USP.

5.4 Placebo

The ingredients in the placebo investigational product are: cantab dextrose, sucrose fatty acid ester, microcrystalline cellulose, and sodium starch glycolate USP.

5.5 Directions

The study product will be supplied in the form of tablets. Subjects will be instructed to take 2 tablets, 3 times daily (TID), preferably with meals. Subjects will be instructed to begin taking the study product on the day following their randomization visit (Treatment Day 1). If a subject

misses a dose, they make take it as soon as they remember that day. A subject should not take more than 3 doses in a single day. Subjects will be instructed to return all original packaging and unused tablets at the next study visit. Subjects will also be instructed to record their use of the study product in the subject treatment diary.

5.6 Unblinding

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 patient's condition, the treatment emergency code for that patient may be broken and the investigational product identified. The sponsor must be notified of any unblinding within 24 hours. Details of patients who are unblinded during the study will be included in the Final Report.

6. STUDY ASSESSMENTS

See Appendix 1 for the Schedule of Assessments and procedures.

6.1 Visit 1 – Screen / Baseline

At screening, a Subject Information and Consent Form will be given to each potential subject. The subject will read the information carefully and will be given the opportunity to seek more information if needed. The subject will also be provided with the option of taking the consent form home to review prior to making his or her decision. If agreeable, the subject will sign the consent form and receive a duplicate. Once consent has been obtained, the screening visit will proceed. Each subject will be assigned a screening number at the screening visit. After the subject has signed the informed consent, the screening number will be assigned sequentially and entered in the Screening and Enrollment Log. Screening numbers will be allocated in the chronological order of the subject's signing the informed consent.

Visit 1 shall include:

- review of medical history and concomitant therapies
- vitals signs (heart rate, blood pressure, temperature)
- physical examination (excluding breast, rectal/vaginal examination)
- self-administered questionnaires (symptoms and VAS)
- urine pregnancy test for women of childbearing potential
- a review of inclusion/exclusion criteria
- laboratory tests (hematology, chemistry, and immunological markers)

Eligible subjects will be randomized to humic acid or placebo via the Randomization Schedule provided to the Investigator on the same day.

Subject randomization numbers are to be allocated in the order listed on the Randomization Schedule.

After all visit assessments are performed, subjects will be dispensed the study product.

Subjects will receive one of the following treatment regimens:

- humic acid as 2 tablets TID for a total of 6 tablets daily for 14 days
- placebo as 2 tablets TID for a total of 6 tablets daily for 14 days

Subjects will be instructed in detail by site personnel about the dosing regimen. The first dose of study product is to be taken the day after Visit 1 (treatment day 1).

Paper diaries and electronic thermometers will be provided to the subjects. Diaries will be used by subjects to record daily symptom scores, daily oral temperature, investigational product use, concomitant therapy use including treatments taken for symptoms, and changes in health status including adverse effects.

Subjects will be allowed to use concomitant therapies for the treatment of symptoms (i.e., antipyretics, expectorants, throat lozenges). Subjects will be asked to refrain from taking acetaminophen, aspirin, ibuprofen or NSAID within 4 hours prior to temperature readings.

The next visit will be scheduled for day 7 (± 2 days).

Subjects will return to the clinic for follow-up at days 7 and 14.

6.2 Visit 2 / Day 7

Subjects will return the clinic on day 7 (± 2 days). Any remaining investigational product and packaging, and diary will be returned and a new supply of product and new diary will be dispensed.

Study visit assessments will include:

- review of subject diary, concomitant therapies and adverse events
- compliance calculation
- vitals signs
- self-administered VAS questionnaire
- laboratory tests (hematology and immunological markers)

The next visit will be scheduled for day 14 (± 2 days).

6.3 Visit 3 / Day 14 – End of Study

Subjects will return to the clinic on day 14 (± 2 days). Any remaining investigational product and packaging, and diary will be returned.

Study visit assessments will include:

- review of subject diary, concomitant therapies and adverse events
- compliance calculation
- vitals signs
- self-administered VAS questionnaire
- laboratory tests (hematology, chemistry and immunological markers)

6.4 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.

6.4.1 Physical Examination

A physical examination (excluding breast, rectal/vaginal examination) will be performed by a physician at baseline. Physical examination will include a standard neurological examination.

6.4.2 Vital Signs

Vital signs will include temperature (measured orally), blood pressure (mm Hg), and heart rate (beats/minute). Vital signs will be measured in the seated position after at least 5 minutes of rest in this position.

6.4.3 Compliance

Compliance will be assessed by counting the returned tablets at each visit. Compliance is calculated by determining the number of tablets taken divided by the number of tablets expected to have been taken.

$$\frac{number\ of\ tablets\ taken}{number\ of\ tablets\ expected\ to\ be\ taken} \times 100\%$$

6.5 Laboratory Analysis

Blood samples will be drawn at each study visit as indicated in the Schedule of Assessments.

Protection of subject confidentiality will extend to all data generated from the assaying of these samples. The samples will be alphanumerically coded and the persons performing the analysis will not be aware of the subject's identity.

Whole blood will be collected into EDTA tubes for CBC (includes WBC differential) and T lymphocyte counts (CD4+, CD8+). Serum will be generated from blood collected into SST tubes for electrolytes (Na, K, Cl), glucose, creatinine, AST, ALT, GGT, bilirubin, TNFα, and IL-8.

The urine pregnancy test will be performed at the clinic site.

7. Safety Instructions and Guidance

7.1 Adverse Events and Laboratory Abnormalities

7.1.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject who has been administered an investigational product and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the

use of a product, whether or not it is considered related to that product. Pre-existing conditions which worsen during a study are to be reported as AEs. Flu symptoms are recorded daily by the subject and may worsen during the trial. These events will be captured as daily symptom scores and are not to be recorded as separated adverse events.

During the study, subjects should record any adverse effects in their diary. At each visit the subject 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 investigator 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 investigator as either:

Most probable:	There is a reasonable relationship between the investigational product and AE. 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 AE. The event responds to dechallenge.
Possible:	There is a reasonable relationship between the investigational product and AE. Dechallenge information is lacking or unclear.
Unlikely:	There is a temporal relationship to investigational product administration but there is no reasonable causal relationship between the investigational product and the AE.
Not related:	No temporal relationship to the investigational product administration or there is a reasonable causal relationship between non-investigational product, concurrent disease or circumstance and the AE.

7.1.2 Serious Adverse Events

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

- Death
- A life-threatening adverse event
- In-patient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly/birth defect in the offspring of a subject who received the study treatment
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but which may jeopardize the subject 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

7.1.3 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).

7.1.4 Laboratory Test Abnormalities

Any treatment-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 AE form in the study record:

- Accompanied by clinical symptoms
- Leading to interruption or discontinuation of the investigational product
- 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 investigational product that falls outside the laboratory reference range and meets the clinical significance criteria (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 a serious adverse event (SAE) should be reported as such, in addition to being reported as an AE in the study record.

7.2 Treatment and Follow-up of AEs and Laboratory Abnormalities

7.2.1 Treatment and Follow-up of AEs

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

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

7.2.2 Follow-up of Laboratory Abnormalities

In the event of clinically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded in the study record.

7.3 Reporting of SAEs and Unexpected Adverse Reactions

Notification of any serious adverse events must be made in writing to the study sponsor within 24 hours of learning of the event. The IRB will be notified of all SAEs and unexpected adverse reactions.

8. STATISTICAL EVALUATION

8.1 Determination of sample size

Forty subjects will be randomized in an equal ratio to one of the two treatments. As this is a pilot study a formal sample size calculation was not performed.

8.2 Analysis Plan

The distribution of baseline characteristics in the two groups will be compared descriptively. Efficacy analysis will include all subjects completing at least one follow-up visit post randomization. For analysis of symptom scores, there will be no imputation of missing data. The average score will be based on the available number of days of data. Treatment group comparisons for primary and secondary outcomes will be made using the ANOVA (analysis of variance) model. Safety analysis will include all subjects randomized to treatment. Safety analysis will include parameters of haematology, general chemistry, and adverse events. Compliance with investigational product usage and the usage of concomitant medications will be compared between groups using Chi-square.

8.2.1 Study Population Description

Frequency counts and proportions will be used to describe categorical variables. The mean, standard deviation, minimal and maximal values, and median will be calculated for continuous variables.

8.2.2 Premature Discontinuation Description

For each premature discontinuation, the following parameters will be listed: subject number, dates of treatment start and end of treatment, and the reason for premature discontinuation. Drop-outs during the treatment period will not be replaced.

8.2.3 Safety

For adverse events, a descriptive analysis will be given. Adverse events will be presented in a frequency table, by body system/group and treatment. Furthermore, nature, incidence, severity, and causality will be reported for each adverse event.

8.2.4 Protocol Deviation Description

All protocol deviations will be listed in the final study report.

9. DATA COLLECTION AND STORAGE

All data collection and record storage will be done in compliance with ICH GCP Guidelines Current Step 4 version dated June 10, 1996; and all applicable local regulatory guidelines.

10. 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. 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.

11. REFERENCES

1. Eccles R (2005). "Understanding the symptoms of the common cold and influenza". Lancet Infect Dis 5(11): 718–25.
2. Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M (2007). "Transmission of influenza A in human beings". Lancet Infect Dis 7(4): 257–65.
3. World Health Organization. World now at the start of 2009 influenza pandemic. on Dec 15, 2009. http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/index.html
4. Horwood F, Macfarlane J (2002). "Pneumococcal and influenza vaccination: current situation and future prospects". Thorax 57(Suppl 2): II24–II30.
5. Mentel R *et al.* (1983). "Effectiveness of phenol body polymers (humic acids) against influenza virus". Biochem Acta 42(10): 1353-1356.
6. Kilbourne ED (1975). "The influenza virus and influenza". Academic Press, New York.
7. Centers for Disease Control and Prevention (2009). http://www.cdc.gov/Other/about_cdcgov.html- on Dec15.
8. Kuhnert M *et al.* (1982). "Humates and Inflammation". Arch E-p. Veterinarmed 36: 169-77.
9. Huck TA, Porter N, Bushell, ME (1991). "Effects of humates on microbial activity". J Gen Microbiol 137(10): 2321-2329.
10. Ansorg R, Rochus W (1978). "Studies on the antimicrobial effect of natural and synthetic humic acids". Arzneimittelforschung 28(12): 2195-2198.
11. Laub R (2000). "Laub developing humate with anti-HIV, HSV, HPV and other antiviral activity". Biotechnology Information Institute, Antiviral Drug and Vaccine Development Information 12(2).
12. Laub R (1995). "The chemically induced inhibition of HIV-1 replication". Laub BioChemicals Corp. www.laubbiochem.com.
13. Laub R (1999). "Process for preparing synthetic soil-extract materials and medicament based thereon". **US** 5,945,446.
14. Sydow G *et al.* (1986). The effects of phenolic polyments on retroviruses". Pharmazie 41(12): 865-868.
15. Helbig B *et al.* (1987). "Therapeutic effect of E-5-2-bromovinyl 2-deoxyuridine, caffeic acid oxidation product, and trisodiumphosphonoformate on cutaneous herpes simplex virus type 1 infected guinea pigs". Med Viral 23(3): 303-309.
16. Kloecking R. "Interaction of humic acids and humic acid like polymers with herpes simplex virus type 1". "Humic Substances in the Aquatic and Terrestrial Environment", Berlin: 408-412.
17. Thiel KD, Heibig B, Kloecking R, Vutzler P, Sprossig M, Schweizer H (1981). "Comparison of the in vitro activities of ammonium humate and of enzymically oxidized chlorogenic and caffeic acids against type 1 and type 2 human herpes virus". Pharmazie 36(1): 50-53.

18. Lu F-J, Tseng S-N, Li M-L, Shih S-R (2002). "*In vitro* anti-influenza virus activity of synthetic humate analogues derived from protocatechuic acid". Arch Virol 147(2):273-284.
19. Blick TJ, Sahasrabudhe A, McDonald M, Owens IJ, Morley PJ, Fenton RJ, McKimm Breschkin JL(1998). "The interaction of neuraminidase and hemagglutinin mutations in influenza virus in resistance to 4-guanidino-Neu5 Ac2en". Virology 246:95-103.
20. Sidwell RW, Huffman JH, Barnard DL, Bailey KW, Wong MH, Morrison A, Syndergaard T, Kim CU (1998). "Inhibition of influenza virus infections in mice by GS4104, an orally effective influenza virus neuraminidase inhibitor". Antiviral Res 37:107-120.
21. Li Y, Yamakita Y, Krug RM (1998). "Regulation of a nuclear export signal by an adjacent inhibitory sequence: the effector domain of the influenza virus NS1 protein". Proc Natl Acad Sci USA 95: 4864-4869.

12. APPENDICES

Appendix 1. Schedule of Assessments

Procedures/assessments	Visit 1 Screen/Baseline Week 0 Day 0	Visit 2 Week 1 Day 7 ± 2	Visit 3 End of Study Week 2 Day 14 ± 2
Informed consent	X		
Review inclusion/exclusion criteria	X		
Review medical history	X		
Review concomitant therapies	X	X	X
Vital Signs (Heart rate, blood pressure, temperature)	X	X	X
Urine pregnancy test as required	X		
Physical exam	X		
Laboratory Tests: General Chemistry electrolytes (Na, K, Cl), creatinine, AST, ALT, GGT, bilirubin	X		X
Laboratory Tests: Hematology CBC, T lymphocyte counts	X	X	X
Laboratory Tests: Cytokines TNFα, IL-8	X	X	X
Symptoms questionnaire	X		
VAS (self-administered)	X	X	X
Dispense investigational product	X	X	
Dispense thermometer	X		
Dispense diary[1]	X	X	
Daily symptoms scores recorded[1]	X	X	X
Daily oral temperature recorded[1]	X	X	X
Return investigational product		X	X
Return/review subject diary		X	X
Compliance calculated		X	X
Review adverse events		X	X

1. Subject is to record daily symptom scores and daily oral temperature in the diary. Investigational product use, concomitant therapy use (including treatments taken for flu symptoms), and changes in health status (including adverse effects) are also to be recorded in the diary.

Appendix 2. Flu Symptoms Questionnaire

Subjects will be asked to indicate by means of interview all symptoms present at screening in order to assess eligibility. Investigator or designate will record the presence of the following symptoms:

Respiratory symptoms

1. *Cough*
2. *Sore throat*
3. *Nasal symptoms*
4. *Sneezing*

Fever

5. *≥ 38.0 °C (≥ 100.4 °F) taken orally*
6. *Subject report of fever within the past 24 hours*

Constitutional symptoms

7. *Headache*
8. *Myalgia (muscle pain)*
9. *Sweats/chills*
10. *Fatigue*

Appendix 3. Daily Symptoms Scores

Subjects will be asked to rate how severe their flu symptoms are by means of a self-administered questionnaire to be completed daily. Each response will be based on a 4-point scale:

0 = absent
1 = mild
2 = moderate
3 = severe

Symptoms

1. *Cough*
2. *Fever*
3. *Runny nose*
4. *Stuffy nose*
5. *Aches and pains*
6. *Headache*
7. *Chills*
8. *Sneezing*
9. *Ear aches*
10. *Fatigue*

Appendix 4. Visual Analog Scale

The following question will be asked at each study visit (including Visit 1). Subjects will be asked to respond by means of placing a mark on the Visual Analog Scale (VAS) line (0-100 mm) to indicate their best response. Words in parentheses are right and left anchors.

1. *How would you currently rate your ability to perform your usual activities? ("Not able at all" vs. "Extremely able")*

APPENDIX B

SUBJECT INFORMATION AND CONSENT FORM

STUDY TITLE: A Pilot Study to Investigate the Effects of Humic Acid on Flu Symptoms.

PROTOCOL NUMBER: 10HFHL

SPONSOR: Laub BioChemicals Corporation

INVESTIGATOR (Study Doctor): **Dr. «FN» «LN»**
«Institution»
«Address»
«City», «State» «Zip_Code»
«Main_TEL_»

You are being asked to participate in a clinical research study. To decide whether or not you want to be part of this research, you should understand the study risks and benefits in order to make an informed decision. This process is known as informed consent. This consent form describes the purpose, procedures, possible benefits and risks of the study. This form will also describe how your medical information will be used and who may see it. You are being asked to take part in this study because the study doctor feels that you meet the qualifications of the study. Once you understand the study, you will be asked to sign this form if you wish to participate. You may have a copy of this form in advance of agreeing to participate to review at your leisure or to ask advice from others.

