

Comprehensive Cancer Center of Wake Forest University  
CCOP Research Base CCCWFU # 98308; NCI # WFU 07-02-03; FDA/IND # - Exempt

**Title: A Phase III Randomized, Double-Blind, Placebo Controlled Trial of North American Ginseng Extract (CVT-E002; COLD-fX<sup>®</sup>) to Prevent Respiratory Infection and Reduce Antibiotic Use in Patients with Chronic Lymphocytic Leukemia.**

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**For sites participating through CTSU:**

**This study is supported by the NCI Cancer Trials Support Unit (CTSU).**

**Institutions not affiliated with the CCCWFU CCOP Research Base will participate through the CTSU mechanism as outlined below and detailed in the CTSU Logistical Appendix 8.**

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at <https://members.ctsu.org>
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU Logistical Appendix 8 for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix 8 for specific instructions and forms to be submitted.
- Data management will be conducted by the CCCWFU CCOP Research Base Data Management Center (DMC). **Case report forms** (with the exception of patient enrollment forms); **signed consents, clinical reports, symptom and medication diaries, and transmittals** must be mailed or faxed to the CCCWFU CCOP Research Base DMC unless otherwise directed by the protocol. A completed CCCWFU Research Base DMC Data Submission Checklist (appendix I) and your institution's standard fax transmittal coversheet should accompany all data submissions. Please do not send study data or case report forms to CTSU Data Operations.
- **Quality Control (QC) reports** containing data query and delinquency information will be generated on a monthly basis by the CCCWFU CCOP Research Base DMC and posted on the CTSU members' website for retrieval and reconciliation by clinical site staff. Sites will be notified when new reports are posted. Please send query responses and delinquent data to the CCCWFU CCOP Research Base DMC and do not copy CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator. Only the Administrator or Data Administrator will have access to QC reports and must keep their CTEP account contact information current. This will ensure timely communication between the site and the CCCWFU CCOP Research Base.

**CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION**

<b>To submit site registration documents:</b>	<b>For patient enrollments:</b>	<b>Mail or FAX study data directly to the CCCWFU CCOP Research Base unless otherwise specified in the protocol:</b>
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSUS Fax – 215-569-0206	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays)  [Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, call 301-704-2376 between the hours of 9:00 am and 5:30 pm.]	Data Management Center Outpatient Comprehensive Cancer Center Dept of Radiation Oncology WFUBMC Medical Center Blvd. Winston-Salem, NC 27157-1030 FAX: 336-713-6476  A completed CCCWFU Research Base DMC Data Submission Checklist (app.1) and your institution's standard fax transmittal cover sheet should accompany all data submissions. Do not submit study data or forms to CTSU Data Operations. <u>Do not</u> copy the CTSU on data submissions.
<b><u>For patient eligibility or treatment-related questions</u></b> contact the Research Nurse listed on the protocol cover page.		
<b><u>For questions unrelated to patient eligibility, treatment, or data submission</u></b> contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or <a href="mailto:ctsucontact@westat.com">ctsucontact@westat.com</a> . All calls and correspondence will be triaged to the appropriate CTSU representative.		
<b>The CTSU Public Web site is located at: <a href="http://www.ctsu.org">www.ctsu.org</a></b>		
<b>The CTSU Registered Member Web site is located at <a href="https://members.ctsu.org">https://members.ctsu.org</a></b>		





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**Any CTSU Participating Member**

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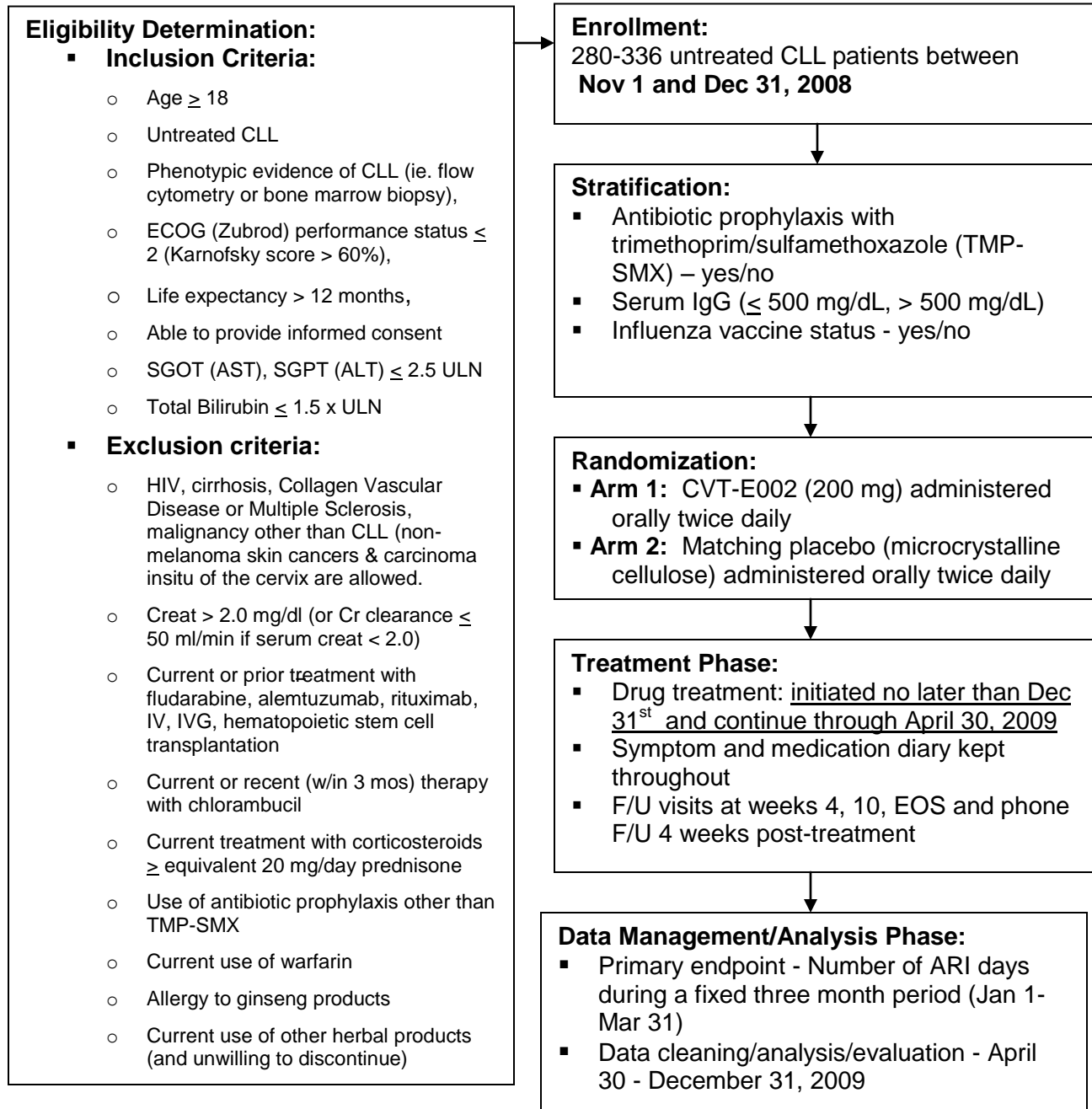
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**Title: A Phase III Randomized, Double-Blind, Placebo Controlled Trial of North American Ginseng Extract (CVT-E002; COLD-fx®) to Prevent Respiratory Infection and Reduce Antibiotic Use in Patients with Chronic Lymphocytic Leukemia.**

