CLINICAL PROTOCOL COVER PAGE

Protocol Title:	A Pilot Study to Investigate the Effects of Humic Acid on Flu Symptoms
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Amendment(s):	
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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

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

Protocol 10HFHL

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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

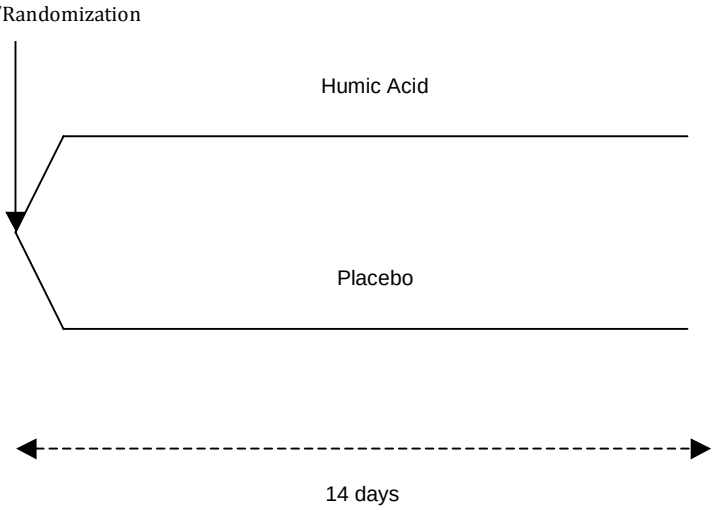
The primary objective of this study is to assess the efficacy of humic acid on flu symptoms as assessed by the alleviation of symptoms after 7 and 14 days of treatment in adults with influenza A or B. This will be determined by the use of a daily diary to assess the following symptoms during the trial 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 ºC (≥100.4 ºF) 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	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[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")*