The study doctor or staff will answer any questions you may have about this form or about this study. Please read this document carefully and do not hesitate to ask anything about this information. This form may contain words that you do not understand. Please ask the study doctor or staff to explain the words or information that you do not understand.

INTRODUCTION

Influenza, or the flu, is a respiratory infection that is caused by a number of viruses. These viruses can pass through the air and enter the body through the nose and mouth. In the United States, between 5% and 20% of the population get the flu each year. The flu can be serious, especially for the elderly, newborn babies and people with chronic illnesses. Every year, More than 200,000 people are hospitalized from flu-related complications.

The symptoms of the flu come on suddenly and may include: a high fever, chills, cough, headache, muscle and joint pain, weakness, general discomfort, sore throat and runny nose. The flu is often confused with the common cold but it is caused by a different type of virus and is more severe.

The best way to prevent the flu is to get a yearly flu vaccine. However, because the success of the vaccines is often in question, side effects, or other concerns, approximately 15-20% of the population does not get vaccinated. If you get the flu, your doctor may prescribe antiviral medication to help your body fight the infection and lessen symptoms.

 Subject Initials: _____

INFORMATION ABOUT THE STUDY PRODUCT

Humic acid is a natural molecule that is isolated from the soil. Studies have shown that humic acid exhibits anti-inflammatory and antiviral properties. It is believed that humic acid may inhibit (reduce the activity of)_viral infection by preventing the attachment of virus particles onto host cells, limiting virus replication. Live-animal and *in vitro* (in glass, or outside of organism, i.e. in a test tube) studies have demonstrated the therapeutic potential of humic acid as well as safety up to 50 mg/kg of body weight in animal studies.

This study will be the first test of the effects of humic acid on flu symptoms in people.

This is a randomized, double-blind, placebo controlled study which means you will receive either humic acid or a placebo (a substance that looks like humic acid but does not contain any active ingredients) during the treatment period. You have a 50% chance (like the flip of a coin) of receiving either humic acid or placebo. Neither you nor the study staff will know which product you will receive until after the study is over. This information is available in the event of an emergency.

The investigational product will be provided as a tablet. You will be asked to consume two tablets, 3 times daily (TID) for a 2 week study period.

One humic acid tablet contains the following ingredients:

Active: 250 mg humic acid

Inactive: dextrose, sucrose fatty acid ester, silicon dioxide USP/FCC, and sodium starch glycolate USP.

One placebo tablet contains:

Ingredients: cantab dextrose, sucrose fatty acid ester, microcrystalline cellulose, and sodium starch glycolate USP.

PURPOSE OF THE STUDY

The purpose of this research study is to investigate the effect of humic acid on flu symptoms in adults with influenza A or B. Your participation in this study is strictly voluntary. If you decide to join the study, you will be one of up to 40 adults participating in the United States.

STUDY PROCEDURES

You may participate in this study if you test positive for influenza A or B and meet the following study entry requirements:

- You are able to understand the nature of the study and provide written informed consent
- You are able to communicate with the study doctor and study staff and to complete the required study procedures
- You are 18 years or older
- You currently have flu symptoms
- You must not have taken any antibiotic or antiviral medications within the past 7 days

- You must not have had cancer chemotherapy or radiation treatment within the past 3 months
- You must not have received blood or blood products and/or plasma derivatives or any immunoglobulin preparations within the past 4 months
- You must not have chronic obstructive pulmonary disease (COPD) or severe asthma or be in respiratory distress
- You must not have any known or suspected impairment/alteration of the immune system or be immuno-compromised within the past 5 years
- You must not have any coagulation disorders or have surgery planned during the study period
- You must not have a history or alcohol or drug abuse
- You must not have participated in another clinical research trial within the past 30 days
- You must not have any allergy or sensitivity to the study supplement ingredients

Your study doctor will discuss other specific study enrollment requirements with you.

- You will be allowed to use some of your own medications for the treatment of your flu symptoms such as antipyretics (fever reducers), decongestants, expectorants, and throat lozenges. These will not be provided to you. For your safety, it is very important to tell the study doctor about all medications you are taking, including herbal or "natural" remedies. Please check with the study doctor before you begin taking a new medication while in this study.

Females
You may not participate if you are pregnant or breastfeeding. Females able to become pregnant must agree to a urine pregnancy test and must be using an approved method of birth control one month prior to and during the study. Some examples of approved methods of birth control include oral contraceptives ("the pill"), under-skin long-term contraceptive implants (Norplant®), long-acting contraceptive injections (Depo Provera®) or double-barrier methods (e.g. condoms and spermicide or diaphragms and spermicide). Subjects who are currently taking prescribed birth control must agree to maintain the current method and dosing regimen during the course of the study. The study doctor will discuss these contraceptive methods with you.

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

Study Duration
Your participation in this study will last approximately 2 weeks. There will be three visits to the clinic. The first visit will take approximately 1 hour. Additional study visits will occur on Day 7 and Day 14 and take approximately 30 minutes.

Visit 1 – Screen/Baseline
If you agree to participate in this study, you will be asked to sign this Informed Consent Form. You will then undergo the procedures listed below to determine if you are eligible to participate in this study. This visit will take approximately one hour. The following procedures will be performed:

- Demographic data (including age, gender, race/ethnicity)
- Medical history (including diseases, procedures and treatments)

 Subject Initials: _____

- Review of your current medications (including prescription and over-the-counter medicines and dietary supplements and vitamins/minerals)
- Vital signs (heart rate, blood pressure, temperature)
- Flu symptoms assessment
- Physical exam performed by the study doctor
- Visual Analog Scale. A question to assess your current ability to perform your usual activities which will take about one minute to complete.
- Blood sample (approximately 25 ml or 5 teaspoons) to determine your general health including a complete blood count, T lymphocyte counts (measures specific white blood cells to show your ability to fight infection), liver and kidney function tests, and inflammatory markers (a part of your body's immune system response). Blood samples will be collected by inserting a sterile disposable needle into a vein in your arm.
- A urine pregnancy test will be performed on all females who are able to become pregnant

- An electronic thermometer will be provided to you to measure your temperature daily and you will be instructed on the completion of a paper diary. The diary is used to record daily symptom scores, daily oral temperature, the time study product is taken, the use of other treatments flu symptoms and other changes in medications, and any side effects (unwanted effects or health problems) you experience. This will take approximately 5-10 minutes to complete each day. The daily diary entries will be reviewed with you at each visit.

- Study product will be given to you. The study product will be provided as tablets. You are to take 2 tablets, 3 times daily, preferably with your meals. You are to begin taking the study product the day after the baseline visit is completed. The day you begin taking the study product will be called Treatment Day 1. If you forget a dose of the study product, you may take it as soon as you remember that day. You should not take more than 3 doses (6 tablets total) on a single day. You must return all original packaging and unused tablets at the next visit.

- Schedule your study visits for Week 1 (Day 7 ±2 days) and Week 2 (Day 14 ±2 days)

Your responsibilities for participating in the study are taking the study product as directed, complying with study instructions and maintaining the study visit schedule.

Visit 2 and Visit 3 – Week 1 and Week 2
The following procedures will be performed:

- You will return all the study product packaging and unused tablets and diary
- Your compliance will be assessed
- Review of your current medications and health status
- Vital signs
- Visual Analog Scale. A question to assess your current ability to perform your usual activities which will take about one minute to complete.
- Blood sample (approximately 25 ml or 5 teaspoons) to determine your general health including a complete blood count, T lymphocyte counts (measures specific white blood cells to show your ability to fight infection), liver and kidney function tests, and inflammatory markers (a part of your body's immune system response).
- Your diary will be reviewed. At Visit 2 you will be given a new diary to be completed daily during the remainder of the treatment period as described above.
- More study product given to you at Visit 2

 Subject Initials: _____

ADDITIONAL SAFEGUARDS

The study staff will take all foreseeable (known) safety precautions on your behalf during your participation in the study.

The tests performed as part of this research study are not intended to replace any medical treatments you may be currently receiving. If you need regular medical care for current medical conditions, you should continue with this medical care unless otherwise instructed by your regular physician. For your safety, you must discuss your current medical care with the study doctor or staff.

The test product is intended for your use only, as the study participant. It should not be given to anyone else or left in a place where a small child could accidentally swallow it. All packaging and unused study product are to be returned to the study staff at each follow-up visit.

ALTERNATIVE TREATMENTS

You do not have to take part in this study to receive treatment for your condition. A number of other medications are available. Possible treatments may include over the counter pain relievers such as acetaminophen (Tylenol) or prescribed medication. The most common type of medication used to treat the flu are antiviral drugs such as Tamiflu (oseltamivir), fever reducers such as acetaminophen and ibuprofen (Advil) and decongestants.

Your study doctor will be able to tell you which, if any, of these alternative treatments might or might not be suitable for you.

RISKS TO YOU

Any side effects (unwanted effects or health problems), including changes in medical conditions you had when you started the study, should be reported to the study doctor or staff. In addition, if you need to take any new medications during the study, you should report this to the study doctor or staff.

The company's human-consumption-grade humic acid product has been on the market since mid-2004. Laub BioChem has been selling about 500,000 to 2,000,000 tablets (or tablet-equivalents) per month since early 2006 worldwide.
Clinical observations of humic acid given to 514 patients under medical supervision for a period of 4.3 months (on average) have been reported. Although no significant adverse events (unwanted effects or health problems) were reported for any patients, 30 out of 214 individuals (5.8%) reported transient (temporary) symptoms while taking humic acid, including headache, nausea, heartburn, diarrhea, or skin reactions. Since these types of transient events may be due to random chance, it is not possible to attribute them to humic acid consumption.

A comprehensive analysis of trials conducted with humic acid was carried out in 2001. Data from 1141 subjects was analyzed and revealed a very low occurrence of adverse effects (2.6%). Most of the adverse effects observed were gastrointestinal in nature (i.e. nausea and diarrhea)

 Subject Initials: _____

If you suffer a serious or lasting injury as part of your participation in this study, it may affect your ability to obtain private health insurance, your employability, and/or quality of life.

Blood samples will be drawn from a vein with a sterile needle, usually in the arm. You may experience some discomfort when the blood is drawn and it is possible that you may have some slight bruising at the area of blood collection. There is also a risk of infection at the puncture site, but since standard sterile procedures are used, this risk is considered very slight. Fainting could occur, but this is unlikely. If the results of any blood test are abnormal, the study doctor may request that you return to the clinic to have an additional blood sample drawn in order to repeat that test. The maximum amount of blood expected to be drawn for this study is 100 ml (less than half a cup, or approximately seven tablespoons)

NEW FINDINGS

Any significant new findings that become available during the course of the study which may relate to your willingness to continue participating in the research study will be disclosed to you as soon as possible. You are free to choose to stop your participation in the study at any time without penalty or loss of benefits to which you are otherwise entitled.

BENEFITS

Your participation in this study may not benefit you directly. You will receive observation by the study staff during the study. Your participation in the study may help researchers develop more effective dietary supplements.

COSTS TO YOU

All of the tests and study product, examinations, and medical care required as part of this study are provided at no cost to you your private medical insurance (if any) or any governmental program and will be paid for by the study sponsor, Laub BioChemicals Corporation. You or your personal medical insurance (if any) should continue to pay for expenses for your current medical care and/or prescriptions. These expenses will not be paid as part of your participation in this study.

The sponsor is paying your study doctor for the time, effort and expenses to conduct this study.

REIMBURSEMENT

«REIMBURSEMENT1» If you are unable to complete the entire study, reimbursement will be given based on the portion of the study completed.

«REIMBURSEMENT2»

COMPENSATION AND TREATMENT FOR INJURY

In case of an injury or illness suffered by participation in this study, you will receive appropriate medical care. The sponsor will cover necessary medical costs not covered by a governmental program or your private medical insurance (if any). By signing this form, you are not giving up your legal rights, nor releasing the study doctor or sponsors from their legal and professional obligations.

Subject Initials: _____

VOLUNTARY PARTICIPATION

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

The sponsor, Laub BioChemicals Corporation, has the right to stop the study at this clinic at any time.

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

- missing scheduled clinic visits
- not taking test product as directed
- choosing not to complete required tests and documents
- development of medical conditions or serious side effects that may pose a health risk to you
- as directed by Laub BioChemicals Corporation

CONFIDENTIALITY OF RECORDS

As part of this research, the study doctor will collect the results of your study-related tests and procedures and may also access your personal medical records for health information such as past medical history and test results. This personal health information may be used by and/or disclosed to KGK Synergize contract research staff (the organization managing this trial), representatives of the sponsor, Laub BioChemicals Corporation and possibly other entities working with the sponsor for this study. All of your medical information will be kept confidential to the extent permitted by law. All research data will be kept in a locked file. Forms on which your information is entered will not contain your name. You will not be identified in any publication that might result from the study.

Unless required by law, only the study doctor, the sponsor, members of the Institutional Review Board (IRB Services, an independent ethics committee that reviewed this study to help ensure that the rights and welfare of participants are protected and that the study is carried out in an ethical manner), and government regulatory drug agencies (e.g. the Food and Drug Administration - FDA and/or Health Canada) can have access to this confidential study data at the study site. This inspection is to check the accuracy of study records. Study records will be kept by the investigator, KGK Synergize at 255 Queens Ave, Suite 1440, London, ON and the sponsor for a minimum of 25 years.

Information from this study will be submitted to the sponsor and possibly to governmental agencies (e.g. FDA and/or Health Canada) where the study medication may be considered for approval. Information sent from the study site will not contain your name.

Your family doctor will be told about your taking part in this study, unless you do not give permission. You have the right to check your study records and request changes if the information is not correct. While every effort will be made to protect the privacy of your information, absolute confidentiality cannot be guaranteed. This does not limit the duty of the researchers and others to protect your privacy.

Subject Initials: _____

The study doctor is required by law to protect your health information. By signing this document, you authorize the study doctor to use and disclose your health information, as described in this section, in order to conduct this research study. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Your authorization does not have an expiration date. You have the right to revoke this authorization, at any time, and can do so by writing to the study doctor at the address on the first page. Even if you revoke the authorization, the study doctor and/or sponsor may still use health information they have collected about you, if necessary for the conduct of the study. However, no new information will be collected.

You do not have to sign this information and consent form, but if you do not, you will not be able to take part in this research study.

By signing the consent form you give your consent to collect, use and disclose your health information as described above.

CONTACT PERSONNEL

If you have questions regarding the conduct of this study, you should contact Dr. «FN» «LN» at «Main_TEL_» or the study coordinator, at «Study_Coord_TEL».

«Emerg_Tel»

If you have any questions about your rights as a research participant or about the conduct of this study, please contact your family doctor, lawyer or write to the committee that reviewed the ethical aspects of this study at:

The Director, Human Research Protection Program
IRB Services
372 Hollandview Trail
Suite 300
Aurora ON L4G 0A5

You may also call IRB Services at 1-866-449-8591, or contact IRB Services by email at subjectinquiries@irbservices.com.

Subject Initials: _____

VOLUNTARY CONSENT TO PARTICIPATE

A Pilot Study to Investigate the Effects of Humic Acid on Flu Symptoms

I confirm that I have read this subject information and consent form and the information it contains regarding study 10HFHL and the risks of taking part in the study.

The study has been explained to me. I have been given an opportunity to ask questions and all of my questions have been satisfactorily answered. At any time, I may consult the study doctor or his/her staff should anything become unclear or if I have any more questions.

I will follow the medical instructions, which are important to the study. I reserve the right to withdraw from the study at any time without penalty and without prejudice to my further treatment. I will not donate blood while I am in the study and for at least 30 days after.

I consent to the examination of my medical records by properly authorized representatives of Laub BioChemicals Corporation and its agents, by IRB Services (the research ethics review board) and by regulatory authorities (e.g., FDA). All personal information will be treated as strictly confidential, except where disclosure is required by law, and not made publicly available. I will not be identifiable as an individual in any report resulting from this study. However, as discussed above, absolute confidentiality cannot be guaranteed.

By signing this document, I do not waive any of my rights under the law, or release the study doctor or sponsors from their legal and professional obligations.

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

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

YES_____NO_____

Subject's Name: _____
Printed

_____ _____
Subject's Signature Date signed

Subject Initials: _____

_____
Name (printed) of person
responsible for obtaining the consent of the participant

_____ _____
Signature of person Date signed
responsible for obtaining the consent of the participant

STATEMENT OF INVESTIGATOR:

(Investigator preferably to sign the consent form on the same day as the subject, but prior to first patient visit)

I acknowledge my responsibility for the care and well being of the above subject, to respect the rights and wishes of the subject, and to conduct the study according to applicable Good Clinical Practice guidelines and regulations.