**SCHEMA**



**Total anticipated sample size:** 280 - 336 subjects (See Section 14.1)

**Total anticipated study duration:** 12 months

**Note: Biologics, Inc will be closed on the following days for the Holiday Season: November 27<sup>th</sup> and 28<sup>th</sup>, December 24<sup>th</sup>, 25<sup>th</sup>, 26<sup>th</sup>, 31<sup>st</sup> and January 1<sup>st</sup> and 2<sup>nd</sup>.**

## 1. BACKGROUND

### 1.1 STUDY DISEASE

Chronic Lymphocytic Leukemia (CLL) is the most common adult leukemia in developed countries occurring at a rate of 20/100,000 population and accounting for 22-30% of all leukemias (Keating and Kantarjian, 2004; Stephens, 2005). Nearly all cases of CLL occur in older adults with a median age of diagnosis of 60-70 years (Stephens, 2005; Morrison, 2001). As the name implies, CLL is a chronic illness that may remain stable or progress very slowly over many years. Median survival depends on stage at presentation. Overall median survival is 4-5 years after initiation of treatment, but early stage patients often do not require treatment for many years after initial diagnosis (Keating and Kantarjian, 2004). Because of CLL's slow pace aggressive "induction" chemotherapy such as that used in acute leukemias is not indicated, and most patients are observed for a time or initiated on outpatient therapy when indicated using a variety of interventions including prednisone (P), chlorambucil (C), fludarabine (F), C/F/P combinations, or rituximab (R) (Keating and Kantarjian, 2004). Both the underlying CLL and its treatment result in immune compromise and a markedly increased risk of infection. Infection is the most common complication of CLL (Anaissie, 1998; Keating and Kantarjian, 2004). Most CLL patients are over the age of 60, also a risk factor for infection (High, 2004).

Because CLL patients are managed over many years, the best measure of infection risk is incidence density, or number of infections over time. ***Many of these illnesses may be viral, but antibiotics are frequently prescribed since it is difficult to differentiate viral from bacterial infection, particularly in acute respiratory infection (ARI).*** The rate of major infection, i.e. infection severe enough to require hospitalization or treatment with parenteral antibiotics, is 0.04, 0.06, and 0.14 (per patient per month) in patients being treated with chlorambucil, fludarabine or the combination, respectively (Morrison, 2001).

It is very difficult to determine the exact number of ARIs or days with ARI in untreated CLL patients. There are no published data. Untreated CLL patients are more prone to infection than similar age patients with non-malignant co-morbidity (ie. myocardial infarction) based on data published over 30 years ago (Twomey, 1973). There are no more recent data. However CLL patients are almost universally over age 60, and recent studies ( e.g. McElhaney, 2004) suggest the mean number of ARI days during the respiratory illness/winter season in this age group is about 8 (7.8 days in the McElhaney study). The study outlined below uses this conservative estimate for ARI days in untreated CLL patients.

### 1.2 STUDY AGENT(S)

Recently, a natural product, an extract of North American Ginseng, called CVT-E002 (COLD-fX<sup>®</sup>, CV Technologies, Edmonton, AB, Canada) has been evaluated as an immune enhancer and infection preventative in animals and humans (Wang, 2003; Predy 2005; McElhaney, 2004; McElhaney, 2006). The active ingredient appears to be poly-furanosyl-pyranosyl-saccharides that enhance macrophage and natural killer cell function (Wang, 2001; Wang, 2003). In three randomized, controlled trials (Predy, 2005; McElhaney, 2004; McElhaney, 2006), CVT-E002 has been shown to significantly reduce the risk of ARI. Importantly, two of these studies were performed in older adults, the population most affected by CLL. One study in older adults was performed in community-dwelling elderly who were relatively healthy; CVT-E002 reduced the number of days with respiratory illness symptoms by over 50% (McElhaney, 2006). The other study in older adults was conducted in long-term care (nursing home) residents in whom multiple co-morbidities were prevalent and infection risk multi-factorial. In that study (McElhaney, 2004) the main endpoint was laboratory-confirmed influenza; 7/101 placebo recipients had confirmed influenza vs. only 1/97 CVT-E002 recipients (p=0.033). In all studies, CVT-E002 was well

tolerated (adverse events equal to placebo). Importantly, there are several parallels of the subjects in these studies with CLL patients. First, all subjects were elderly. Second, subjects in the long-term care study were highly immunized (more than 90% of subjects had received an influenza vaccine within the last two years); thus, most cases of influenza represented vaccine failure. Third, the characteristics of long-term care residents in the latter study: older age, multiple co-morbidities, and impaired immunity including ineffective vaccine responses, closely resemble the population and immune milieu of CLL patients. Based on these strong data, we propose a randomized, double-blind, placebo controlled trial of CVT-E002 to reduce ARI and the need for antibiotic treatment in CLL patients.

### 1.3 **RATIONALE**

The most common infections in CLL patients are upper- and lower-respiratory infections (Anaissie, 1998). Typical strategies to prevent infection in CLL patients are fraught with difficulties. Vaccines are poorly effective in CLL patients because the immune system inadequately responds. Infusion of antibodies using intravenous immunoglobulin (IVIG) has been used in subjects with low serum immunoglobulin G (IgG) (< 500 mg/dl). However, IVIG use is very controversial since the product is often in short supply, there is no clear consensus on frequency of administration or dose, and the cost-effectiveness of this very expensive therapy is questionable (estimated to be approximately \$11,000,000/quality-adjusted life year gained) (Stephens, 2005). Prophylactic antibiotics are much less expensive and frequently prescribed in CLL patients with advanced disease, but this strategy is likely to enhance antimicrobial resistance and compliance is often poor. Thus there is a pressing need for effective, low-cost interventions that enhance immunity, reduce infection risk and limit the need for antibiotics in CLL patients.

## 2. **OBJECTIVES**

### 2.1 **Primary Protocol Objectives**

- 1) To assess the effect of CVT-E002 on the number of days of acute respiratory illness (ARI) during the peak respiratory illness season (January-March) in subjects with CLL. An ARI day will be defined as a day with: one or more respiratory symptom (cough, sore throat, nasal or sinus congestion, or runny nose) and one or more systemic symptom (feverishness, chills/sweats, myalgia, fatigue, headache, poor endurance or increased shortness of breath).
- 2) To determine the safety of CVT-E002 in CLL patients as evaluated by standard toxicity criteria for studies in oncology (Common Toxicity Criteria – NCI Version 3.0).

### 2.2 **Secondary Protocol Objectives**

- 1) To assess the effect of CVT-E002 in CLL patients on:
  - a. Antibiotic use days (AUDs). AUDs will be defined as the number of days a subject receives antimicrobial therapy other than prophylactic trimethoprim-sulfamethoxazole.
  - b. The rate of all infections diagnosed by a physician.
  - c. The duration and severity of each ARI episode. Severe ARI days will be defined by the number of days on which ARI symptoms (as defined above) are experienced AND one of the following: fever > 100°F OR limited participation in usual activities.
  - d. Major infections defined as infection severe enough to require hospitalization or intravenous antibiotics.
  - e. Incidence of herpes zoster defined as an episode of MD-diagnosed zoster, and
  - f. CLL disease activity (serum IgG, total lymphocyte count, platelet count, Rai staging).

- 2) To determine the incidence of acute respiratory illness and type of illness in an untreated cohort of CLL patients over an entire winter respiratory illness season (Jan 1- April 30).

### 2.3 Exploratory Protocol Objectives

- 1) To determine the effect of CVT-E002 in CLL patients on the incidence of confirmed influenza and RSV by a physician will be defined as an ARI + at least one of the following: positive rapid antigen test OR a positive viral culture of a nasal swab or wash for influenza or RSV, OR a 4-fold rise in serum antibody titer vs. influenza or RSV within 8-12 weeks after an ARI.

## 3. PATIENT SELECTION

### 3.1 Eligibility Criteria

- 3.1.1 Age  $\geq$ 18 years
- 3.1.2 Subjects must have phenotypic evidence (ie. flow cytometry or bone marrow biopsy) of chronic lymphocytic leukemia (MEDDRA Code – 10008960; ICD-O3-9823),
- 3.1.3 Life expectancy of greater than 12 months,
- 3.1.4 Ability to understand and the willingness to sign a written informed consent document.
- 3.1.5 ECOG performance status 0-2 or Karnofsky  $>$ 60%
- 3.1.6 Patients must have normal organ function as defined below:
- AST(SGOT), ALT (SGPT)  $\leq$  2.5 X institutional upper limit of normal
  - Total Bilirubin  $\leq$  1.5 x institutional upper limit of normal
  - Creatinine  $<$  2.0 mg/dL
- OR
- Creatinine clearance  $>$ 50 mL/min/1.73 m<sup>2</sup> for patients
    - with creatinine levels above institutional normal
- 3.1.7 Patients may not be receiving any other investigational agents.
- 3.1.8 Untreated CLL

### 3.2 Exclusion Criteria

- 3.2.1 History of HIV-1, cirrhosis, collagen vascular disease or multiple sclerosis, malignancy other than CLL (non-melanoma skin cancer & carcinoma insitu of the cervix are allowed). Patients with previous malignancies and have been disease free for more than 5 years are allowed.
- 3.2.2 History of seasonal or environmental allergies that requires ongoing treatment with antihistamines, or intranasal or systemic corticosteroids

- 3.2.3 Use of other herbal ginseng products (and unwilling to discontinue their use for at least one month prior to initiating therapy with either CVT-E002 or placebo).
- 3.2.4 History of allergy or other adverse response to ginseng products.
- 3.2.5 History of or current treatment with fludarabine, rituximab, alemtuzumab, intravenous immunoglobulin, or hematopoietic stem cell transplantation (HSCT) Current treatment with chlorambucil is NOT allowed, however, prior history of chlorambucil treatment is allowed provided it was discontinued > 90 days prior to enrollment.
- 3.2.6 Current therapy with corticosteroids at a dose equivalent to 20 mg prednisone daily.
- 3.2.7 Use of antibiotic prophylaxis other than trimethoprim-sulfamethoxazole.
- 3.2.8 Current use of warfarin (due to potential drug interaction)
- 3.2.9 Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- 3.2.10 Pregnant women are excluded from this study because CVT-E002 is agent with unknown potential for teratogenic or abortifacient effects. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.
- 3.2.11 Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with CVT-E002, breastfeeding should be discontinued if the mother is treated with CVT-E002/placebo.

#### 4. SUPPLEMENT THERAPY

##### 4.1 Drug Information

CVT-E002 is comprised of >80% poly-furanosyl-pyranosyl-saccharides extracted by a proprietary process from the root of North American ginseng (*Panax quinquefolius*). The investigational formulation is orally administered as a gelatin capsule containing 200 mg of dry powdered extract. No fillers or non-medicinal ingredients are added. Repeat testing for stability indicates that the product is stable for 5 years. Serious adverse effects are not expected and CVT-E002 has an excellent safety profile. In humans, clinical data, market experience, and toxicity studies suggest that CVT-E002 is safe and well tolerated. The overall safety record of the source material, American ginseng, and the related species, Asian ginseng (*Panax ginseng*) is also good to excellent and there is a regulatory basis suggesting that water extracts of ginseng (which would include CVT-E002) are generally recognized as safe. CVT-E002 has been authorized for sale under the brand name "COLD-fX" by Health Canada as a non-traditional medicine based on review of clinical and other scientific data, as well as the manufacturing process and product specifications.

CVT-E002 safety and manufacturing related information was also reviewed as part of a New Dietary Ingredient submission to the FDA with the result of no objection to sale. CVT-E002 will be supplied by CV Technologies Inc. (Edmonton, Canada) for this study.

CVT-E002 (COLD-fX®). CVT-E002 is a well-standardized natural health product that has received a natural product number (NPN) from the Natural Health Products Directorate of Health Canada (NPN # 80002849, received in February 2007). CVT-E002 is not a sterilized product. It is manufactured according to the high standards outlined below and this process includes meticulous testing for microbes, heavy metal and pesticide contamination.

CVT-E002 was developed at the University of Alberta, Canada, following over a decade of research. Much of this research was dedicated to overcoming the challenges in standardization of natural health products. A proprietary methodology to reliably standardize natural health products was developed (termed ChemBioPrint) which ensures that highly specific multi-component mixtures have consistent composition and biological activity. The ChemBioPrint process characterizes natural substances in terms of two important properties. First the active constituents are identified and characterized chemically. This is followed by a series of specific assays to ascertain pharmacological activity. A further critical element integral to this standardization methodology is a precise manufacturing process, to ensure that the product is consistently made from batch to batch. CV Technologies conducts an analysis for each product batch of the levels of five monosaccharide molecules found in CVT-E002, in addition to analyzing other physicochemical properties and constituents. Each batch is also subjected to tests of relevant immune parameters to meet specifications required to verify appropriate biological activity. Only lots meeting specifications are released for sale or will be used in this study. The consistency achieved between CVT-E002 product batches is carefully monitored and has been documented (Wang, 2001). In addition to the precise standardization and manufacturing methods which assure product consistency, the study agent (CVT-E002) has been subjected to stability studies (real-time and accelerated) demonstrating a minimum shelf life of 5 years (assessed on micro, chemical composition, and biological activity through ability to stimulate mouse lymphocyte proliferation in vitro).

CV Technologies follows rigorous quality and manufacturing standards, including the Natural Health Product Regulations for Good Manufacturing Practices (GMP) recently established by Health Canada. These standards are very similar to the GMP required for drugs, with a few unique considerations for extracts. The production of CVT-E002 is compliant with these regulations which govern the quality standards of all premises, equipment, facility sanitation, health and hygiene of personnel, material control, process control, product specifications, stability, records, and recall reporting. The facilities are licensed and audited to ensure compliance with the regulations. CV Technologies has a rigorous quality control program with well-trained quality assurance personnel.

***An independent analysis of the CVT-E002 and placebo preparation will be performed by American Analytical to ensure the ginseng content and purity of the preparations used in this study.***

#### **4.1.1 Availability Commercially Available/Sponsor Supplied Agents**

CVT-E002 (COLD-fX) is sold as a dietary supplement and has been on the market for 11 years. The product is available over-the-counter to consumers in Canada and the United States.