_____
Investigator's name (printed)

_____ _____
Investigator's signature Date signed

Subject Initials: _____

APPENDIX C

Curriculum Vitae *Dale R. Wilson, M.D., CCFP (EM), FCFP*

EDUCATION:

1987-1988	CCFP (EM)	UWO Family Medicine/Emergency Program, London Health Science Centre, London, ON
1985-1987	CCFP	UWO Family Medicine Residency Program, St. Joseph's Health Care, London, ON
1981-1985	M.D.	The University of Western Ontario, London, ON
1978-1981	BSc (Biology)	The University of University of Western Ontario, London, ON

EMPLOYMENT RECORD :

2008- Present	Medical Director	KGK Synergize Inc. 1440-255 Queens Avenue, London, ON
Nov. 2006- 2008	Contract Physician	KGK Synergize Inc. 1440-255 Queens Avenue, London, ON
2005- Present	Hospitalist	Regional Mental Health Care, London, ON
2003-2005	Palliative Care Physician	Parkwood Hospital, London, ON
1990- Present	Adjunct Professor	Faculty of Medicine, Department of Family Medicine, UWO, London, ON
1988- Present	Family Physician	London, ON
1988- Present	Veteran's Care Physician	Parkwood Hospital, London, ON
1988-1995	Emergency Medicine Physician	London Health Sciences Centre/ St. Joseph's Hospital Campus, London, ON

PROFESSIONAL SOCIETIES:

The College of Family Physicians of Canada
Ontario Medical Association
Canadian Medical Association
London Academy of Medicine
Canadian Medical Protective Association

CLINICAL RESEARCH EXPERIENCE:

Allergy

Efficacy and Safety of XXX Product in Subjects with Chronic Allergic Rhinitis.

A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Long-Term Safety of Ragweed Sublingual Tablet in Adult Subjects With a History of Ragweed-Induced Rhinoconjunctivitis With or Without Asthma.

Alzheimer's Disease

(Randomized, double-blind) Evaluating Efficacy and Safety of XXX in patients with mild to moderately severe Alzheimer's Disease.

Antioxidant

An Open Label Pilot Study to Investigate the Effect of XXX on Antioxidant Status.

Arthritis

(Randomized, double-blind, placebo-controlled, 5-arm study) Efficacy and Tolerability of XXX in the Treatment of Osteoarthritis of the Knee in comparison to XXX plus XXX: A Randomized, Double-Blind Clinical Trial.

(Randomized, double-blind study) Efficacy and Tolerability of XXX, a Novel Undenatured Collagen II Derived from XXX in comparison to XXX plus XXX. A Randomized, Double-Blind Clinical Trial.

(Single-center, double blind, placebo controlled, and randomized two-arm parallel group pilot study) Efficacy of XXX Extra Strength Joint Care Formula in Adults with Osteoarthritis of the Knee.

Bioavailability

Bioavailability and Health Effects of XXX in Healthy Human Adults.

(Randomized, double-blind, 4-arm crossover) Comparison of Calcium Absorption from Calcium-Containing Products in Healthy Premenopausal Women: A Bioavailability Study.

(Randomized, double-blind, 4-arm crossover) Comparison of Magnesium Absorption from Magnesium-Containing Products in Physically Active Volunteers: A Bioavailability Study.

(Randomized, double-blind, crossover, 72-hour, peak absorption study) A Randomized, Double-blind, Crossover Trial Comparing the Bioavailability of Two XXX Formulations in a 72 Hour Peak Absorption Study.

A randomized, double-blind, crossover single-dose supplementation study comparing the bioavailability of two XXX formulations in healthy subjects.

Randomized, double-blind, placebo controlled crossover study to Evaluate the Effect of Digestive Enzyme on Nutrient Bioavailability.

Blood Pressure

Two Period, Cross-over Intervention Study to Evaluate the Effects of XXX and XXX on Blood Pressure in Pre-hypertensive Adults.

Cardiovascular/Lipids

Controlled Onset XXX Investigation of Cardiovascular Endpoints.

A prospective, descriptive, multi-national, multi-center observational study of burden of upper GI-systems in subjects with cardiovascular risk or disease receiving treatment with XXX.

(Randomized, placebo-controlled, double-blind, parallel group) Safety, Tolerability and Efficacy of XXX in Subjects with Elevated Cholesterol and LDL Cholesterol Levels.

Diabetes

A 12-week, open-label, multi-center, prospective study evaluating the effect of individualizing starting doses of XXX according to baseline LDL-cholesterol levels on achieving cholesterol targets in type 2 diabetic patients previously treated with another statin and not and not at LDL-cholesterol targets.

A multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy, safety and tolerability of XXX compared to placebo, in patients with type 2 diabetes mellitus inadequately controlled with xxx plus xxx.

A multicenter, randomized, double blind (double dummy), active-comparator controlled study to compare the efficacy, safety and tolerability of XXX versus xxx in type 2 diabetes patients inadequately controlled with sulfonylurea (SU) monotherapy or xxx plus sulfonylurea combination therapy.

A randomized, double-blind, placebo-controlled, 2-arm parallel-group, multicenter study with a 24-week main treatment period and an extension assessing the efficacy and safety of XXX on top of xxx in patients with type 2 diabetes not adequately controlled with xxx.

Diet

The Effect of XXX using XXX Compared to the American Diabetes Association Diabetes Meal Plan on Body Weight and Satiety in Overweight Diabetic Women.

The Effect of XXX on Body Weight and Satiety in Overweight Women Following the XXX Compared to a Traditional Calorie Restricted Diet in Non-Diabetic Women.

Digestive Health

A Randomized, Double-blind, Crossover Trial Evaluating the Tolerance and Plasma Vitamin C Levels of XXX Compared with XXX in Adults with Sensitivity to Acidic Foods.

(Randomized, placebo-controlled, double-blind, crossover study) Efficacy of Probiotic XXX on Digestion and Survival of Bacteria in Human Intestinal Tract: A Pilot Crossover Trial.

A Randomized, Double-blind, Crossover Trial Evaluating the Tolerance and Plasma Vitamin C Levels of XXX Compared with Ascorbic Acid in Adults with Sensitivity to Acidic Foods.

A prospective descriptive, multi-national, multi-centre observational study of burden of upper GI symptoms in subjects with cardiovascular risk or disease receiving treatment with low-dose XXX.

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of XXX in the Treatment of Subjects With Non-Constipation Irritable Bowel Syndrome.

Effects on Changes in Glucose and Insulin with Ingestion of XXX: A Double-blind, Placebo-Controlled, Crossover Study in Individuals with Impaired Fasting Glycemia.

Menopause

The Effect of XXX on Menopause Symptom Management in Healthy Premenopausal Women: A Placebo- Controlled Pilot Study.

Nutrient Status

Vitamin D Screening at Toronto Man to Man Prostate Center Support Group.

Stress

A Randomized, Placebo Controlled, Parallel, 12 Week Intervention Study Evaluating the Effect of XXX on Oxidative Stress, Cardiovascular Function, and Glycemic Control in Adults with Increased Oxidative Stress.

Safety and Tolerability

(Randomized, double-blind, placebo-controlled, 3-arm study) Safety and Tolerability of XXX in Premenopausal Women.

BIBLIOGRAPHY: N/A

ORAL PRESENTATIONS: N/A

Dale R. Wilson, M.D., CCFP (EM), FCFP

Jan 26, 2010.
Date

CURRICULUM VITAE FOR: **Mandeep S. Oberoi, MD**
Reviewed and updated on:

Central Jersey Medical Research Center
240, Williamson St. Suite # 305
Elizabeth, NJ 07202

Tel:: (908)354-5353
Fax: (908) 351-6911
Cell: (908)346-1537
Email: Oberoimd@hotmail.com

Experience & Training:

1999-Present	Clinical Medical Research @ Central Jersey Medical Research Center. I have been involved in many phase II, III and IV clinical trials for various Pharmaceutical companies. I have been the principal Investigator for more than 50 clinical trials and oversee about six physicians involved with me in clinical research.
1999-Present	I have been in Group private practice (full time) in Elizabeth, NJ. Provide primary care medical management in outpatient, inpatient and nursing home set up to all the patients in a group practice.
1997-2002	Worked as an Emergency Room Physician at St. Michael Medical Center, Newark, NJ. The work involved providing medical care to Emergency room patients. Was involved in teaching of the medical students and residents. Total experience of more than 7,000 ER hours.

Academic Qualifications:

Board Certified in Internal Medicine

July 1, 1994-June 1997 — ***Residency in Internal Medicine***
University of Medicine & Dentistry of New Jersey
New Jersey Medical School
30 Bergen Street Newark, NJ 07103

January 1989-December 1990 — ***Residency in Internal Medicine***
Government Rajindra Medical College, Patiala, India

January 1987-December 1988 — ***Clinical Rotating Internship at***
Government Rajindra Medical College & Hospital, Patiala, India.

August 1983-December 1987 — ***M.B, BS*** at Govt. Rajindra Medical College, Patiala, India.

Honors & Awards:

Declared as the Best ***Resident*** by Medicine Dept. twice in UMDNJ. I was ranked among ***top ten students*** in Medical school. I received ***Roll of Honor*** awarded by Dean, Medical College, and Patiala, India for exceptional community services.

Publications:

1. ***"HIV & Pulmonary Hypertension" with review of literature.*** A case report published in Hospital Practice.
2. ***"Emerging Role of Computerized Tomography as morbidity in predictor pancreatitis".*** A prospective study conducted in UMDNJ and Newark Beth Israel Hospital, Newark, NJ.

Professional Organizations Affiliation:
Member, Pharmacy, Therapeutics and Dietary Committee, Trinitas Hospital, Elizabeth.
Member, Institutional Review Board, Trinitas Hospital, Elizabeth.
Member of American Medical Association
Member of American College of Physicians
Member of New Jersey Medical Society
Executive Member, North American Association of Sikh Physicians and Dentists.
General Secretary, Punjabi Cultural Society of New Jersey.

License:

Active New Jersey License: MA66667

Hospital Affiliation:

Trinitas Hospital
225 Williamson Street
Elizabeth, NJ 07202

Union Hospital
Galloping Hill Road
Union, NJ

Rahway Hospital
Stone Street
Rahway, NJ

Clinical Research Experience:

1. **Principal Investigator**, "**RADIUS-I Study**". Rheumatoid Arthritis DMARD Intervention and Utilization Study by **Immunex/ Amgen**. Protocol # 016-0034.

2. **Principal Investigator**, An Open-label, Non-comparative Study to asses the Efficacy and safety of Oral Augmentin SR 2000/125 mg Twice Daily for 7 Days for the Treatment of Bacterial Community Acquired Pneumonia. In Adults. Study by **GlaxoSmithKline Beecham**. Protocol # SB BRL-025000/547.

3. **Principal Investigator**, A Randomized, Double-blind, Double dummy, Multicenter, parallel Group Study to Asses the Efficacy and Safety of Oral Augmentin SR 2000/125mg Twice daily for 5 days versus Oral Augmentin 875/125 mg for 7 Days in the Treatment of Adults with Acute Exacerbation of Chronic Bronchitis. Study by **SmithKline** under Protocol # BRL-25000/630. (**Highest Enroller**).

4. **Principal Investigator, "RADIUS – II Study**". Rheumatoid Arthritis DMARD Intervention and Utilization Study. Study by **Immunex/ Wyeth/Amgen**. Protocol # 016.0035

5. **Principal Investigator**, A Prospective, Open-label, Non-comparative, Multicenter Trial to evaluate the Efficacy and Safety of Ciprofloxacin Extended Release(Cipro XR) 500 mg Daily for 3 days in the Treatment of Female patients with Acute, Uncomplicated Symptomatic, Lower Urinary Tract Infections. Study by **Bayer** under Protocol# 100546.

6. **Principal Investigator, MOVE Study** to evaluate the Pain Intensity Changes in Patients with Osteoarthritis Knee by Using Intraarticular Hyaluronic Acid Injections. Study by **Stanford University, CA.**

7. **Principal Investigator**, Chronic NSAID induced Gastritis and Nexium by **AstraZeneca.**

8. **Principal Investigator**, A Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel-arm Study to asses the Long-term Effects of Platel(Cilostazol) versus Placebo Administered Orally to Patients with Intermittent Claudication Secondary to Peripheral Vascular Disease. Phase III Study by **Otsuka**. Protocol # 21-98-214-01.

9. **Principal Investigator**, A Prospective, randomized, Double-blind, Multicenter, Comparative Trial to Evaluate the Efficacy and Safety of Ciprofloxacin Once-Daily (QD) Modified Release (CiproMR) Tablets Versus Conventional Ciprofloxacin 500 mg Tablets BID in the 7-14 Day Treatment of patients With Complicated Urinary Tract Infections (cUTI) or Acute Uncomplicated Pyelonephritis. Study by **Bayer.** Protocol # 100275.

10. **Principal Investigator**, Kineret Study for Rheumatoid Arthritis by **Amgen.**

11. **Principal Investigator**, A Randomized, Multicenter, Blinded Study of The Efficacy and Safety of High dose (750 mg), Short course (3-5 days) Levofloxacin Therapy in Uncomplicated and Complicated Acute Bacterial Exacerbation of Chronic Bronchitis. Study by **Bayer** under Protocol #CAPSS-197.

12. **Principal Investigator**, A Prospective, Randomized, Double-blinded, Active controlled Study for the evaluation of the Efficacy, Safety, and Pharmacoeconomics of Oral Telithromycin (Ketek) 800mg once a day for 5 days vs. Moxofloxacin (Avelox) 400 mg once a day for 10 days in the Treatment of Acute Maxillary Sinusitis (AMS) in Adults. Study by **Aventis.** Protocol # HMR3647A/4017.

13. **Principal Investigator**, Cipro XR Excellence in the Therapeutic Response and Activity (eXtRa)-Assessing Symptom Relief in Urinary Tract Infections. Study by **Bayer** under Protocol # 100544.

14. **Principal Investigator**, A 4-week, Randomized, Multicenter, Double-blind, Placebo and Active Controlled, parallel-group, Forced-titration Phase II B Study Comparing Efficacy and Safety of Ascending Doses of CG5503 Prolonged Release Up to 233 mg BID and Oxycodone Prolonged release Up to 20 mg BID in Subjects with Moderate to Severe Chronic Pain due to Osteoarthritis of the Knee. Study by **Johnson & Johnson Research & Development** . Protocol # R331333-PAI-2001.

15. **Principal Investigator**, A Randomized, Double-blind, Multicenter, Positive-controlled, parallel group Study to evaluate the Safety of Amlodipine and Benzapril Administered in combination Compared to Amlodipine Monotherapy in Hypertensive patients Not Adequately with Amlodipine Alone. Study by **Novartis**. Protocol # CCIN002H2304.

16. **Principal Investigator**, "**ACS-RESCUE Study**". A Prospective, Open-label, Randomized, Parallel- group Investigation to Evaluate the efficacy and Safety of Enoxaparin versus Unfractionated heparin in Subjects who present to the Emergency Room with Acute Coronary Syndrome. Phase IV Study. Protocol # XRP4563B/4001 by **Aventis.** (**Highest Enroller**). Enrolled 50 patients in this inpatient study.

17. **Principal Investigator**, "**STARSHIP STUDY**". A 6 week, Randomized, Open-label, Comparative Study to Evaluate the Efficacy and safety of Rosuvastatin and Atorvastatin in the Treatment of Hypercholesterolemia in Hispanic Subjects. Study by **AstraZeneca** under Protocol # 4522US/0007 (**Highest enroller**)

18. **Principal Investigator**, A Multicenter, Double-blind, Randomized, parallel Groups, placebo-controlled, Study to Asses the Efficacy and Safety of Fexofenadine 120 mg BID in Subjects with Mild to Moderate Persistent Asthma. Study by **Aventis**. Protocol # MO16455P/3002

.

19. **Principal Investigator**, "**JUPITER STUDY**". A randomized, Double-Blind, Placebo-controlled, Multicenter, Phase III Study of Rosuvastatin (Crestor) 20mg in the Primary Prevention of Cardiovascular Events among Subjects with Low Levels of LDL-Cholesterol and Elevated Levels of C-Reactive Protein.
Study By **AstraZeneca** under Protocol # 4522US/0011.

20. **Principal Investigator**, A Multicenter, randomized, Double-blind, Placebo Controlled, Parallel Comparison of the Efficacy and safety of Fixed-dose Extended-Release Hydrocodone Bitartarate/Acetaminophen in the Relief of Moderate to Moderately Severe Chronic Osteoarthritis Pain of the Hip joint.
Phase III Study by **Watson Laboratories**. Protocol#HA03028.