#### **4.1.2 Agent Ordering and Distribution**

COLD-fX and matching placebo will be manufactured by CV Technologies and provided free of charge to study participants. The study drugs will be shipped to Biologics, Inc. in sealed bottles and will be stored at room temperature.

Biologics, Inc. will distribute the COLD-fX or placebo directly to sites following patient registration for each patient enrolled in the study. Study drug will be sent via Federal Express 2<sup>nd</sup> day delivery. Upon patient registration, Biologics Inc. will automatically be notified and will call the site for further information. Each bottle will contain a patient-specific label.

#### 4.1.3 Packaging & Labeling

- The study will remain open approximately 6 months
- A total of 280-336 patients will enroll
- Each patient enrolled receives 1 shipment of study drug (Biologics to ship direct-to-site)
  - Each patient-specific shipment includes enough study supply to last until 4/30/09
  - Study supply sent in 3 bottles including patient-specific and auxiliary safety labels

##### **Packaging:**

Biologics will prepare and ship the entire supply of study drug for each patient randomized. Drug supply will be divided into 3 bottles according to patients' scheduled site visits and shipped direct-to-site for dispensing. Bottles are prepared as follows:

- Bottle #1: Visit #1 → Weeks 1-4 Supply
- Bottle #2: Visit #2 → Weeks 5-10 Supply
- Bottle #3: Visit #3 → Weeks 11- enough to complete treatment through 4/30/09

For easy identification at the site, Biologics will place a label on the lid of each bottle indicating the week and visit designation. Bottles will also include a patient-specific label including:

- ✓ Patient's name/initials
- ✓ Administration instructions/signatures
- ✓ Dispense date
- ✓ Expiration date
- ✓ Storage instructions

##### **Enrollment and Processing ("Patient Kit" Preparation):**

Once official notification is received via email that a new patient is enrolled to the study, Biologics prepares and ships a "Patient Kit" that includes the entire supply of study drug (or placebo) based on arm assignment provided by Wake Forest University Health Sciences.

A clinical pharmacist checks off package for accuracy of contents.

21 CFR Part 11 accountability records including date of dispense, lot number, unique patient identifier, quantity dispensed and remaining inventory balance are completed with each order. All accountability records are stored in a secured area throughout the duration of study.

##### **Expedited Delivery and Logistic Services:**

Biologics ships study drug "same day" for orders received before 4:00 p.m. EST Monday through Friday. Orders received after 4:00 p.m. Monday through Friday will be processed the next business morning.

All shipments are sent via Federal Express Second Day Delivery. Biologics distribution team monitors packages throughout duration of transit via Federal Express website and FedEx One Call Solution (live support). Real-time monitoring enables the Biologics distribution team to mitigate potential delivery delays.

**Communications / Clinical Support Line / Emergency Unblinding:**

Upon notification of a new patient registration, Biologics places an outbound call to the site contact confirming their shipment is being processed, while providing the courier, date and time of anticipated delivery.

Throughout the course of the study, a 24/7/365 clinical hotline support, staffed with clinical pharmacists, is made available in the event an investigator or site coordinator has a question or emergency unblinding is required.

**Drug Destruction:**

At the conclusion of the study Biologics will destroy any remaining study drug at the Biologics site. Clinic sites will destroy on site any remaining/returned study drug per their site institution's guidelines.

**4.1.4 Storage & Stability**

CVT-E002 is stable for 5 years stored at ambient temperature and humidity

**4.1.5 Preparation**

CVT-E002 is provided prepared for administration.

**4.1.6 Toxicities**

In the 11 years since CVT-E002 (COLD-fX) has been on the market, over 400 million doses have been sold to consumers in Canada and the United States and less than 250 adverse events have been filed with the company, indicating a low rate of adverse reactions. Of these reports, most commonly, individuals have reported allergic reactions such as rashes or other skin conditions. Less frequently filed have been changes in blood pressure, headaches, insomnia, nosebleeds, increased blood glucose levels, nervousness/confusion, dizziness, drowsiness, hyperactivity, nausea/vomiting, heartburn, diarrhea, diuresis and joint pain. Causality of these events has not been attributed to the study product in the vast majority of events, with the exception of allergic reactions.

Adverse event profiles from clinical trials conducted in a variety of populations (high performance athletes, generally healthy adults and seniors) have shown that CVT-E002 (COLD-fX) is safe and well-tolerated with no adverse events (serious or otherwise) attributed to its use. Clinical studies, including a phase 2 FDA IND study, with CVT-E002 have not identified a significantly different rate of adverse events versus placebo at 400 mg/day in generally healthy adults (total n = 604). Additional open label and case series clinical studies have not identified adverse events (total n = 75). Acute intake of higher doses of CVT-E002 (1800, 600, and 300 mg on intake days 1-3 respectively) has not been associated with adverse events at a rate significantly different than placebo (total n = 272 for adults, n = 46 for children 3-12 years old).

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There were no significant findings in either the acute (2000 mg / kg body weight) or sub-acute repeat (50 mg / kg body weight for daily for 18 days) dose toxicity studies completed on CVT-E002 in normal virus antibody free, pathogen free Sprague Dawley rats. A probable interaction between warfarin and the source material of CVT-E002, American ginseng has been reported. Although it has been suggested that this is likely due to the bioactive components, ginsenosides, which are present in very low quantities in CVT-E002 (<3%), patients taking anti-coagulants should be cautioned about this potential interaction, and warfarin therapy is an exclusion criterion. Three separate randomized, double-blind, placebo-controlled trials have shown no significant difference in adverse event rates between CVT-E002 and placebo. Adverse events reported included headache, difficulty sleeping, nervousness, gastrointestinal (nausea, heartburn and diarrhea) and rashes.

#### 4.1.7 Administration

CVT-E002 will be administered as capsules (200 mg), taken orally twice daily, one capsule in the AM and one in the PM.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described. Appropriate dose modifications for CVT-E002 are described. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

#### 4.2 Treatment Plan

The research PI or designee at each site, which may include the clinic physician, resident, research nurse or research assistant, will review cancer registry and medical chart information to identify patients eligible for this protocol. Patients identified using these methods will be asked to join the study during their next clinic visit or consult. Patients not scheduled for a clinic visit within the next few weeks will be sent a letter from their physician informing them about the study, and indicating that a research nurse/assistant will be calling them within the next 10 days to tell them more about the study and to see if they are eligible to participate.

**All subjects will be enrolled between November 1 and December 31, 2008.** Once subjects are identified and informed consent obtained, subjects will be stratified by: use of prophylactic trimethoprim-sulfamethoxazole (yes/no), serum IgG ( $\leq 500$  mg/dL vs.  $> 500$  mg/dL), and influenza vaccine status for the enrollment year (yes/no). Control variables collected for analysis but not used for stratification will include: age, Rai Stage, serum  $\beta$ 2-microglobulin, serum albumin, absolute neutrophil count, CD4 cell count, and serum creatinine (Anaissie, 1998; Morrison, 2001). These will be used to establish infection risk at baseline, and to allow exploratory analyses as described.

Subjects will be randomized (1:1) to receive the intervention CVT-E002 (200 mg twice daily) or a matching placebo (microcrystalline cellulose) administered orally. This dose has been shown to be safe and effective in randomized controlled trials in young adults (Predy, 2005), older community-dwelling adults (McElhaney, 2006) and institutionalized older adults with multiple co-morbidities (McElhaney, 2004). Treatment will continue from within 2 weeks of site receiving drug and continue through April 30, 2009. All subjects MUST start drug therapy no later than Dec. 31<sup>st</sup> (note: drug shipping to the site will take at least 2 business days, and subjects must receive in time to start therapy no later than December 31<sup>st</sup> so please plan accordingly). This allows for a consistent period of time during which all subjects will be on protocol (Jan 1- April 30) which assures all subjects will be enrolled during the time of maximum respiratory tract infection and influenza risk (Jan-Apr) regardless of geography in the U.S. CVT-E002 or placebo will be provided at no cost to the subject. **BIOLIGICS, INC. WILL BE CLOSED ON THE FOLLOWING DATES: NOVEMBER 27<sup>TH</sup>, AND 28<sup>TH</sup>, DECEMBER 24<sup>TH</sup>, 25<sup>TH</sup>, 26<sup>TH</sup>, AND 31<sup>ST</sup>. JANUARY 1<sup>ST</sup> AND 2<sup>ND</sup>.**

The main outcome to be measured is ARI days during a fixed three-month period (Jan 1-Mar 31). Subjects will take CVT-E002/placebo for an additional month to ensure secondary endpoints can be met and to be sure a late influenza season is encompassed in the treatment period should it occur. All subjects will stop treatment on April 30, 2009. An end of study (EOS) visit will coincide with this event and a follow-up phone call 4 weeks later performed to assess any adverse events.

#### 4.3 Dose Modification

Toxicity Management- No dose modifications are allowed. If a subject develops adverse effects significant enough to warrant dose modification, the drug should be discontinued altogether.

#### 4.4 Treatment Schedule

CVT-E002 or placebo is administered by mouth twice daily (morning and evening), must be initiated no later than December 31, 2008 and continue through April 30, 2009 of the following year (one winter respiratory season).

**Biologics, Inc. will be closed on the following dates: November 27<sup>th</sup>, and 28<sup>th</sup>, December 24<sup>th</sup>, 25<sup>th</sup>, 26<sup>th</sup>, and 31<sup>st</sup>. January 1<sup>st</sup> and 2<sup>nd</sup>.**

#### 4.5 Pre-Medication – Not applicable

#### 4.6 Treatment Duration

Treatment will continue until April 30, 2009 (i.e. one winter respiratory season) unless one of the following occurs:

- Inter-current illness that prevents further administration of treatment (this includes progression of CLL that requires initiation of CLL-specific therapy - subjects will be removed from the study and included in the analysis censored at that time),
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- If patient is placed on  $\geq 20$  mg/day of Prednisone for  $> 2$  weeks, they need to be taken off study

#### 4.7 Concomitant Treatment

Patients should receive full supportive care including: transfusions of blood and blood products, antibiotics, antiemetics, etc. as appropriate – Record reasons and treatment on the flow sheets.

#### 4.8 Supportive Care Guidelines - Not Applicable

### 5. RADIATION THERAPY – Not Applicable

### 6. SURGERY – Not Applicable

### 7. OTHER THERAPY – Not Applicable

### 8. LABORATORY SPECIMEN COLLECTION PROCEDURES

**8.1 Pilot Phase Specimen Collection**

All sites will participate in the pilot phase of this study for testing of Influenza and RSV Serology. The pilot phase includes collecting one gold top tube from patients at visits Baseline, Weeks 4, 10, End of Study (EOS). Patient samples should be collected and frozen for batch shipping to WFU.

**8.2 Receiving Specimen Shipping Kits**

In order for each site to receive specimen kits, a copy of their institution's IRB approval letter and completed Shipping Kit Form must be faxed to the WFU Immunology Lab. Following receipt of the IRB approval letter, a specimen collection kit will be shipped directly to the address provided by each site. (Submission of this letter is in addition to each sites normal IRB notification process.) (See Appendix 13 for further information). **[CTSU Participants: Refer to the CTSU Logistical Appendix 8]**

**9. PROTOCOL SPECIFIC TRAINING REQUIREMENTS – See Section 10.2**

**10. STUDY PARAMETERS**

- 10.1 Baseline evaluations are to be conducted within one week prior to registration. Protocol therapy must begin within two weeks after the site receives Cold-fX from Biologics, Inc. and all subjects must initiate drug no later than December 31<sup>st</sup>.

Assessment	Baseline	Weeks After Starting Drug			
		4	10	*EOS (Apr 30 ± 1 week)	4 weeks post-Rx
Signed Consent Form	x				
Clinical History/Concomitant Meds (1)	x	x	x	X	
Physical Examination	x	x	x	X	
Blood Tests					
- CBC, Plts., Diff	x	x	x	x	
- CMP (2)	x	x	x	x	
- Serum IgG	x			x	
- Beta – 2 microglobulin	x			x	
- CD4 Count	x			x	
Toxicity Assessment Sheet (TAS)	x	x	x	x	
Antibiotic Use Days (3)		x	x	x	x
Acute Respiratory Infection Diary (4)	x	x	x	x	
Influenza/RSV Serology (5)	x	x	x	x	
Telephone Assessment Form (Appendix 10)					x
Current Medication Form	x	x	x	x	
Flow Sheet	x	x	x	x	
Serum Pregnancy Test (6)	x				

- (1) Including Rai stage, current meds, major infections, H. zoster
- (2) Complete metabolic panel including creatinine, SGOT(AST), SGPT(ALT), Total Bilirubin and albumin
- (3) An "Antibiotic Use Day" will include each day a systemic (oral or parenteral) antibiotic is administered. Each day will be a single day regardless of whether antibiotics are given once or multiple times that day.
- (4) To record Acute Respiratory Infections (ARIs) that occur between visits
- (5) One 5 ml blood sample required at the four timepoints specified; for processing/shipping instructions. See Appendix 13.
- (6) A negative serum pregnancy test is required within 10 days of registration.

\*Note: EOS = End of Study

**Biologics, Inc. will be closed on the following dates: November 27<sup>th</sup>, and 28<sup>th</sup>,  
December 24<sup>th</sup>, 25<sup>th</sup>, 26<sup>th</sup>, and 31<sup>st</sup>. January 1<sup>st</sup> and 2<sup>nd</sup>.**

**10.2 Description of study parameter measures and planned training of site personnel:**

Many of the above measures are standard clinical data gathered on CLL patients as part of the standard of care and thus require no specific training. However, several items used will require specific training and are described below. Training for these assessments for on-site personnel will be accomplished through a slide set produced by the PI and reviewed during a conference call with local PIs/Study Coordinators. Several dates will be used to assure all sites can participate. Training slide sets will also be posted on the Research Base website for those who are not able to participate in the conference calls. Reviewing these slide sets on the website are sufficient for study participation.

**Diary Card**

- **Acute Respiratory Infection Diary:** All subjects will be asked to keep a daily log of symptoms in a diary provided by study personnel to determine the number of days of ARI during the treatment period. Study personnel will specifically address each item in the diary and symptoms will be specifically queried daily: cough, sore throat, nasal or sinus congestion, runny nose, feverishness, chills/sweats, myalgia, fatigue, headache, poor endurance or increased shortness of breath. Each symptom will be rated on a 1-4 scale of severity (0=symptom absent; 1=mild, 2=moderate, 3=severe). If they feel feverish, the subjects are asked to take their temperature orally with a home thermometer. Subjects will also be asked to indicate whether any of these symptoms limited participation in usual activities.