21. **Principal Investigator**, A Strafied, Randomized, Prospective, Unblinded, Active-control Trial of Factive Versus BiaxinXL for the Treatment of Community Acquired Pneumonia & Versus Amoxicillin/clavulanate for the Treatment of Acute Bacterial Exacerbation of Chronic Bronchitis.
Phase IV Study by **Oscient Pharmaceuticals**. Protocol # OS-001.

22. **Principal Investigator**, Prospective, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and safety of Moxifloxacin 400 mg QD for 5 days versus Placebo in the Treatment of Acute Bacterial Sinusitis.
Study by **Bayer**. Protocol # 11566.

23. **Principal Investigator**, A Multicenter, Phase III Study to Confirm the Safety and Efficacy of Intravenous Doripenem in Complicated Urinary Tract Infections or Pyelonephritis. Study by **Peninsula Pharmaceuticals**. Protocol # DORI-06.

24. **Principal Investigator**, "**CUSP Study**". An 8-week randomized, Double-Blind, Placebo-Controlled Trial Examining The Efficacy and Safety of Caduet in Simultaneously achieving Blood Pressure and Lipid Goals in An Untreated Hypertensive & Dyslipidemic Subject Population.
Protocol # A3841046 by **Pfizer**. Phase IV Study.(**Highest Enroller**).

25. **Principal Investigator**, A Randomized, Double-blind, Multicenter, Placebo-controlled, Parallel-group Study to evaluate the efficacy and safety of Valsatan (320mg) and Hydrochlorthiazide (12.5 and 25 mg) combined and alone, Valsartan 160 mg and Valsartan 160 mg/hydrochlorthiazide 12.5 mg in Hypertensive Patients.
Study by **Novartis** under Protocol # CVAH 631C2301.

26. **Principal Investigator**, "**RACER STUDY**.PhaseII Study. A Multicenter, Double-blind, Randomized, parallel, Placebo-controlled Study to evaluate the Safety, Efficacy, and Pharmacokinetics of 2 oral doses, 25 mg Twice daily and 100 mg twice daily, of PG-760564 in Adult Patients with Rheumatoid Arthritis Receiving Methotrexate.
Phase II Study by **Procter & Gamble**. Protocol # 206012.

27. **Principal Investigator**, A Randomized, Double-Blind, Active-Comparator Controlled, Parallel-Group Study to Evaluate the effectiveness of Etoricoxib in Patients with Osteoarthritis or Rheumatoid Arthritis (**MEDAL STUDY**).
Study by **Merck**. Protocol # 066-03 IND #54,464. **(42 Patients)**

28. **Principal Investigator**, "**GRADE Study**". A Multicenter, Randomized , Double-blind, Placebo-controlled Study of Safety and Efficacy of CS-917 as Monotherapy for Type II Diabetes.
A Phase II Study by **Daichii Sankyo** Pharmaceutical Development.
Protocol # CS917-A-U205.

29. **Principal Investigator**, A Prospective, Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel-group study if Intranasal Amphoterecin B suspension in patients with Refractory, Post surgical Chronic Sinusitis.
Phase III protocol # ACC-05-01 by **Accecia**.

30. **Principal Investigator**, "**PRECISION Study**" A Prospective, Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or naproxen in A Randomized, Double-blind, Parallel-Group Study of Cardiovascular Disease comparing Celecoxib with Naproxen and Ibuprofen.
Protocol # A3191172 by **Pfizer**.

31. **Principal Investigator**, A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Study to Evaluate the Efficacy and safety of Alvimopan 0.5 mg Once daily and 0.5mg Twice Daily for 12 Weeks for the Treatment of Opioid-Induced Bowel Dysfunction in Adults taking Opioid Therapy for Persistent Non-Cancer Pain.
Study by **GlaxoSmithKline.** Protocol # 767905-012.

32. **Principal Investigator**, A Multicenter, randomized, Double-blind, Placebo-controlled Trial To Evaluate the safety and efficacy of a New Tablet Formulation and Dosing regimen of balsalazide Disodium 3.3G BID Versus Placebo In Mildly To Moderately Active Ulcerative Colitis.
Study by **Salix Pharmaceuticals**. Protocol# BZUC3002.

33. **Principal Investigator**, An 8-week Randomized, Double-Blind, Parallel Group, Multicenter, Placebo and Active Controlled Dose Escalation Study to Evaluate the Efficacy and Safety of Aliskiren (150 mg and 300 mg) Administered alone and in Combination with Valsartan (160mg and 320 mg) in patients with Hypertension.
Study by **Novartis**. Protocol # CSPP100A2327.

34. **Principal Investigator**, A 24-Week, Multicenter, Double-Blind, Parallel Group, Randomized, Controlled Study of Roflumilast(250mcg and 500 mcg) versus Placebo in Patients with Bronchial Asthma. **FLASH STUDY**.
Protocol # BY217/M2-023 by **Altana** Pharmaceutical.

35. **Principal Investigator**, A Randomized, Double-blind, Placebo-controlled, factorial Study Evaluating the Efficacy and Safety of Co administration of Olmesartan Modoxomil Plus Amlodipine Compared to Monotherapy in Patients with Mild to Severe Hypertension.
    Study by **Daiichi Sankyo Pharma**. Protocol # CS8663-A-U301.

36. **Principal Investigator**, A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Study to Evaluate the Long Term Safety of Alvimopan 0.5 mg Twice Daily for 12 Months for the Treatment of Opioid-Induced Bowel Dysfunction in Adults taking Opioid Therapy for Persistent Non-Cancer Pain.
    Study by **GlaxoSmithKline.** Protocol# 767905-014.

37. **Principal Investigator**, A 12-month, Randomized, Open-label, Multicenter, study to asses the Long term Safety of Aliskiren 150 mg alone and 300 mg Alone or with the Optional Addition of Hydrochlorthiazide (12.5mg or 25 mg) in patients with Essential Hypertension. Protocol# CSPP100A2302. Phase III by **Novartis.(Highest Enroller)**

38. **Principal Investigator**, Liraglutide Effect and Action in Diabetes (**LEAD 3**): Effect on Glycemic Control of Liraglutide versus Glimepiride in Type2 Diabetes (A Fifty-two Week Double-blind, Multicenter, Randomized, Parallel Study to Investigate the Safety and Efficacy with a Fifty-two Week Open-label Extension.
    Study by **Novo Nordisk Inc**. Protocol # NN2211-1573.

39. **Principal Investigator**, All To target Trial-Lantus (Insulin Glargine) with Stepwise Addition of Apidra (insulin glulisne) or Lantus with one injection of Apidra vs. a Twice-daily premixed insulin regimen (Novolog Mix 70/30) in Adult Subjects with Type 2 Diabetes failing dual or triple therapy with Oral Agents: A 64-Week, Multicenter, Randomized, Parallel, Open-Label Clinical Study.
    Protocol# HMR1964A/3515 by **Sanofi-Aventis**. **(FDA Audit: Oct 2008)**

40. **Principal Investigator**, An Open-label, Multicenter, Study to Evaluate the Safety of Long-Term Administration of TAK-128 in Subjects With Mild to Moderate Diabetic Peripheral Neuropathy.
    Study by **Takeda.** Protocol # 01-05-TL-128-006.

41. **Principal Investigator**, A Randomized, Double-blind, Multicenter Study Comparing the Effects of carvedilol Phosphate Modified Release Formulation (COREG-MR) with Metoprolol Succinate (TOPROL-XL) on the Lipid Profile in Normolipidemic, or Mildly Dyslipidemic Hypertensive Patients.
    Study by **GlaxoSmithKline.** Protocol # COR103561.

42. **Principal Investigator**, "**TOGETHER STUDY**". A 6-week, Prospective, Randomized, Double-blind, Double-dummy Phase IV Clinical Trial designed to Evaluate the Efficacy of an Aggressive Multi-risk factor Management Strategy with Caduet versus a Guideline based approach in Achieving Blood Pressure and Lipid Control in Hypertensive subjects With Additional Risk factors.

Protocol# A3841045 by **Pfizer. (Highest Enroller)**

43. **Principal Investigator**, A Multicenter, Double-Blind Study to Determine the Efficacy and Safety of SYR-322 plus Pioglitazone HCL (Actos), SYR-322 Alone or Pioglitazone Alone in Subjects with Type 2 Diabetes. **(Sponsor Audit)**
Protocol # 01-06-TL-322OPI-002 by **Takeda** Global Research & Development.

44. **Principal Investigator**, A Randomized, Double-Blind, Active-Controlled, Parallel Group, Multi-center, 12 Week Study Comparing the Safety and Efficacy of Fluticasone and Formoterol Combination (Flutiform 100/10 Mcg twice daily) in a Single Inhaler (SkyePharma HFA pMDI) with the Administration of Fluticasone (100 mcg twice daily) and Formoterol (10 mcg twice daily) Alone in Adolescent and Adult patients with Mild to Moderate Asthma.
Protocol # SKY2028-3-002 by **SkyePharma AG.**

45.**Principal Investigator**, "A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to compare the safety and Efficacy of an Olmesartan medoxomil Based Treatment Regimen to Placebo in patients With Stage I and stage II Hypertension.
Study Protocol# 866-451 by **Daiichi Sankyo Pharma** Development.

46. **Principal Investigator**, **"EXTRA STUDY"**. A Phase IIIb Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Xolair in subjects with Moderate to Severe Persistent Asthma Who are Inadequately Controlled With High-Dose Inhaled Corticosteroids and Long-Acting Beta-Agonists.
Study Protocol # Q3662g by **Genentach Inc.** & **Novartis.**

47. **Principal Investigator,** A Double-Blind, Randomized, Placebo-Controlled Study of the efficacy and Safety of EUFLEXXA for the treatment of painful Osteoarthritis of the Knee, With an Open-Label Safety Extension.
Study Protocol # FPI-EUFLX-2005-01D by **Ferring Pharceuticals Inc.**

48. **Principal Investigator,** A 12-week, Multicenter, randomized, Double-Blind, Parallel Group Study of the Combination of ABT-335 and Rosuvastatin Compared to ABT-335 and Rosuvastatin Monotherapy in Subjects with Type IIa and IIb Dyslipidemia.
Study Protocol # M06-844 by **Abbott.**

49. **Principal Investigator, "ARISTOTLE Study".** A Phase III, Active (Warfarin) Controlled, Randomized, Double-Blind, Parallel Arm Study to Evaluate Efficacy and safety of Apixaban in Preventing Stroke and Systemic Embolism in Subjects with Non Valvular Atrial Fibrillation.
Protocol # CV 185030 by **Bristol-Myers Squibb**.

50 **Principal Investigator,** A Phase III b, Double-Blind Randomized Study to determine the Efficacy and Safety of Pioglitazone HCL and Metformin HCL Fixed-Dose Combination Therapy Compared to Pioglitazone HCL Monotherapy and to Metformin HCL Monotherapy in the treatment of Subjects with Type 2 Diabetes.

Protocol # 01-06-TL-OPIMET-008 by Takeda Global Research.

51. **Principal Investigator,** A Phase III Randomized, Double-Blind, Placebo Controlled Multicenter Study to Determine the Safety and Efficacy of V1-0521 in the Treatment of Obesity in Adults With Obesity- Related Co-Morbid Conditions.
Protocol # OB 303 by **Vivus Inc. (High Enroller) (Sponsor Audit)**

52. **Principal Investigator, "GRAVITY STUDY"** A 12-week Open-Label, Randomized, Parallel-group, Multicenter, Phase IIIB Study to compare the Efficacy and safety of Rosuvastatin(Crestor) 10 mg and 20 mg in Combination with Ezetimide 10 mg and Simvastatin 40 mg and 80 mg in combination with Ezetimide 10 mg (Fixed dose combination) in Patients with Hypercholesterolemia and Coronary artery disease (CHD) or a CHD Risk Equivalent Atherosclerosis or a 10-year CHD Risk of >20%.
Protocol # D356FC00003 by **AstraZeneca. (High Enroller) (Sponsor Audit)**

53. **Principal Investigator, "Improve Study".** A Phase III Multicenter, Randomized, Double-Blind, Placebo controlled Study to Evaluate the Efficacy and safety of Intramuscular Peramivir in Subjects with Uncomplicated Acute Influenza.
IND # 76,350 by **BioCryst Phamaceuticals Inc.**

54. **Principal Investigator "INCYTE STUDY":** A Phase II double blind, dose-ranging, placebo controlled, randomized study to evaluate the safety, tolerability and pharmacodynamic activity of INCB019602 plus metformin compared to metformin alone in type 2 diabetic subjects not adequately controlled by metformin monotherapy.
Protocol # INCB 19602-201 by **Incyte**

55. **Prinicpal Investigator "ROCHE STUDY":** A Phase III, double-blind, randomized placebo-controlled study, to Evaluate the effects of RO4607381 on cardiovascular (CV) risk in stable CHD patients, with a documented recent Acute Coronary Syndrome (ACS).
Protocol # NC20971 by **Roche**

56. **Principal Investigator "SALIX IBS STUDY":** A Phase III, Randomized, Double-Blind, Placebo-controlled, Multicenter study to access the efficacy and safety of Rifaximin 550mg TID in the treatment of subjects with non-constipation Irritable Bowel Syndrome.
Protocol # RFIB3007 by **Salix**

57. **Principal Investigator "SINUSITIS STUDY":** A Phase III Study to know the efficacy and safety of 200 mcg BIDMometasone Furoate Nasal Spray (MFNS) vs Placebo of Adjunctive Treatment to Antibiotics in Relief of symptoms of Acute Bacterial Sinusitis.
Protocol # PO4824 by **Schering Plough**

58. **Principal Investigator "DIABETES STUDY":** A Phase II, Randomized, Double-Blind, Placebo-controlled, Parallel
Group study to evaluate the efficacy and safety of 12-week administration of PF-00734200 to subjects with Type 2 Diabetes Mellitus and insufficient glycemic control of metformin treatment.
Protocol # A7941006 by **Pfizer**

59. **Principal Investigator "ABBOTT STUDY":** A Phase III, Randomized, Double-Blind, Prospective Study Comparing the Safety and Efficacy of ABT-335 in Combination with Atorvastatin and Ezetimibe to Atorvastatin in Combination with Ezetimibe in Subjects with Combined (Atherogenic) Dyslipidemia.
Protocol # Abbott M10-275 by **Abbott**

60. **Principal Investigator "SUCAMPO OBD STUDY":** A Phase III, Multi-Center, Randomized Placebo Controlled, Double-Blinded Study of the Efficacy and Safety of Lubiprostone in Patients with Opoid-Induced Bowel Dysfunction.
Protocol # SPI/0211OBD-0632 by **Sucampo**

61. **Principal Investigator "ABBOTT STUDY":** A Phase III, 8 week, Multicenter, Randomized, Double Blind, Parallel Group Study Comparing the Safety and Efficacy of ABT 143 to Simvastatin in Subjects with Hypercholesterolemia.
Protocol # Abbott M10-667 by **Abbott**

62. **Principal Investigator "TAKEDA 012 DIABETES STUDY":** A Long Term, Open Label Extension Study to Investigate the Long-Term Safety of SYR110322 (SYR 322) in Subjects with Type 2 Diabetes.
Protocol # SYR-322-OLE-012 by **Takeda**

63. **Principal Investigator "TRINITY STUDY":** A Phase III Randomized, Double Blind, Parallel Group Study Evaluating the Efficacy and Safety of Co-administration of a Triple Combination Therapy of Olmesartan Medoxomil, Amlodipine Besylate and Hydrochlorthiazide in Subjects with Hypertension.
Protocol # CS8635-A-U301 by **Daiichi Sankyo (Sponsor Audit)**

64. **Prinicpal Investigator "ENGAGE ATRIAL FIBRILLATION STUDY":** A Phase III, Randomized, Double Blind Double Dummy, Parallel Group, Multi Center, Multi-Nationality Study for Evaluation of Efficacy and Safety of DU- 176b Versus Warfarin in Subjects with Atrial Fibrillagion-Effective Anticoagulation with Factor X a Next Generation in Atrial Fibrillation (ENGAGE-AF TIMI 48)
Protocol # DU176b-C-U301 by **Daiichi Sankyo.**

65. **Principal Invesitgator "OSTEOARTHRITIS STUDY-PFIZER" :** A Phase III, Multi-Center, Randomized, Double Blind, Controlled Study of the Long Term Analgesic Efficacy and Safety of Tanezumab Alone or in Combination with Non steroidal Anti Inflammatory Drugs (NSAIDS) Versus NSAIDS Alone in Patients with Osteoarthritis of the Knee or Hip.
Protocol # A4091025 by **Pfizer**

66. **Prinicpal Invesitgator "TAKEDA DIABETES STUDY":** A Phase II, Randomized, Double-Blind, Placebo and Active-Controlled, Multi-Center Study to determine the Efficacy and Safety of TAK 379 in Subjects with Type 2 Diabetes.
Protocol # TAK-379_201 by **Takeda**

67. **Principal Investigator "GSK CHRONIC CHD STUDY":** A Phase III Clinical Outcomes Study of Darapladib Versus Placebo in Subjects with Chronic Coronary Heart Disease to Compare the Incidence of Major Adverse Cardiovascular Events (MACE).