An "ARI day" will be defined as any day on which the subject experienced one or more respiratory symptoms (cough, sore throat, nasal or sinus congestion, or runny nose) and one or more systemic symptom (feverishness, chills/sweats, myalgia (muscle aches), fatigue, headache, poor endurance or increased shortness of breath). ARI days will be calculated by the study personnel, not the subject.

Severe ARI days will be defined by the number of ARI days on which one of the following occurred: fever (defined as an oral temperature > 100°F), or limited participation in usual activities.

The assessment tools to be used have been validated in prior CVT-E002 studies (McElhaney, 2006; McElhaney, 2004; Predy, 2005). Use of the rating scale for each symptom will allow us to validate the use of this tool in CLL patients with other commonly used URI scales such as the modified Jackson criteria for "colds" (Jackson, 1958) as later refined by Gwaltney (Gwaltney, 2003) – this has not been previously accomplished for CLL patients.

- **Antibiotic Use Diary:** Antibiotic use is defined as a day on which systemic (oral or parenteral) antibiotics are given once or multiple times for any reason. Prophylactic TMP-SMX is NOT considered in this count. Subjects will be asked to record this information on the Diary Card form and entries will be confirmed by study personnel at the F/U visits. An "Antibiotic Use Day" will include each day a systemic (oral or parenteral) antibiotic is administered. Each day will be a single day regardless of whether antibiotics are given once or multiple times that day.

Toxicity evaluation: Toxicities will be evaluated by the standard Common Toxicity Criteria – NCI Version 3.0.

**11. REGISTRATION PROCEDURES****11.1 Online Registration**

A form 310 or IRB letter of approval and an IRB approved consent form must be received by the Research Base Protocol Information Office – Attn: Site Coordinator prior to patient registration. Fax:

(336)716-6275. **CTSU Participants: Refer to the CTSU Logistical Appendix 8 for site registration and patient enrollment instructions.**

Fill out Appendix 2, "Eligibility Checklist / Registration Form". Use this to complete the on-line registration.

Log on to the CCCWFU Research Base registration web site at <https://phsapps3.phs.wfubmc.edu/ccrbis/>. Enter your user name and password (which may be obtained by contacting Ping Tan at pttan@wfubmc.edu or June Fletcher-Steede at jsteede@wfubmc.edu.) *In the 'Patient Registration and Protocol Information' table, click the 'Register Patient/Patient Info', with the corresponding protocol number found in the drop down box to the right. Fill in the eligibility criteria forms using the drop down boxes.* If further information is needed by Biologics or Data Management, they will contact you. Once the patient information has been entered online print a copy of the eligibility checklist/registration form for your records. Press the submit button, a confirmation page will appear. **Print this confirmation sheet for your records.** The CCCWFU On-line Protocol Registration/Eligibility form, initial flow sheet, signed consent, histology reports, scan reports and lab reports (as required in protocol) should be faxed to (336) 713-6476 or mailed to Data Management:

Data Management Center  
Outpatient Comprehensive Cancer Center  
Department of Radiation Oncology  
WFUBMC  
Medical Center Boulevard  
Winston-Salem, NC 27157-1030

These forms should be retained in the patient's study file. These forms will be evaluated during an institutional NCI/CCCWFU CCOP Research Base site member audit.

If you have questions related to the registration process or require assistance with registration, please contact the CCCWFU CCOP Research Base DMC between 8:30am and 4:00pm EST, Monday through Friday at (336) 713-6507. **CTSU Participants: Refer to the CTSU Logistical Appendix 8 for site registration and patient enrollment instructions.**

## 12. DATA SUBMISSION PROCEDURES

### 12.1 Submission Schedule

The Eligibility Checklist/Registration Form should be completed on-line prior to placing the patient on study. Data forms will be submitted to the CCCWFU CCOP Research Base, Attn: Data Management Center, Outpatient Comprehensive Cancer Center, Dept. of Radiation Oncology, WFUBMC, Medical Center Boulevard, Winston-Salem, NC 27157-1030 or faxed to (336) 713-6476 according to the timetable below:

Form	Submission Schedule
Signed Consent Form	Baseline
Eligibility Checklist/Registration Form	Baseline
Lab Reports	Baseline, Week 4, Week 10, EOS
Toxicity Assessment Sheet	Baseline, Week 4, Week 10, EOS, EOS+ 4 wks
ARI Diary/Antibiotic Use Diary	Baseline, Week 4, Week 10, EOS, EOS + 4 wks
Telephone Contact Form	4 wks Post Treatment
Flow Sheet	Baseline, Week 4, Week 10, EOS
Current Medication Form	Baseline, Week 4, Week 10, and EOS

## 12.2 CTSU Participants: Refer to the CTSU Logistical Appendix 8 for data submission procedures.

## 13. ADVERSE EVENT REPORTING

Federal regulations require that investigators report adverse events and reactions in a timely manner.

Toxicity Criteria- Toxicity will be determined using the revised NCI Common Toxicity Criteria (CTC) Version 3.0 for Toxicity and Adverse Event Reporting. A copy of the CTC Version 3.0 can be downloaded from CTEP homepage (<http://ctep.info.nih.gov>) and is included as an Appendix.

### 13.1 Definitions and Terminology

An adverse event is defined as an undesirable, unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure. This may be a new event that was not pre-existing at the beginning of treatment, a pre-existing event that recurs with increased intensity or frequency subsequent to the beginning of treatment or an event though present at the beginning of treatment becomes more severe following initiation of treatment. These undesirable effects may be classified as “known or expected” or “unknown or unexpected”.

Known/expected events are those that have been previously identified as having resulted from administration of the agent or treatment. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown/unexpected events are those thought to have resulted from the agent, e.g. temporal relationship but not previously identified as a known effect.

#### Assessment of Attribution

In evaluating whether an adverse event is related to a procedure or treatment, the following attribution categories are utilized:

- Definite The adverse event *is clearly related* to the treatment/procedure.
- Probable The adverse event *is likely related* to the treatment /procedure.
- Possible The adverse event *may be related* to the treatment/procedure.
- Unlikely The adverse event *is doubtfully related* to the treatment/procedure.
- Unrelated The adverse event *is clearly NOT related* to the treatment/procedure.

### 13.2 Grading Of Adverse Events

Unless specified otherwise, the NCI Common toxicity Criteria (CTC) Version 3.0 is used to grade severity of adverse events for this protocol.

- Grade 1 Mild AE
- Grade 2 Moderate AE
- Grade 3 Severe AE
- Grade 4 Life-Threatening or disabling AE
- Grade 5 Death related to AE

### 13.3 General Guidelines

In order to assure complete and timely reporting of adverse events and toxicity, the following general guidelines are to be observed. When protocol-specific guidelines indicate more intense monitoring than the standard guidelines, the study-specific reporting procedures supersede the General Guidelines. A protocol may stipulate that specific grade 4 events attributable to treatment are expected and may not require the standard reporting, however, exceptions to standard reporting must be specified in the text of the protocol.

Adverse Event reporting begins after the patient is registered to the study (or begins the run-in period of the study or begins the wash out period of the study). Adverse Events occurring within 30 days of study completion must be reported via FDA Form 3500 (MedWatch).