Protocol # LP100601 by **GlaxoSmithKline**

68.**Principal Investigator "GSK DIABETES STUDY":** A Phase III, Randomized, Double Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide When Used in Combination with Pioglitazone With or Without Metformin in Subjects with Type 2 Diabetes Mellitus.
Protocol # GLP112755 by **GlaxoSmithKline**

A Randomized, Double Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide Compared with Placebo in Subjects with Type 2 Diabetes Mellitus.
Protocol # GLP112756 by **GlaxoSmithKline**

A Randomized, Double Blind, Placebo-and Active-Controlled, Parallel Group, Multicenter Study to determine the Efficacy and Safety of Albiglutide When Used in Combination With Metformin Compared With Metformin plus Sitagliptin, Metformin Plus Glimipiride, and Metformin Plus Placebo in Subjects with Type 2 Daibetes Mellitus.
Protocol # GLP 112753 by **GlaxoSmithKline**

A Randomized, Open-Label, Parallel-Group, Multicenter Study to determine the Efficacy and Long-Term Safety of Albiglutide Compared With Insulin in Subjects With Type 2 Diabetes Mellitus.
Protocol # GLP 112754 by **GlaxoSmithKline**

A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel Group, Multicenter Study to determine the Efficacy and Safety of Albiglutide Administered in Combination with Metformin and Glimepiride Compared With Metformin Plus Glimepiride and Pioglitazone in Subjects with Type 2 Diabetes Mellitus.
Protocol # GLP 112757 by **GlaxoSmithKline**

70. Principal Investigator " GOUT STUDY": A Multi-Center, Randomized, Double Blind, Placebo Controlled Trial of the Safety of Rilonacept for the Prophylaxis of Gout Flares in Patients on Urate Lowering Therapy.
Protocol # IL 1T-GA-0815 by **Regeron**

71. Principal Investigator. "APPRAISE-2". A Phase 3, Randomized, Double-Blind, Evaluation of the Safety and Efficacy of Apixaban in Subjects with a Recent Acute Coronary Syndrome by **Bristol-Myers Squibb**

72. Principal Investigator.. "MOA-728". An Open-Label Study to Evaluate the Long-term Safety of Subcutaneous MOA-728 for Treatment of Opioid- Induced Constipation in Subjects With Nonmalignant Pain by **Wyeth**

73. Principal Investigator. "GERD 302". A Randomized Double-Blind Parallel Study of Rabeprazole Extended-Release 50 mg Versus Esomeprazole 40 mg for Healing and Symptomatic Relief of Moderate to Sever Erosive Gastroesophageal Reflux Disease (GERD) by **Eisai.**

74. Principal Investigator. "EXACT". A Prospective, Randomized, Double-Blind Study of the Efficacy of Xolair in Atopic Asthmatics with Good Lung Capacity who Remain Difficult to Treat, by **Genentech**

75. Principal Investigator. "GAFA". A Proof of Concept Study to Evaluate the Co-administration of TT223 Given Daily and LY2428757 Given Once-Weekly for Four Weeks in Patients with Type 2 Diabetes Mellitus by **Lily.**

76. Principal Investigator. "P05234". A multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Long-Term Safety of Ragweed Sublingual Tablet in Adult Subjects with a History of Ragweed-Induced Rhinoconjunctivitis With or Without Asthma by **Schering-Plough.**

77. Principal Investigator. "M10-313" A 30-week, multicenter, Randomized, Double-Blind, Parallel-Group Study of the combination of ABT-335 and Rosuvastatin compared to Rosuvastatin monotherapy in dyslipidemic subjects with stage 3 chronic kidney disease by **Abbott.**

78. Principal Investigator. "NEB-MD-04" Blood Pressure and metabolic effects of Nebivolol compared with Hydrochlorothiazide and placebo in Hypertensive patients with impaired glucose tolerance or impaired fasting glucose, by **Forest.**

79. Principal Investigator. "TIMI 52" A clinical outcomes study of Darapladib versus placebo in subjects following acute coronary syndrome to compare the incidence of major adverse cardiovascular events (MACE) by **GSK**

THIS DOCUMENT IS PRINTED ON WATERMARKED PAPER, WITH A MULTI-COLORED BACKGROUND AND MULTIPLE SECURITY FEATURES. PLEASE VERIFY AUTHENTICITY.

State Of New Jersey
New Jersey Office of the Attorney General
Division of Consumer Affairs

THIS IS TO CERTIFY THAT THE

Board of Medical Examiners

HAS REGISTERED

MANDEEP S. OBEROI
240 WILLIAMSON STREET
Suite # 305
ELIZABETH, NJ 07202674

FOR PRACTICE IN NEW JERSEY AS A(N): Medical Doctor

25MA06666700
LICENSE/REGISTRATION/CERTIFICATION #

06/19/2009 TO 06/30/2011
VALID

Mandeep Singh Oberoi MD
Signature of Licensee/Registrant/Certificate Holder

DIRECTOR

M. Ann Socolofsky, MD, MBA, FAAFP, FAAUCM
American Medical Exams, PA
837 NW Harrison
Topeka KS 66610
785-234-5777
gwydd314@yahoo.com

Experience

American Medical Exams, PA.
Director of Clinical Trials, 2006-present
Medical Director, 2006 to present

Marian Clinic, Topeka KS
Clinical Physician, 1997 to present
Board of Directors, 2001 to 2004
Medical Advisory Committee, 2001 to present

Shawnee County Health Agency, Topeka KS
Part-time clinician, 1997 to 2001

Independent practitioner, clinician, and nurse practitioner supervisor
Topeka KS 2000 to 2002
Prairie Moon Health Clinic
McClouth Family Medicine
Lyndon Family Health

Prison Health Services, Inc., Topeka KS
Regional Medical Director, Kansas, 1996-1997
Medical Director, Topeka Correctional Facility, 1995-1996
Acting State Medical Director, November/December 1995

Johnson County Health Department, Olathe KS
Part-time clinician in women's health and TB management, 1994 to 2000

Kaiser Permanente Urgent Care, Overland Park KS
Part-time clinician, 1993 to 2000

Douglas Community Health Center, Kansas City KS
Clinician, 1995

Professional Details

Kansas Medical License # 04-23023
Certified Physician Investigator 2008-2010
Board Certified in Family Medicine 1995- 2015
Board Certified in Urgent Care Medicine 2001- 2011
Active DEA License
Basic Disaster Life Support Training 2008
Board Certified in Hospice and Palliative Care 2008-2018
Adjunct Physician, Midland Hospice
Specialty training in Anthropological Genetics 2008
Principal Investigator- 2007- Clinical trials in hyperlipidemia, influenza vaccination
2008- Clinical trials in hyperlipidemia, influenza treatment, childhood immunizations and geriatric pneumonia prevention
Member of Board of Directors, American Academy of Urgent Care Medicine
National Board Exams Passed: Part I- 1986, Part II- 1987, Part III- 1989
Professional Memberships: American Academy of Family Medicine
American Academy of Urgent Care Medicine
Awards- Outstanding Philanthropist, City of Topeka, 2004
Don Carlos Guffey Award for Outstanding Paper in Medical History, 1988

Credentials/ Awards

2008 Renewed Family Practice certification and elected to the Board of Directors, American Academy of Urgent Care Medicine
2006 Renewed DEA license
2005 Philanthropist of the Year, Topeka Kansas
2004 Awarded status of Fellow by American Academy of Family Practice
Awarded status of Fellow by American Academy of Urgent Care Medicine
Completed re-certification in Urgent Care Medicine through 2011
2003 Completed MBA
2002 Awarded Civil Surgeon status by INS
2001 Completed re-certification in Family Practice through 2008
Certified in Urgent Care Medicine

Education

MBA, emphasis on Health Care Systems
Regis University, Denver CO- Physician Distance Education Program
August 2001- February 2003

Family Practice Residency
University of Kansas Medical Center, Department of Family Medicine
March 1992- December 1994

Psychiatric Internship
University of Kansas Medical Center, Department of Psychiatry
June 1988- June 1989

Doctor of Medicine (MD)
University of Kansas Medical Center, School of Medicine
August 1983- May 1988

Undergraduate Degrees
BA in Biology, Kansas State University, Manhattan KS, 1981-1983
BS in Agriculture, Kansas State University, Manhattan KS, 1976-1980

Martha Ann Socolofsky, CPI

has on September 6, 2008 demonstrated a high level of competence by successfully completing an examination documenting professional and educational achievement and has fulfilled the prescribed standards of performance and conduct required to earn the designation of Certified Physician Investigator (CPI®) as determined by APPI's FDA CPI Exam Committee.

The CPI® designation is further evidence that this certified professional subscribes to the promotion and advancement of the highest ethical standards and practices in the clinical research profession. Certification maintenance is required by October 31, 2010.

Greg Koski, PhD, MD, CPI
President & Chairman, APPI

Thomas L. Adams, LHD, CAE
President & Chief Executive Officer, ACRP

Academy of Pharmaceutical Physicians and Investigators (APPI) is an affiliate of the Association of Clinical Research Professionals (ACRP).

KANSAS STATE BOARD of HEALING ARTS

Certificate of Renewal

This is to certify that the individual named below is authorized to practice as indicated.

MARTHA A SOCOLOFSKY MD

Profession: Medical Doctor (MD)
Certificate #: 04-25023 Status: ACTIVE
Date Issued: 07/01/2009 Expiration: 06/30/2010
CE Due: 2011

Signature of Practitioner

BRIAN DOUGLAS HALE, M.D., F.A.C.S.
CURRICULUM VITAE
2010

ADDRESS:

Advanced Research Institute, Inc. **10/2009- Present**
3633 Little Road, Suite 102
Trinity, FL 34655

Urology Specialists of West Florida **1995- Present**
35095 US Hwy. 19 N, Suite 202
Palm Harbor, Florida 34684

Urology Specialists of West Florida **1995- Present**
2148 Duck Slough Blvd., Suite 102
New Port Richey, FL 34655

Urology Specialists of West Florida **1995- Present**
13061 West Linebaugh Ave.
Tampa, FL 33626

LICENSE:

Florida Medical License # ME 67771- expiration 01/31/2010

CERTIFICATIONS:

Diplomate - American Board of Urology, 02/28/97- Present

RESEARCH TRAINING AND CERTIFICATIONS:

National Institute of Health- November 2009
Good Clinical Practice- November 2009

EDUCATION:

Urology Resident	Emory University Atlanta, GA	1991-1995
Surgical Resident	Emory University Atlanta, GA	1989- 1991
Doctorate Of Medicine	Emory University School of Medicine Atlanta, GA	1989
Bachelor of Arts- History & Chemistry	Emory University Atlanta, GA	1985

PROFESSIONAL ORGANIZATIONS:

American Medical Association
Southern Medical Association
American Urological Association
American College of Surgeons
Pinellas County Medical Society
Greater Tampa Bay Urological Association
Clinical Instructor for Laparoscopic Nephrectomy
Ethicon Training Center, University of Miami, FL

PUBLICATIONS:

1. Hale BD, Kassabian VS, Graham SD Jr.;
" The Effects of Aspirin Use on the Presentation and Outcome of Bladder Cancer."
Presented at AUA Southeastern Section, April 1993, Nashville, TN

2. Hale BD, Witt MA, O'Brien, DP;
" Penile Prosthesis Implanation in the Transplant Population."
Submitted to AUA Southeastern Section and National Meeting for 1994

PUBLICATIONS (continued):

3. Hale BD, Kassabain VS, Graham SD Jr.;
" Value of Prostate Specific Antigen Levels in Dectecting Recurreces After Radical Prostatectomy."
Submitted to AUA Southeastern Section and National Meeting for 1994

4. Hale BD, Singla A, Galloway N;
" Malacoplakia of the Kidney."
Infections in Urology. Vol.10, No. 4, 1997

RESEARCH EXPERIENCE:

Urology Research- Emory School of Medicine- 1988

Urge Incontinence- 2001

Watson-BPH- 2004

Amgen- Prostate Cancer-2009

Pfizer- Interstitial Cystitis- 2010

HOSPITAL AFFILIATIONS:

Helen Ellis Memorial Hospital Tarpon Springs, FL	2005- Present
*Chief of Surgery	2005-2006
Mease Countryside Hospital Clearwater, FL	Present
Community Hospital of New Port Richey New Port Richey, FL	Present
NorthBay Community Hospital New Port Richey, FL	Present

Brian Hale, MD

1/7/10

Date

AC# 3617290

STATE OF FLORIDA
DEPARTMENT OF HEALTH
DIVISION OF MEDICAL QUALITY ASSURANCE

DATE	LICENSE NO.	CONTROL NO.
10/14/2009	ME 67771	288394

The MEDICAL DOCTOR named below has met all requirements of the laws and rules of the state of Florida.

Expiration Date: **JANUARY 31, 2012**

BRIAN DOUGLAS HALE, M.D.
35095 U.S. HWY 19 NORTH
STE 202
PALM HARBOR, FL 34684
UNITED STATES

Charlie Crist
GOVERNOR

Ana M. Viamonte Ros, M.D., M.P.H.
STATE SURGEON GENERAL

DISPLAY IF REQUIRED BY LAW

CHARLES E. WEBSTER
CURRICULUM VITAE
2010

ADDRESS:

Advanced Research Institute, Inc. **06/2009- Present**
3633 Little Road, Suite 102
Trinity, FL 34655

Advanced Urology Associates **01/2009- Present**
5305 Gulf Drive, Suite 4
New Port Richey, FL 34652

Advanced Urology Associates **01/2009- Present**
1822 Wellness Lane
Trinity, FL 34655

LICENSE:

Florida Physician Assistant License #: PA 1866-expiration 01/31/2010

EDUCATION:

Associate Science Degree	Cleveland Clinic PA Program Cleveland, OH	1973- 1975
Hospital Corpsman	United States Navy	1969-1972
	Ohio State University Marion, OH	1967-1969
High School Diploma	Elgin High School Marion, OH	1963-1967

RESEARCH EXPERIENCE:

Astellas- COPD- 2009
Pfizer- Overactive Bladder- 2009
Forest Labs- COPD- 2009
Astellas- Renal Impairment- 2009
Salix- Proctitis- 2009
Amgen- Prostate Cancer- 2009
Amgen- Prostate Cancer- 2009
ProMedDx- Influenza- 2009
Forest Labs- IBS-c- 2009
Forest Labs- Chronic Constipation- 2009
UCB- Crohns- 2009
Centocor- Ulcerative Colitis- 2009
Pfizer- Interstitial Cystitis- 2010

PROFESSIONAL AFFILIATIONS:

American Academy of Physician Assistants
Florida Academy of Physician Assistants

PROFESSIONAL EXPERIENCE:

Physician Assistant	Citrus Urology Associates Homosassa, FL	2006- 11/2008
Physician Assistant	Urology Health Center New Port Richey, FL	1987- 2006
Physician Assistant	VA Medical Center Iowa City, IA	1981- 1987

PUBLICATIONS:

Evolutions of Techniques for Ultrasound Guided- Palladium 103 Brachytherapy in 950 Patients with Prostate Cancer- Techniques in Urology- Volume 6, No. 2 PP 128- 134

Minimally Invasive Treatment for Localized Adenocarcinoma of the Prostate- Review of 1048 Patients treated with Ultrasound Guided Palladium 103 Brachytherapy- Journal of Endourology, Volume 14, No. 4, May, 2000

Signature

4 Jan 2010
Date

AC# 2705712

STATE OF FLORIDA
DEPARTMENT OF HEALTH
DIVISION OF MEDICAL QUALITY ASSURANCE

DATE	LICENSE NO.	CONTROL NO.
12/19/2009	PA 1866	30374

The **PHYSICIAN ASSISTANT** named below has met all requirements of the laws and rules of the state of Florida.