1. The protocol Principal Investigator will report to the RB Data Management Staff within 24 hours of discovering the details of all unexpected severe, life-threatening (grade 4) and fatal adverse events (grade 5) if there is reasonable suspicion that the event was definitely, probably, or possibly related to protocol treatment.
2. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of attribution require notification within 24 hours of discovery.
3. Any medical event which precipitates hospitalization or prolongation of existing hospitalization must be reported regardless of attribution or whether the adverse event is expected or unexpected.
4. A written report, including all relevant clinical information and all data collection forms due up to and including the date of the event will be sent by mail or FAX to the Research Base (RB) Data Management Center (DMC) within 10 calendar days unless specified otherwise within the protocol. The material must be labeled: "Attention: Adverse Event Reporting".
5. The Research Base Grant PI, Clinical Research Oversight Committee and/or Study Chair will take appropriate action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.
6. Serious adverse events will be communicated by phone and MedWatch as soon as identified to the CCCWFU RBDMC at (336) 713-3172. The DMC is responsible for communicating with the FDA, the drug sponsor, WFU IRB, and other regulatory agencies, as well as reporting all SAE's grade 4 or 5 to the Clinical Research Oversight Committee (CROC).
7. For events that require telephone reporting to the NCI, Investigational Drug Branch, the FDA or study sponsor, the investigator may first call the RB DMC unless this will unduly delay the required notification process.
8. A copy of all correspondences sent recipients of the notification, e.g. NCI-DCP, FDA must be submitted to the Research Base DMC. Copies must include the RB study and case (PID #).
9. Institutions must comply with their individual Institutional Review Board (IRB) policy regarding submission of documentation of adverse events. All MedWatch reports should be sent to the local IRB in accordance with the local IRB policies.

10. When submitting AE, SAE reports and supporting documentation , the study number and the case number (PID #) must be recorded on the FDA Form 3500 (MedWatch) so that the case may be associated with the appropriate study file.

#### **13.4 Commercial Study Agents**

Cancer Prevention / Control Study agents may or may not be commercially available, may or may not be sponsored by a third party and may or may not be under an IND. Adverse Event Reporting for all commercially available drugs should be reported via the FDA Form 3500 (MedWatch).

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**13.5 Table A: Reporting requirements for Adverse Events (AEs) and Serious Adverse Events (SAEs) for this protocol.**

	MILD				MODERATE				SEVERE			
	1		1		2		2		3		3	
	Unexpected		Expected		Unexpected		Expected		Unexpected		Expected	
	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization
<b>Unrelated Unlikely</b>	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days
<b>Possible Probable Definite</b>	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days

	LIFE-THREATENING/DISABLING				DEATH			
	4		4		5		5	
	Unexpected		Expected		Unexpected		Expected	
	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization
<b>Unrelated Unlikely</b>	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days	10 Calendar Days
<b>Possible Probable Definite</b>	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days	24-hour; 5 Calendar Days

### 13.6 Unblinding Guidelines

In the event a patient on this study develops a toxicity (adverse event or severe adverse event) for which the patient's physician or other health care professional feels that it is in the patient's best interest to know what drug they are taking (active study drug(s) or placebo), the following procedure should be followed:

- Step 1: the patient's physician or a designated health care professional should call the Wake Forest University Baptist Medical Center Physician Access Line (336-716-7654) and ask that Dr. Ed Shaw, Principal Investigator of the CCCWFU CCOP Research Base, be contacted immediately either in his office, by pager, or at home. In the event Dr. Shaw cannot be reached, the PAL operator should contact Dr. Glenn Lesser, Chair, Cancer Treatment Protocols in his office, by pager, or at home. If neither Dr. Shaw nor Dr. Lesser can be reached, the PAL operator should contact Gina Enevold, GNP, Research Base Administrator, either in her office, by pager, or at home.
- Step 2: Once contact has been made; the patient's physician or health care professional should explain the reason for the request to unblind the treatment arm that the patient is on. If the Research Base representative feels that the toxicity (AE/SAE) is possibly, probably or definitely related to the study drug, then the next step will be followed.
- Step 3: The responsible Research Base representative will call the pharmacist @ Biologics, Inc.(phone: 1-800-850-4306). There is an "on-call" service provided 24 hours a day, seven days a week for the Chemical Drug Trials unblinding service. The Biologics pharmacist may contact the patients' physician and/or health care professional directly with the unblinding information. Written documentations of the unblinding process will be sent to the Research Base Principal Investigator by Biologics, Inc.

**-OR-**

The responsible Research Base representative will locate the envelope which contains the code for all CCCWFU CCOP Research Base clinical trials which are double-blind. It is located in the Outpatient Comprehensive Cancer Center, Department of Radiation Oncology (first floor) in the Research Base Clinical Trials Office (phone: 336-713-6519), in a locked file cabinet drawer which bears the label "Unblinding Code". Only Dr. Shaw, Dr. Lesser and Ms. Enevold have a copy of the key.

- Step 4: In the event that the patient's treatment is unblinded, that patient will be taken off study with no further study follow-up. Appropriate procedures for grading toxicities, assigning causality, and reporting severe adverse events (if applicable), should be followed for each protocol for all Phase III Clinical Trials. The event will be reviewed by the CCCWFU Clinical Research Oversight Committee. All Phase III Clinical Trials will be reviewed by the CCOP Research Base Data Safety and Monitoring Board.

**13.7 CDUS Reporting**

The CCCWFU CCOP Research Base Data Management Center will submit quarterly reports to DCP/CTEP by electronic means using the Clinical Data Update System (CDUS)

**14.0 STATISTICAL CONSIDERATIONS****14.1 Study Design**

The primary objective of this randomized trial is to assess the effect of the North American Ginseng Extract CVT-E002 (COLD-fX) on the duration of acute respiratory illness (ARI) during the peak months of the flu season (January – March) in patients with Chronic Lymphocytic Leukemia. Patients who meet the eligibility criteria will be randomized to receive either COLD-fX or a placebo with equal probability. The primary end point used to quantitate treatment efficacy for this trial is the number of ARI days in January, February, and March of the flu season. Secondary objectives are to estimate the incidence of ARI among untreated CLL patients and to assess the effect of COLD-fX on the number of antibiotic days, ARI and overall infection rates, serum IgG levels, CD4 counts, and toxicity. Analysis of all outcome measures will be carried out based on an 'intent to treat' approach. That is, all randomized patients will be used in all analyses, whether or not they were actually treated or whether or not they were treated according to protocol.

A double-blind, randomized, parallel group design will be used to assess the effect of COLD-fX on the primary and secondary endpoints. For design purposes we will base our sample size on data provided by McElhaney et al (2006) from a study evaluating COLD-fX for the prevention of respiratory symptoms in community-dwelling adults. In their study, the mean ( $\pm$  SD) duration of respiratory symptoms was 7.8 ( $\pm$  6.0) for the participants receiving the placebo and 1.8 ( $\pm$  1.6) for those participants receiving the COLD-fX (after adjusting their numbers to account for those who did not experience any ARI-related symptoms). We expect the duration of respiratory symptoms to be longer in our study because our patients have CLL. However, it is clear that the standard deviation increases as the mean increases and we will assume a proportionate relationship in our study with a coefficient of variation (CV) of approximately .8.