Expiration Date: **JANUARY 31, 2012**

QUALIFICATION(S):
PRESCRIBING #00000398

CHARLES E WEBSTER
1822 WELLNESS LANE
TRINITY, FL 34655
UNITED STATES

VOID VOID VOID VOID VOID VOID VOID VOID VOID VOID VOID VOID

Charlie Crist
GOVERNOR

Ana M. Viamonte Ros, M.D., M.P.H.
STATE SURGEON GENERAL

DISPLAY IF REQUIRED BY LAW

CURRICULUM VITAE
DANIEL H. RODRIGUEZ, M.D.
2010

ADDRESS:

Advanced Research Institute, Inc. **10/2007 to Present**
3633 Little Road, Suite 102
Trinity, FL 34655

Optimum Family Care **2002 to Present**
3531 Little Road
New Port Richey, FL 34655

LICENSE:

Florida Medical License # ME 81923- expiration 01/31/2011

CERTIFICATIONS:

Affiliated	American Academy of Family Practice	2001 to Present

EDUCATION:

Residency	Mountainside Family Practice Associates Montclair, NJ	1998 to 2001
	Chief Resident	2000 to 2001
Internship	New York Medical College Valhalla, NY	1997 to 1998
Doctorate Of Medicine	Universidad Autonoma de Guadalajara, Mexico	1993 to 1997
	Florida International University Miami, FL	1989 to 1993

RESEARCH EXPERIENCE:

Takeda – Diabetes Mellitus Type II – 2007

Kendle – Resistant Hypertension – 2007

Daiichi Sankyo – Diabetes Mellitus Type II – 2007

Plethora – Rapid Ejaculation – 2007

Oakwood – Prostate Cancer – 2007

Duramed - Overative Bladder Ring - 2007

Veridex - Prostate Cancer - 2007

Daiichi Sankyo – Hypertension - 2007

Halozyme - Bladder Cancer – 2008

Roche - Diabetes Mellitus Type II - 2008

Tolerx - Diabetes Mellitus Type I - 2008

Forest Labs - Constipation - 2008

Forest Labs – Constipation with IBS - 2008

Astellas – COPD - 2009

Astellas - Renal Impairment - 2009

Pfize r- Overactive Bladder - 2009

Amgen - Prostate Cancer - 2009

Forest Research – COPD - 2009

Salix - Proctititis/ Protosigmoiditis - 2010

ProMedDx – Influenza - 2010

RESEARCH TRAINING AND CERTIFICATIONS:

National Institute of Health – October 2007
Good Clinical Practice – October 2007

PROFESSIONAL EXPERIENCE:

Medical Doctor	Clearwater Family Practice 1217 Ewing Avenue Clearwater, FL 33756	2001 to 2002

HOSPITAL AFFILIATIONS:

Community Hospital of New Port Richey 5637 Marine Parkway New Port Richey, FL	2003 to Present
* Vice Chief of Department of Medicine	2006 to Present
*Chairman of Medical Quality Assurance Committee	2006 to Present
North Bay Hospital 6600 Madison Avenue New Port Richey	2003 to Present

Daniel Rodriguez, M.D.

1/7/10
Date

AC# 2190559

STATE OF FLORIDA
DEPARTMENT OF HEALTH
DIVISION OF MEDICAL QUALITY ASSURANCE

DATE	LICENSE NO.	CONTROL NO.
11/27/2008	ME 81923	264304

The MEDICAL DOCTOR named below has met all requirements of the laws and rules of the state of Florida.
Expiration Date: JANUARY 31, 2011
DANIEL HECTOR RODRIGUEZ
3531 LITTLE ROAD
NEW PORT RICHEY, FL 34655

Charlie Crist
GOVERNOR

Ana M. Viamonte Ros, M.D., M.P.H.
STATE SURGEON GENERAL

DISPLAY IF REQUIRED BY LAW

AC# 2190559

STATE OF FLORIDA
DEPARTMENT OF HEALTH
DIVISION OF MEDICAL QUALITY ASSURANCE

DATE	LICENSE NO.	CONTROL NO.
11/27/2008	ME 81923	264304

The MEDICAL DOCTOR named below has met all requirements of the laws and rules of the state of Florida.
Expiration Date: JANUARY 31, 2011
DANIEL HECTOR RODRIGUEZ

EXPIRATION DATE: JANUARY 31, 2011

Your license number is ME 81923, please use it in all correspondence with your board/council. Each licensee is solely responsible for notifying the department in writing of the licensee's current mailing address and practice location address. If you have not received your renewal notice 90 days prior to the expiration date shown on this license, please call (850) 488-0595.

Use this section to report name change. Name changes require legal documentation showing the name change. Please make sure that a photocopy of one of the following accompanies this form: a marriage license, a divorce decree or a court order. A driver's license or social security card is not considered legal documentation.

Medical Quality Assurance offers you the convenience of several online services. These services give you the ability to renew your license, update your mailing and practice location addresses and update your profile information.

1. Go to www.flhealthsource.com
2. Click on Licensee/Provider
3. Click on Practitioner Login
4. Select your profession
5. Enter the account ID and password here (Account ID and Password are case sensitive) Account ID: OPTIMUM1 Password: OPTIMUM1
   Where '1' is number ONE, 'I' is uppercase letter 'I' and 'O' is uppercase letter 'O'.
6. Click on Login

MAIL TO: DEPARTMENT OF HEALTH
DIVISION OF MEDICAL QUALITY ASSURANCE
LICENSING AND AUDITING SERVICES UNIT
P.O. BOX 6320
TALLAHASSEE, FLORIDA 32314-6320

☐ NAME CHANGE (ATTACH LEGAL DOCUMENTATION)

FROM: _____ (LAST / FIRST / MIDDLE)

TO: _____ (LAST / FIRST / MIDDLE)

DH 2103, 5/98

JAY CHOWDAPPA, M.D.
CIRRICULUM VITAE
2010

ADDRESS:

Advanced Research Institute, Inc. **05/2009- Present**
3633 Little Road, Suite 102
Trinity, FL 34655

Apollo Medical Center **05/1999- Present**
3535 Little Road
Trinity, FL 34655

LICENSE:

Florida Medical License # ME 73247- expiration 01/31/2011

CERTIFICATIONS:

Board Certified- Internal Medicine 1995

EDUCATION:

Fellowship in Ambulatory/ Primary Care	Catholic Medical Center New York 11432	07/1995- 6/1996
Residency: Internal Medicine	Catholic Medical Center New York 11432	07/1992- 6/1995
General Medicine	Bangalore Medical College Bangalore, India	01/1986- 1/1989
M.B.B.S.	Bangalore Medical College Bangalore, India	07/1979- 3/1985

PROFESSIONAL EXPERIENCE:

Apollo Medical Spa- Medical Director	12/2008- Present
Apollo Medical Center- M.D & Medical Director New Port Richey, FL	05/1999- Present
Goli Hospital Medial Center- Internist/PCP (aka Sargent District Hospital) Sargent, NB	07/1996- 3-1999
Catholic Medical Center- Primary Care New York	07/1995- 6/1996

RESEARCH EXPERIENCE:

Novo Nordisk- Diabetes Mellitus Type II- 2004
Bangalore University- Tuberclous Pleural Effusions- 1988
Pfizer- Overactive Bladder- 2009
ProMedEx- Influenza- 2009
Astellas- Renal Impairment- 2009

HOSPITAL AFFILIATIONS:

Community Hospital of New Port Richey New Port Richey, FL	1999- Present
Northbay Hospital New Port Richey, FL	1999- Present
Bayonet Point Regional Hospital Hudson, FL	1999- Present

RESEARCH TRAINING AND CERTIFICATIONS:

National Institute of Health	11/2009
Good Clinical Practice	11/2009

Signature

Jan 7th 2010

Date

AC# 3168150

STATE OF FLORIDA
DEPARTMENT OF HEALTH
DIVISION OF MEDICAL QUALITY ASSURANCE

DATE	LICENSE NO.	CONTROL NO.
11/04/2008	ME 73247	258001

The **MEDICAL DOCTOR** named below has met all requirements of the laws and rules of the state of Florida.

Expiration Date: **JANUARY 31, 2011**

JAYADEVA CHOWDAPPA
ATTN: BARABARA J TOWNSEND
3535 LITTLE ROAD
NEW PORT RICHEY, FL 34655

QUALIFICATION(S):
DISPENSING PRACTITIONER

Charlie Crist
GOVERNOR

Ana M. Viamonte Ros, M.D., M.P.H.
STATE SURGEON GENERAL

DISPLAY IF REQUIRED BY LAW

STATE OF FLORIDA
DEPARTMENT OF HEALTH
DIVISION OF MEDICAL QUALITY ASSURANCE
AC# 3168150

DATE	LICENSE NO.	CONTROL NO.
11/04/2008	ME 73247	258001

The MEDICAL DOCTOR named below has met all requirements of the laws and rules of the state of Florida.
Expiration Date: JANUARY 31, 2011

JAYADEVA CHOWDAPPA

QUALIFICATION(S):
Dispensing Practitioner

SIVAKUMAR AMAR, M.D.
CURRICULUM VITAE
2010

ADDRESS:

Advanced Research Institute, Inc. **04/2008- Present**
3633 Little Road, Suite 102
Trinity, FL 34655

Amar & Amar, M.D., P.A. **1981- Present**
3535 Little Road
New Port Richey, FL 34655

PERSONAL:

Born: June 20, 1947
Place of Birth: Vuyyur, India
Married with two children

LICENSE:

Florida Medical License #: ME 38311- expiration 01/31/2012

CERTIFICATIONS:

Board Certified – Internal Medicine, 1982
Pulmonary Medicine, 1984

RESEARCH TRAINING AND CERTIFICATIONS:

National Institute of Health – April 2008
Good Clinical Practice – April 2008

EDUCATION:

Fellowship in Pulmonary Medicine:	Columbia University College of Physicians and Surgeons Harlem Hospital Center New York, NY	1979- 1981
Residency: Internal Medicine	Englewood Hospital Englewood, NJ	1976- 1979
Flexible Internship:	Detroit-Macomb Hospital Detroit, MI	1975- 1976
Private Practice:	Vijayawada A.P., India	1974- 1975
Rotating Internship:	Government General Hospital Gunter, India	1973- 1974
M.B.B.S.:	Kakatiya Medical College Warangal, India	1966-1973

RESEARCH EXPERIENCE:

Kendle- Resistant Hypertension- 2008

Plethora- Premature Ejaculation- 2008

Duramed- Overactive Bladder- 2008

Daiichi Sankyo- Hypertension- 2008

GlobeImmune- Hepatitis C- 2008

Halozyme- Bladder Cancer- 2008

Forest Research- Chronic Constipation- 2008

Forest Research- IBS with Constipation- 2008

Roche- Diabetes Mellitus Type II- 2008

Uroplasty- Overactive Bladder Device- 2008

Tolerx- Diabetes Mellitus Type I- 2008

Eisai- GERD- 2009

Ferring- Prostate Cancer- 2009

STEP- Overactive Bladder Device- 2009

Astellas- COPD/Asthma- 2009

Astellas- Renal Impairment- 2009

ProMedDx- Lymphoma- 2009

Pfizer- OAB- 2009

Amgen- Non-Metastatic Cancer- 2009

ProMedDx- Influenza- 2009

Bayer- NAION- 2009

Salix- Proctitis/ Protosigmoiditis- 2009

Pfizer- IC- 2009

RESEARCH EXPERIENCE (continued):

Forest Research- COPD- 2009

Amgen- Prostate Cancer- 2009

UCB- Crohns- 2009

HOSPITAL AFFILIATIONS:

Consulting Privileges Bayonet Point Medical Center	1981- Present
Active Privileges Community Hospital of New Port Richey	1981- Present
Active Privileges NorthBay Medical Center	1981-Present
Director of the Department of Medicine & Family Medicine – Riverside Hospital	1988-1991
Director of Respiratory Therapy Department NorthBay Hospital	1983 - 2003
Chief of Staff at NorthBay Medical Center	1992- 1993
Member of Medical Executive Committee NorthBay Medical Center	1988-1995

Sivakumar Amar, M.D.

1/6/10
Date

SIVAKUMAR AMAR, M.D.
CURRICULUM VITAE
2010

ADDRESS:

Advanced Research Institute, Inc. **04/2008- Present**
3633 Little Road, Suite 102
Trinity, FL 34655

Amar & Amar, M.D., P.A. **1981- Present**
3535 Little Road
New Port Richey, FL 34655

PERSONAL:

Born: June 20, 1947
Place of Birth: Vuyyur, India
Married with two children

LICENSE:

Florida Medical License #: ME 38311- expiration 01/31/2012

CERTIFICATIONS:

Board Certified – Internal Medicine, 1982
Pulmonary Medicine, 1984

RESEARCH TRAINING AND CERTIFICATIONS:

National Institute of Health – April 2008
Good Clinical Practice – April 2008

EDUCATION:

Fellowship in Pulmonary Medicine:	Columbia University College of Physicians and Surgeons Harlem Hospital Center New York, NY	1979- 1981
Residency: Internal Medicine	Englewood Hospital Englewood, NJ	1976- 1979
Flexible Internship:	Detroit-Macomb Hospital Detroit, MI	1975- 1976
Private Practice:	Vijayawada A.P., India	1974- 1975
Rotating Internship:	Government General Hospital Gunter, India	1973- 1974
M.B.B.S.:	Kakatiya Medical College Warangal, India	1966-1973

RESEARCH EXPERIENCE:

Kendle- Resistant Hypertension- 2008

Plethora- Premature Ejaculation- 2008

Duramed- Overactive Bladder- 2008

Daiichi Sankyo- Hypertension- 2008

GlobeImmune- Hepatitis C- 2008

Halozyme- Bladder Cancer- 2008

Forest Research- Chronic Constipation- 2008

Forest Research- IBS with Constipation- 2008

Roche- Diabetes Mellitus Type II- 2008

Uroplasty- Overactive Bladder Device- 2008

Tolerx- Diabetes Mellitus Type I- 2008

Eisai- GERD- 2009

Ferring- Prostate Cancer- 2009

STEP- Overactive Bladder Device- 2009

Astellas- COPD/Asthma- 2009

Astellas- Renal Impairment- 2009

ProMedDx- Lymphoma- 2009

Pfizer- OAB- 2009

Amgen- Non-Metastatic Cancer- 2009

ProMedDx- Influenza- 2009

Bayer- NAION- 2009

Salix- Proctitis/ Protosigmoiditis- 2009

Pfizer- IC- 2009

RESEARCH EXPERIENCE (continued):

Forest Research- COPD- 2009

Amgen- Prostate Cancer- 2009

UCB- Crohns- 2009

HOSPITAL AFFILIATIONS:

Consulting Privileges Bayonet Point Medical Center	1981- Present
Active Privileges Community Hospital of New Port Richey	1981- Present
Active Privileges NorthBay Medical Center	1981-Present
Director of the Department of Medicine & Family Medicine – Riverside Hospital	1988-1991
Director of Respiratory Therapy Department NorthBay Hospital	1983 - 2003
Chief of Staff at NorthBay Medical Center	1992- 1993
Member of Medical Executive Committee NorthBay Medical Center	1988-1995

Sivakumar Amar, M.D.

1/6/10
Date

AC# 3623971

STATE OF FLORIDA
DEPARTMENT OF HEALTH
DIVISION OF MEDICAL QUALITY ASSURANCE

DATE	LICENSE NO.	CONTROL NO.
10/21/2009	ME 38311	290294

The **MEDICAL DOCTOR**
named below has met all requirements of
the laws and rules of the state of Florida.
Expiration Date: **JANUARY 31, 2012**

SIVAKUMAR V AMAR
3535 LITTLE ROAD
TRINITY, FL 34655
UNITED STATES

Charlie Crist
GOVERNOR

Ana M. Viamonte Ros, M.D., M.P.H.
STATE SURGEON GENERAL

DISPLAY IF REQUIRED BY LAW

APPENDIX D

APPENDIX E (electronic on CD)

CURRICULUM VITAE FOR: **Mandeep S. Oberoi, MD**
Reviewed and updated on:

Central Jersey Medical Research Center
240,Williamson St. Suite # 305
Elizabeth, NJ 07202

Tel:: (908)354-5353
Fax: (908) 351-6911
Cell: (908)346-1537
Email: Oberoimd@hotmail.com

Experience & Training:

1999-Present	Clinical Medical Research @ Central Jersey Medical Research Center. I have been involved in many phase II, III and IV clinical trials for various Pharmaceutical companies. I have been the principal Investigator for more than 50 clinical trials and oversee about six physicians involved with me in clinical research.
1999-Present	I have been in Group private practice (full time) in Elizabeth, NJ. Provide primary care medical management in outpatient, inpatient and nursing home set up to all the patients in a group practice.
1997-2002	Worked as an Emergency Room Physician at St. Michael Medical Center, Newark, NJ. The work involved providing medical care to Emergency room patients. Was involved in teaching of the medical students and residents. Total experience of more than 7,000 ER hours.

Academic Qualifications:

Board Certified in Internal Medicine

July 1, 1994-June 1997	***Residency in Internal Medicine*** University of Medicine & Dentistry of New Jersey New Jersey Medical School 30 Bergen Street Newark, NJ 07103
January 1989-December 1990	***Residency in Internal Medicine*** Government Rajindra Medical College, Patiala, India
January 1987-December 1988	***Clinical Rotating Internship at*** Government Rajindra Medical College & Hospital, Patiala, India.
August 1983-December 1987	***M.B, BS*** at Govt. Rajindra Medical College, Patiala, India.

Honors & Awards: Declared as the Best ***Resident*** by Medicine Dept. twice in UMDNJ. I was ranked among ***top ten students*** in Medical school. I received ***Roll of Honor*** awarded by Dean, Medical College, and Patiala, India for exceptional community services.

Publications:

1. ***"HIV & Pulmonary Hypertension" with review of literature.*** A case report published in Hospital Practice.
2. ***"Emerging Role of Computerized Tomography as morbidity in predictor pancreatitis".*** A prospective study conducted in UMDNJ and Newark Beth Israel Hospital, Newark, NJ.

Professional Organizations Affiliation:
Member, Pharmacy, Therapeutics and Dietary Committee, Trinitas Hospital, Elizabeth.
Member, Institutional Review Board, Trinitas Hospital, Elizabeth.
Member of American Medical Association
Member of American College of Physicians
Member of New Jersey Medical Society
Executive Member, North American Association of Sikh Physicians and Dentists.
General Secretary, Punjabi Cultural Society of New Jersey.

License:

Active New Jersey License: MA66667

Hospital Affiliation:

Trinitas Hospital
225 Williamson Street
Elizabeth, NJ 07202

Union Hospital
Galloping Hill Road
Union, NJ

Rahway Hospital
Stone Street
Rahway, NJ

Clinical Research Experience:

1. **Principal Investigator**, "**RADIUS-I Study**". Rheumatoid Arthritis DMARD Intervention and Utilization Study by **Immunex/ Amgen**. Protocol # 016-0034.

2. **Principal Investigator**, An Open-label, Non-comparative Study to asses the Efficacy and safety of Oral Augmentin SR 2000/125 mg Twice Daily for 7 Days for the Treatment of Bacterial Community Acquired Pneumonia. In Adults. Study by **GlaxoSmithKline Beecham**. Protocol # SB BRL-025000/547.

3. **Principal Investigator**, A Randomized, Double-blind, Double dummy, Multicenter, parallel Group Study to Asses the Efficacy and Safety of Oral Augmentin SR 2000/125mg Twice daily for 5 days versus Oral Augmentin 875/125 mg for 7 Days in the Treatment of Adults with Acute Exacerbation of Chronic Bronchitis. Study by **SmithKline** under Protocol # BRL-25000/630. (**Highest Enroller**).

4. **Principal Investigator, "RADIUS – II Study"**. Rheumatoid Arthritis DMARD Intervention and Utilization Study. Study by **Immunex/ Wyeth/Amgen**. Protocol # 016.0035

5. **Principal Investigator**, A Prospective, Open-label, Non-comparative, Multicenter Trial to evaluate the Efficacy and Safety of Ciprofloxacin Extended Release(Cipro XR) 500 mg Daily for 3 days in the Treatment of Female patients with Acute, Uncomplicated Symptomatic, Lower Urinary Tract Infections. Study by **Bayer** under Protocol# 100546.

6. **Principal Investigator**, **MOVE Study** to evaluate the Pain Intensity Changes in Patients with Osteoarthritis Knee by Using Intraarticular Hyaluronic Acid Injections. Study by **Stanford University, CA.**

7. **Principal Investigator**, Chronic NSAID induced Gastritis and Nexium by **AstraZeneca.**

8. **Principal Investigator**, A Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel-arm Study to asses the Long-term Effects of Platel(Cilostazol) versus Placebo Administered Orally to Patients with Intermittent Claudication Secondary to Peripheral Vascular Disease. Phase III Study by **Otsuka.** Protocol # 21-98-214-01.

9. **Principal Investigator**, A Prospective, randomized, Double-blind, Multicenter, Comparative Trial to Evaluate the Efficacy and Safety of Ciprofloxacin Once-Daily (QD) Modified Release (CiproMR) Tablets Versus Conventional Ciprofloxacin 500 mg Tablets BID in the 7-14 Day Treatment of patients With Complicated Urinary Tract Infections (cUTI) or Acute Uncomplicated Pyelonephritis. Study by **Bayer.** Protocol # 100275.

10. **Principal Investigator**, Kineret Study for Rheumatoid Arthritis by **Amgen.**

11. **Principal Investigator**, A Randomized, Multicenter, Blinded Study of The Efficacy and Safety of High dose (750 mg), Short course (3-5 days) Levofloxacin Therapy in Uncomplicated and Complicated Acute Bacterial Exacerbation of Chronic Bronchitis. Study by **Bayer** under Protocol #CAPSS-197.

12. **Principal Investigator**, A Prospective, Randomized, Double-blinded, Active controlled Study for the evaluation of the Efficacy, Safety, and Pharmacoeconomics of Oral Telithromycin (Ketek) 800mg once a day for 5 days vs. Moxofloxacin (Avelox) 400 mg once a day for 10 days in the Treatment of Acute Maxillary Sinusitis (AMS) in Adults. Study by **Aventis.** Protocol # HMR3647A/4017.

13. **Principal Investigator**, Cipro XR Excellence in the Therapeutic Response and Activity (eXtRa)-Assessing Symptom Relief in Urinary Tract Infections. Study by **Bayer** under Protocol # 100544.

14. **Principal Investigator**, A 4-week, Randomized, Multicenter, Double-blind, Placebo and Active Controlled, parallel-group, Forced-titration Phase II B Study Comparing Efficacy and Safety of Ascending Doses of CG5503 Prolonged Release Up to 233 mg BID and Oxycodone Prolonged release Up to 20 mg BID in Subjects with Moderate to Severe Chronic Pain due to Osteoarthritis of the Knee. Study by **Johnson & Johnson Research & Development** . Protocol # R331333-PAI-2001.

15. **Principal Investigator**, A Randomized, Double-blind, Multicenter, Positive-controlled, parallel group Study to evaluate the Safety of Amlodipine and Benzapril Administered in combination Compared to Amlodipine Monotherapy in Hypertensive patients Not Adequately with Amlodipine Alone. Study by **Novartis**. Protocol # CCIN002H2304.

16. **Principal Investigator**, "**ACS-RESCUE Study**". A Prospective, Open-label, Randomized, Parallel- group Investigation to Evaluate the efficacy and Safety of Enoxaparin versus Unfractionated heparin in Subjects who present to the Emergency Room with Acute Coronary Syndrome. Phase IV Study. Protocol # XRP4563B/4001 by **Aventis.** (**Highest Enroller**). Enrolled 50 patients in this inpatient study.

17. **Principal Investigator**, "**STARSHIP STUDY**". A 6 week, Randomized, Open-label, Comparative Study to Evaluate the Efficacy and safety of Rosuvastatin and Atorvastatin in the Treatment of Hypercholesterolemia in Hispanic Subjects. Study by **AstraZeneca** under Protocol # 4522US/0007 (**Highest enroller**)

18. **Principal Investigator**, A Multicenter, Double-blind, Randomized, parallel Groups, placebo-controlled, Study to Asses the Efficacy and Safety of Fexofenadine 120 mg BID in Subjects with Mild to Moderate Persistent Asthma. Study by **Aventis**. Protocol # MO16455P/3002

19. **Principal Investigator**, "**JUPITER STUDY**". A randomized, Double-Blind, Placebo-controlled, Multicenter, Phase III Study of Rosuvastatin (Crestor) 20mg in the Primary Prevention of Cardiovascular Events among Subjects with Low Levels of LDL-Cholesterol and Elevated Levels of C-Reactive Protein.
Study By **AstraZeneca** under Protocol # 4522US/0011.

20. **Principal Investigator**, A Multicenter, randomized, Double-blind, Placebo Controlled, Parallel Comparison of the Efficacy and safety of Fixed-dose Extended-Release Hydrocodone Bitartarate/Acetaminophen in the Relief of Moderate to Moderately Severe Chronic Osteoarthritis Pain of the Hip joint.
Phase III Study by **Watson Laboratories**. Protocol#HA03028.

21. **Principal Investigator**, A Strafied, Randomized, Prospective, Unblinded, Active-control Trial of Factive Versus BiaxinXL for the Treatment of Community Acquired Pneumonia & Versus Amoxicillin/clavulanate for the Treatment of Acute Bacterial Exacerbation of Chronic Bronchitis.
Phase IV Study by **Oscient Pharmaceuticals**. Protocol # OS-001.

22. **Principal Investigator**, Prospective, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and safety of Moxifloxacin 400 mg QD for 5 days versus Placebo in the Treatment of Acute Bacterial Sinusitis.
Study by **Bayer**. Protocol # 11566.

23. **Principal Investigator**, A Multicenter, Phase III Study to Confirm the Safety and Efficacy of Intravenous Doripenem in Complicated Urinary Tract Infections or Pyelonephritis. Study by **Peninsula Pharmaceuticals**. Protocol # DORI-06.

24, **Principal Investigator**, "**CUSP Study**". An 8-week randomized, Double-Blind, Placebo-Controlled Trial Examining The Efficacy and Safety of Caduet in Simultaneously achieving Blood Pressure and Lipid Goals in An Untreated Hypertensive & Dyslipidemic Subject Population.
Protocol # A3841046 by **Pfizer**. Phase IV Study.(**Highest Enroller**).

25. **Principal Investigator**, A Randomized, Double-blind, Multicenter, Placebo-controlled, Parallel-group Study to evaluate the efficacy and safety of Valsatan (320mg) and Hydrochlorthiazide (12.5 and 25 mg) combined and alone, Valsartan 160 mg and Valsartan 160 mg/hydrochlorthiazide 12.5 mg in Hypertensive Patients.
Study by **Novartis** under Protocol # CVAH 631C2301.

26. **Principal Investigator**, "**RACER STUDY**.PhaseII Study. A Multicenter, Double-blind, Randomized, parallel, Placebo-controlled Study to evaluate the Safety, Efficacy, and Pharmacokinetics of 2 oral doses, 25 mg Twice daily and 100 mg twice daily, of PG-760564 in Adult Patients with Rheumatoid Arthritis Receiving Methotrexate.
Phase II Study by **Procter & Gamble**. Protocol # 206012.

27. **Principal Investigator**, A Randomized, Double-Blind, Active-Comparator Controlled, Parallel-Group Study to Evaluate the effectiveness of Etoricoxib in Patients with Osteoarthritis or Rheumatoid Arthritis (**MEDAL STUDY**).
Study by **Merck**. Protocol # 066-03 IND #54,464. **(42 Patients)**

28. **Principal Investigator**, "**GRADE Study**". A Multicenter, Randomized , Double-blind, Placebo-controlled Study of Safety and Efficacy of CS-917 as Monotherapy for Type II Diabetes.
A Phase II Study by **Daichii Sankyo** Pharmaceutical Development.
Protocol # CS917-A-U205.

29. **Principal Investigator**, A Prospective, Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel-group study if Intranasal Amphoterecin B suspension in patients with Refractory, Post surgical Chronic Sinusitis.
Phase III protocol # ACC-05-01 by **Accecia**.

30. **Principal Investigator**, "**PRECISION Study**" A Prospective, Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen Or naproxen in A Randomized, Double-blind, Parallel-Group Study of Cardiovascular Disease comparing Celecoxib with Naproxen and Ibuprofen.
Protocol # A3191172 by **Pfizer**.

31. **Principal Investigator**, A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Study to Evaluate the Efficacy and safety of Alvimopan 0.5 mg Once daily and 0.5mg Twice Daily for 12 Weeks for the Treatment of Opioid-Induced Bowel Dysfunction in Adults taking Opioid Therapy for Persistent Non-Cancer Pain.
Study by **GlaxoSmithKline.** Protocol # 767905-012.

32. **Principal Investigator**, A Multicenter, randomized, Double-blind, Placebo-controlled Trial To Evaluate the safety and efficacy of a New Tablet Formulation and Dosing regimen of balsalazide Disodium 3.3G BID Versus Placebo In Mildly To Moderately Active Ulcerative Colitis.
Study by **Salix Pharmaceuticals**. Protocol# BZUC3002.

33. **Principal Investigator**, An 8-week Randomized, Double-Blind, Parallel Group, Multicenter, Placebo and Active Controlled Dose Escalation Study to Evaluate the Efficacy and Safety of Aliskiren (150 mg and 300 mg) Administered alone and in Combination with Valsartan (160mg and 320 mg) in patients with Hypertension.
Study by **Novartis**. Protocol # CSPP100A2327.

34. **Principal Investigator**, A 24-Week, Multicenter, Double-Blind, Parallel Group, Randomized, Controlled Study of Roflumilast(250mcg and 500 mcg) versus Placebo in Patients with Bronchial Asthma. **FLASH STUDY**.
Protocol # BY217/M2-023 by **Altana** Pharmaceutical.

35. **Principal Investigator**, A Randomized, Double-blind, Placebo-controlled, factorial Study Evaluating the Efficacy and Safety of Co administration of Olmesartan Modoxomil Plus Amlodipine Compared to Monotherapy in Patients with Mild to Severe Hypertension.
    Study by **Daiichi Sankyo Pharma**. Protocol # CS8663-A-U301.

36. **Principal Investigator**, A Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Study to Evaluate the Long Term Safety of Alvimopan 0.5 mg Twice Daily for 12 Months for the Treatment of Opioid-Induced Bowel Dysfunction in Adults taking Opioid Therapy for Persistent Non-Cancer Pain.
    Study by **GlaxoSmithKline.** Protocol# 767905-014.

37. **Principal Investigator**, A 12-month, Randomized, Open-label, Multicenter, study to asses the Long term Safety of Aliskiren 150 mg alone and 300 mg Alone or with the Optional Addition of Hydrochlorthiazide (12.5mg or 25 mg) in patients with Essential Hypertension. Protocol# CSPP100A2302. Phase III by **Novartis.(Highest Enroller)**

38. **Principal Investigator**, Liraglutide Effect and Action in Diabetes (**LEAD 3**): Effect on Glycemic Control of Liraglutide versus Glimepiride in Type2 Diabetes (A Fifty-two Week Double-blind, Multicenter, Randomized, Parallel Study to Investigate the Safety and Efficacy with a Fifty-two Week Open-label Extension.
    Study by **Novo Nordisk Inc**. Protocol # NN2211-1573.

39. **Principal Investigator**, All To target Trial-Lantus (Insulin Glargine) with Stepwise Addition of Apidra (insulin glulisne) or Lantus with one injection of Apidra vs. a Twice-daily premixed insulin regimen (Novolog Mix 70/30) in Adult Subjects with Type 2 Diabetes failing dual or triple therapy with Oral Agents: A 64-Week, Multicenter, Randomized, Parallel, Open-Label Clinical Study.
    Protocol# HMR1964A/3515 by **Sanofi-Aventis. (FDA Audit: Oct 2008)**

40. **Principal Investigator**, An Open-label, Multicenter, Study to Evaluate the Safety of Long-Term Administration of TAK-128 in Subjects With Mild to Moderate Diabetic Peripheral Neuropathy.
    Study by **Takeda.** Protocol # 01-05-TL-128-006.

41. **Principal Investigator**, A Randomized, Double-blind, Multicenter Study Comparing the Effects of carvedilol Phosphate Modified Release Formulation (COREG-MR) with Metoprolol Succinate (TOPROL-XL) on the Lipid Profile in Normolipidemic, or Mildly Dyslipidemic Hypertensive Patients.
    Study by **GlaxoSmithKline.** Protocol # COR103561.

42. **Principal Investigator**, "**TOGETHER STUDY**". A 6-week, Prospective, Randomized, Double-blind, Double-dummy Phase IV Clinical Trial designed to Evaluate the Efficacy of an Aggressive Multi-risk factor Management Strategy with Caduet versus a Guideline based approach in Achieving Blood Pressure and Lipid Control in Hypertensive subjects With Additional Risk factors.

Protocol# A3841045 by **Pfizer. (Highest Enroller)**

43. **Principal Investigator**, A Multicenter, Double-Blind Study to Determine the Efficacy and Safety of SYR-322 plus Pioglitazone HCL (Actos), SYR-322 Alone or Pioglitazone Alone in Subjects with Type 2 Diabetes. **(Sponsor Audit)**
Protocol # 01-06-TL-322OPI-002 by **Takeda** Global Research & Development.

44. **Principal Investigator**, A Randomized, Double-Blind, Active-Controlled, Parallel Group, Multi-center, 12 Week Study Comparing the Safety and Efficacy of Fluticasone and Formoterol Combination (Flutiform 100/10 Mcg twice daily) in a Single Inhaler (SkyePharma HFA pMDI) with the Administration of Fluticasone (100 mcg twice daily) and Formoterol (10 mcg twice daily) Alone in Adolescent and Adult patients with Mild to Moderate Asthma.
Protocol # SKY2028-3-002 by **SkyePharma AG.**

45. **Principal Investigator**, "A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study to compare the safety and Efficacy of an Olmesartan medoxomil Based Treatment Regimen to Placebo in patients With Stage I and stage II Hypertension.
Study Protocol# 866-451 by **Daiichi Sankyo Pharma** Development.

46. **Principal Investigator**, "**EXTRA STUDY**". A Phase IIIb Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Xolair in subjects with Moderate to Severe Persistent Asthma Who are Inadequately Controlled With High-Dose Inhaled Corticosteroids and Long-Acting Beta-Agonists.
Study Protocol # Q3662g by **Genentach Inc.** & **Novartis.**

47. **Principal Investigator,** A Double-Blind, Randomized, Placebo-Controlled Study of the efficacy and Safety of EUFLEXXA for the treatment of painful Osteoarthritis of the Knee, With an Open-Label Safety Extension.
Study Protocol # FPI-EUFLX-2005-01D by **Ferring Pharceuticals Inc.**

48. **Principal Investigator,** A 12-week, Multicenter, randomized, Double-Blind, Parallel Group Study of the Combination of ABT-335 and Rosuvastatin Compared to ABT-335 and Rosuvastatin Monotherapy in Subjects with Type IIa and IIb Dyslipidemia.
Study Protocol # M06-844 by **Abbott.**

49. **Principal Investigator, "ARISTOTLE Study".** A Phase III, Active (Warfarin) Controlled, Randomized, Double-Blind, Parallel Arm Study to Evaluate Efficacy and safety of Apixaban in Preventing Stroke and Systemic Embolism in Subjects with Non Valvular Atrial Fibrillation.
Protocol # CV 185030 by **Bristol-Myers Squibb**.

50 **Principal Investigator,** A Phase III b, Double-Blind Randomized Study to determine the Efficacy and Safety of Pioglitazone HCL and Metformin HCL Fixed-Dose Combination Therapy Compared to Pioglitazone HCL Monotherapy and to Metformin HCL Monotherapy in the treatment of Subjects with Type 2 Diabetes.

Protocol # 01-06-TL-OPIMET-008 by Takeda Global Research.

51. **Principal Investigator,** A Phase III Randomized, Double-Blind, Placebo Controlled Multicenter Study to Determine the Safety and Efficacy of V1-0521 in the Treatment of Obesity in Adults With Obesity- Related Co-Morbid Conditions.
Protocol # OB 303 by **Vivus Inc. (High Enroller) (Sponsor Audit)**

52. **Principal Investigator, "GRAVITY STUDY"** A 12-week Open-Label, Randomized, Parallel-group, Multicenter, Phase IIIB Study to compare the Efficacy and safety of Rosuvastatin(Crestor) 10 mg and 20 mg in Combination with Ezetimide 10 mg and Simvastatin 40 mg and 80 mg in combination with Ezetimide 10 mg (Fixed dose combination) in Patients with Hypercholesterolemia and Coronary artery disease (CHD) or a CHD Risk Equivalent Atherosclerosis or a 10-year CHD Risk of >20%.
Protocol # D356FC00003 by **AstraZeneca. (High Enroller) (Sponsor Audit)**

53. **Principal Investigator, "Improve Study".** A Phase III Multicenter, Randomized, Double-Blind, Placebo controlled Study to Evaluate the Efficacy and safety of Intramuscular Peramivir in Subjects with Uncomplicated Acute Influenza.
IND # 76,350 by **BioCryst Phamaceuticals Inc.**

54. **Principal Investigator "INCYTE STUDY":** A Phase II double blind, dose-ranging, placebo controlled, randomized study to evaluate the safety, tolerability and pharmacodynamic activity of INCB019602 plus metformin compared to metformin alone in type 2 diabetic subjects not adequately controlled by metformin monotherapy.
Protocol # INCB 19602-201 by **Incyte**

55. **Prinicpal Investigator "ROCHE STUDY":** A Phase III, double-blind, randomized placebo-controlled study, to Evaluate the effects of RO4607381 on cardiovascular (CV) risk in stable CHD patients, with a documented recent Acute Coronary Syndrome (ACS).
Protocol # NC20971 by **Roche**

56. **Principal Investigator "SALIX IBS STUDY":** A Phase III, Randomized, Double-Blind, Placebo-controlled, Multicenter study to access the efficacy and safety of Rifaximin 550mg TID in the treatment of subjects with non-constipation Irritable Bowel Syndrome.
Protocol # RFIB3007 by **Salix**

57. **Principal Investigator "SINUSITIS STUDY":** A Phase III Study to know the efficacy and safety of 200 mcg BIDMometasone Furoate Nasal Spray (MFNS) vs Placebo of Adjunctive Treatment to Antibiotics in Relief of symptoms of Acute Bacterial Sinusitis.
Protocol # PO4824 by **Schering Plough**

58. **Principal Investigator "DIABETES STUDY":** A Phase II, Randomized, Double-Blind, Placebo-controlled, Parallel
Group study to evaluate the efficacy and safety of 12-week administration of PF-00734200 to subjects with Type 2 Diabetes Mellitus and insufficient glycemic control of metformin treatment.
Protocol # A7941006 by **Pfizer**

59. **Principal Investigator "ABBOTT STUDY":** A Phase III, Randomized, Double-Blind, Prospective Study Comparing the Safety and Efficacy of ABT-335 in Combination with Atorvastatin and Ezetimibe to Atorvastatin in Combination with Ezetimibe in Subjects with Combined (Atherogenic) Dyslipidemia.
Protocol # Abbott M10-275 by **Abbott**

60. **Principal Investigator "SUCAMPO OBD STUDY":** A Phase III, Multi-Center, Randomized Placebo Controlled, Double-Blinded Study of the Efficacy and Safety of Lubiprostone in Patients with Opoid-Induced Bowel Dysfunction.
Protocol # SPI/0211OBD-0632 by **Sucampo**

61. **Principal Investigator "ABBOTT STUDY":** A Phase III, 8 week, Multicenter, Randomized, Double Blind, Parallel Group Study Comparing the Safety and Efficacy of ABT 143 to Simvastatin in Subjects with Hypercholesterolemia.
Protocol # Abbott M10-667 by **Abbott**

62. **Principal Investigator "TAKEDA 012 DIABETES STUDY":** A Long Term, Open Label Extension Study to Investigate the Long-Term Safety of SYR110322 (SYR 322) in Subjects with Type 2 Diabetes.
Protocol # SYR-322-OLE-012 by **Takeda**

63. **Principal Investigator "TRINITY STUDY":** A Phase III Randomized, Double Blind, Parallel Group Study Evaluating the Efficacy and Safety of Co-administration of a Triple Combination Therapy of Olmesartan Medoxomil, Amlodipine Besylate and Hydrochlorthiazide in Subjects with Hypertension.
Protocol # CS8635-A-U301 by **Daiichi Sankyo (Sponsor Audit)**

64. **Prinicpal Investigator "ENGAGE ATRIAL FIBRILLATION STUDY":** A Phase III, Randomized, Double Blind Double Dummy, Parallel Group, Multi Center, Multi-Nationality Study for Evaluation of Efficacy and Safety of DU- 176b Versus Warfarin in Subjects with Atrial Fibrillagion-Effective Anticoagulation with Factor X a Next Generation in Atrial Fibrillation (ENGAGE-AF TIMI 48)
Protocol # DU176b-C-U301 by **Daiichi Sankyo.**

65. **Principal Invesitgator "OSTEOARTHRITIS STUDY-PFIZER" :** A Phase III, Multi-Center, Randomized, Double Blind, Controlled Study of the Long Term Analgesic Efficacy and Safety of Tanezumab Alone or in Combination with Non steroidal Anti Inflammatory Drugs (NSAIDS) Versus NSAIDS Alone in Patients with Osteoarthritis of the Knee or Hip.
Protocol # A4091025 by **Pfizer**

66. **Prinicpal Invesitgator "TAKEDA DIABETES STUDY":** A Phase II, Randomized, Double-Blind, Placebo and Active-Controlled, Multi-Center Study to determine the Efficacy and Safety of TAK 379 in Subjects with Type 2 Diabetes.
Protocol # TAK-379_201 by **Takeda**

67. **Principal Investigator "GSK CHRONIC CHD STUDY":** A Phase III Clinical Outcomes Study of Darapladib Versus Placebo in Subjects with Chronic Coronary Heart Disease to Compare the Incidence of Major Adverse Cardiovascular Events (MACE).

Protocol # LP100601 by **GlaxoSmithKline**

68.**Principal Investigator "GSK DIABETES STUDY":** A Phase III, Randomized, Double Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide When Used in Combination with Pioglitazone With or Without Metformin in Subjects with Type 2 Diabetes Mellitus.
Protocol # GLP112755 by **GlaxoSmithKline**

A Randomized, Double Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Determine the Efficacy and Safety of Albiglutide Compared with Placebo in Subjects with Type 2 Diabetes Mellitus.
Protocol # GLP112756 by **GlaxoSmithKline**

A Randomized, Double Blind, Placebo-and Active-Controlled, Parallel Group, Multicenter Study to determine the Efficacy and Safety of Albiglutide When Used in Combination With Metformin Compared With Metformin plus Sitagliptin, Metformin Plus Glimipiride, and Metformin Plus Placebo in Subjects with Type 2 Daibetes Mellitus.
Protocol # GLP 112753 by **GlaxoSmithKline**

A Randomized, Open-Label, Parallel-Group, Multicenter Study to determine the Efficacy and Long-Term Safety of Albiglutide Compared With Insulin in Subjects With Type 2 Diabetes Mellitus.
Protocol # GLP 112754 by **GlaxoSmithKline**

A Randomized, Double-Blind, Placebo- and Active-Controlled, Parallel Group, Multicenter Study to determine the Efficacy and Safety of Albiglutide Administered in Combination with Metformin and Glimepiride Compared With Metformin Plus Glimepiride and Pioglitazone in Subjects with Type 2 Diabetes Mellitus.
Protocol # GLP 112757 by **GlaxoSmithKline**

70. Principal Investigator " GOUT STUDY": A Multi-Center, Randomized, Double Blind, Placebo Controlled Trial of the Safety of Rilonacept for the Prophylaxis of Gout Flares in Patients on Urate Lowering Therapy.
Protocol # IL 1T-GA-0815 by **Regeron**

71. Principal Investigator. "APPRAISE-2". A Phase 3, Randomized, Double-Blind, Evaluation of the Safety and Efficacy of Apixaban in Subjects with a Recent Acute Coronary Syndrome by **Bristol-Myers Squibb**

72. Principal Investigator.. "MOA-728". An Open-Label Study to Evaluate the Long-term Safety of Subcutaneous MOA-728 for Treatment of Opioid- Induced Constipation in Subjects With Nonmalignant Pain by **Wyeth**

73. Principal Investigator. "GERD 302". A Randomized Double-Blind Parallel Study of Rabeprazole Extended-Release 50 mg Versus Esomeprazole 40 mg for Healing and Symptomatic Relief of Moderate to Sever Erosive Gastroesophageal Reflux Disease (GERD) by **Eisai.**

74. Principal Investigator. "EXACT". A Prospective, Randomized, Double-Blind Study of the Efficacy of Xolair in Atopic Asthmatics with Good Lung Capacity who Remain Difficult to Treat, by **Genentech**

75. Principal Investigator. "GAFA". A Proof of Concept Study to Evaluate the Co-administration of TT223 Given Daily and LY2428757 Given Once-Weekly for Four Weeks in Patients with Type 2 Diabetes Mellitus by **Lily.**

76. Principal Investigator. "P05234". A multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group Study Evaluating the Efficacy and Long-Term Safety of Ragweed Sublingual Tablet in Adult Subjects with a History of Ragweed-Induced Rhinoconjunctivitis With or Without Asthma by **Schering-Plough.**

77. Principal Investigator. "M10-313" A 30-week, multicenter, Randomized, Double-Blind, Parallel-Group Study of the combination of ABT-335 and Rosuvastatin compared to Rosuvastatin monotherapy in dyslipidemic subjects with stage 3 chronic kidney disease by **Abbott.**

78. Principal Investigator. "NEB-MD-04" Blood Pressure and metabolic effects of Nebivolol compared with Hydrochlorothiazide and placebo in Hypertensive patients with impaired glucose tolerance or impaired fasting glucose, by **Forest.**

79. Principal Investigator. "TIMI 52" A clinical outcomes study of Darapladib versus placebo in subjects following acute coronary syndrome to compare the incidence of major adverse cardiovascular events (MACE) by **GSK**

APPENDIX D

IRB APPROVAL/REB ATTESTATION FORM

STUDY UNCONDITIONAL APPROVAL DATE: JANUARY 19, 2010

THE APPROVAL IS VALID FOR ONE YEAR AND EXPIRES ON JANUARY 18, 2011.

ORIGINAL APPLICANT: Ms. Sonya Barss, KGK Synergize

INITIAL REVIEW:
The following protocol, Investigators Brochure for Humic Acid Version 1.0 dated January 2010, Visual Analog Scale dated January 08, 2010, Screening Flu Symptom Questionnaire dated January 08, 2010, Daily Subject Diary dated January 08, 2010 and Informed Consent Document dated January 08, 2010 were reviewed by the Ontario Institutional Review Board (ON IRB) of Institutional Review Board Services on January 15, 2010, and were:

- ☐ APPROVED as submitted
- ☑ CONDITIONALLY APPROVED, reasons previously communicated
- ☐ APPROVAL WITHHELD, reasons previously communicated
- ☐ REJECTED / REFUSED TO APPROVE / DISAPPROVED, reasons previously communicated

Final Protocol Number and Date: 10HFHL dated January 05, 2010

Final Protocol Title: A Pilot Study to Investigate the Effects of Humic Acid on Flu Symptoms

Sponsored by: **NAME:** Laub BioChemicals Corporation
ADDRESS: 1401 Quail St., Ste. 121
Newport Beach, CA 92660

FINAL REVIEW AND APPROVAL DETAILS:
Additional information and/or revised documents have been submitted for review and approval. They have been reviewed for compliance with the changes and/or clarification required at the IRB meeting noted above.

The protocol and informed consent documents as described below now conform to the IRB's requirements, and are hereby UNCONDITIONALLY APPROVED.

Final Protocol Number and Date: 10HFHL dated January 05, 2010

Final Protocol Title: A Pilot Study to Investigate the Effects of Humic Acid on Flu Symptoms

Informed Consent Date: 2010-JAN-18

INVESTIGATOR APPROVAL:
Qualified Investigator Name/Site Address:
Other Investigator(s) at the site:

COMPLIANCE STATEMENT / ATTESTATION: The membership of this IRB complies with the requirements defined in Health Canada regulations, 21 CFR parts 56 and 312.3 and 45 CFR 46. The IRB carries out its functions in accordance with good clinical practices (e.g., ICH GCP Guidelines) and Health Canada regulations and in compliance with FDA 21 CFR parts 50 and 56, *for US federally funded research* DHHS 45 CFR part 46, *for Canadian federally funded research* - and the Tri-Council Policy Statement for Ethical Conduct of Research Involving Humans.

Melvin Freedman, MD

Melvin H. Freedman, MD, FRCPC, FAAP
Co-Chairperson, ON Institutional Review Board

div. 1373737 Ont. Ltd. *address* 372 Hollandview Trail, Suite 300, Aurora, Ontario, Canada L4G 0A5
tel. (905) 727-7989 *fax* (905) 727-7990 *e-mail* info@irbservices.com *web* www.irbservices.com

APPENDIX E (electronic on USB)