Substituting the mean variance into the standard sample size formula for normally distributed outcomes, one obtains the following formula for the sample size needed in each treatment group (Gerald van Belle "Statistical Rules of Thumb " Chapter 2):

$$n = (Z_{\alpha} + Z_{\beta})^2 CV^2 [1 + (1-PC)^2] / PC^2,$$

where  $\alpha$  and  $\beta$  are the probabilities of type I and II errors, respectively, Z is the standard normal deviate, CV is the coefficient of variation, and PC is the proportionate change in means (i.e., relative difference).

Table 15.1.1 below shows the number of patients needed in each group of a single stage study to detect relative group differences of 10% to 50% with 80% and 90% power at the 5% two-sided level of significance assuming the coefficient of variation ranges between .75 and .90. We see that a sample size of 112 patients per group will

allow us to detect a 30% relative difference in the duration of respiratory symptoms with 90% power at the 5% two-sided level of significance, assuming the coefficient of variation is 80%. Note that McElhaney et al (2006) saw a 77% decline in the number of respiratory symptom days. We do not expect to see that dramatic an effect in CLL patients, but a 30% effect would be meaningful and is certainly feasible given the McElhaney data.

Table 15.1.1. Number of patients needed per group in a single stage study to detect the specified differences in number of respiratory symptom days with 80%-90% power at the 5% two-sided level of significance.

CV	Power	Relative Difference								
		10%	15%	20%	25%	30%	35%	40%	45%	50%
0.75	0.8	800	338	182	111	74	52	38	29	23
0.75	0.9	1070	453	243	148	98	69	51	39	30
0.80	0.8	910	385	206	126	84	59	43	33	26
0.80	0.9	1218	515	276	169	112	79	58	44	34
0.85	0.8	1027	435	233	142	94	66	49	37	29
0.85	0.9	1375	582	312	190	126	89	65	49	38
0.90	0.8	1151	487	261	159	106	74	55	41	32
0.90	0.9	1541	652	349	213	141	99	73	55	43

Although it is unlikely that many participants will drop out of the study, we will conservatively assume that 20% of the patients accrued during November and December will drop out prior to the peak flu season, so we will recruit 140 patients on each arm.

In addition, since patients are being accrued over a very short period of time, it is possible that some patients will be in the queue when we reach our accrual target. In this case, we will allow enrollment of up to 56 additional patients (20% of the original number) to accommodate participants who were told about this study and would like to participate. This will increase our power for detecting the anticipated treatment effect. If we accrue the maximum number of patients and all are evaluable, we would be able to detect a 25% treatment effect with 90% power.

#### 14.2 Feasibility

The Comprehensive Cancer Center of Wake Forest University Community Clinical Oncology Program Research Base is comprised of 18 CCOPs and 5 non-CCOPs. Approximately 21 sites have expressed interest in this study. Currently, the CCCWFU CCOP Research base has 3 open cancer control studies, none of which compete with the proposed trial. We will need to accrue approximately 140 patients per month in each of the enrollment months. We conducted a brief survey of the CCOPs to

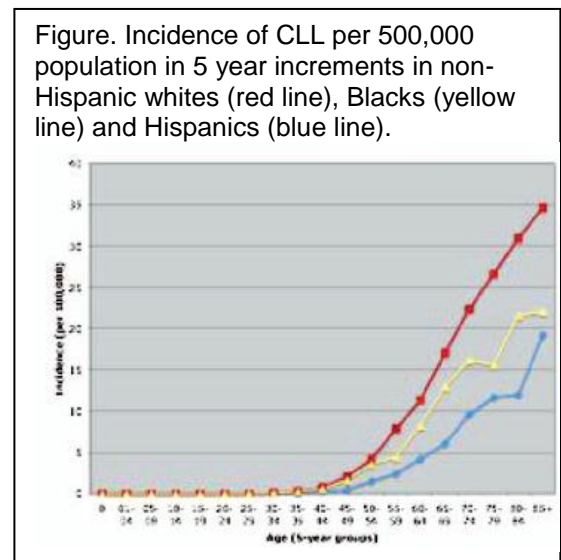
determine the number of untreated CLL patients currently being followed. We received responses from 21 sites; 365 untreated CLL patients were being followed in these 21 sites. Adding CTSU sites will greatly enhance the capacity to enroll subjects in one respiratory illness season.

**14.3 Randomization**

Patients will be stratified by the use of prophylactic antibiotics and randomized within strata to receive COLD-fX or placebo with equal probability, using random permuted block randomization to ensure approximately equal accrual to each treatment throughout the study. Block sizes of varying length will be determined randomly to make it difficult to predict future assignments from past assignments. Treatment assignments will be generated using nQuery Advisor 6.0 and incorporated into the randomization table in our registration facility. Randomization generates a sequence code which is relayed to Biologics where the sequence code is matched to the appropriate treatment.

**14.4 Inclusion of Women and Minorities**

Men and women and members of all ethnic groups are eligible for this trial. The proposed study population is illustrated in the table below. CLL is about twice as common in men as in women during the most prevalent ages (60 years and above) (Cartwright, 2002). Further, CLL is least common in Hispanics, most common in whites, while blacks have an intermediate rate of illness (Figure; Matasar, 2006). There are no firm figures for Asians, Hawaiian/Pacific Islanders, or American Indians so few are included in the table below.



Gender	Race/Ethnicity						
	White	Black	Hispanic	Asian	Hawaiian or Pacific Islander	American Indian	Total
Female	72	14	7	0	0	0	93
Male	145	29	13	0	0	0	187
Total	217	43	20	0	0	0	280

#### 14.5 **Recruitment/Retention Plan**

Study sites will be notified of the protocol opening and receive the final protocol in late summer, 2008. The PI of this protocol (Dr. High) will present the protocol in detail at the annual meeting of the Research Base in September, 2008. The research PI or designee at each WFU Research Base CCOP, which may include the clinic physician, resident, research nurse or research assistant, will review cancer registry and medical chart information to identify patients eligible for this protocol between Sept 2008 and Nov 2008. Patients identified using these methods will be asked to join the study during the enrollment period of November 1- December 31, 2008.

After enrollment, it is recommended that subjects will receive a phone call weekly from site coordinators before the first follow-up study visit at week 4 to remind each subject to fill out the diary and determine if there are any issues of concern.

#### 14.6 **Analysis Plan**

Descriptive reports will consist of summary statistics (means, standard deviations, proportions, etc.) for participant characteristics and outcome measures by treatment arm, actual versus projected accrual, participation by the various CCOPs and WFUSM, and quality control information (retention, missing data, etc.). Tables, graphs, and charts will be used to illustrate the data when appropriate. Any untoward adverse events or other unusual results will be reported to the IRB and the CCCWFU Clinical Research Oversight Committee for further action.

Analysis of covariance (ANCOVA) will be used to assess treatment differences in the number of ARI days between January and March after adjusting for design parameters and pretreatment participant characteristics. Since some participants may have incomplete follow-up during the three-month period of interest, we will actually analyze the number of days of ARI divided by the number of days of follow-up. The analysis of number of days and the analysis of the number divided by the follow-up duration would be the same if everyone has the same amount of follow-up. Adjustments will be made to ensure the analyses match the design, to correct for chance imbalances in important prognostic factors and to improve the precision of the group comparisons by accounting for that part of the variance due to the variability in the patient characteristics. Regression diagnostics, residual plots, and exploratory analyses will be done to find appropriate transformations for the variables in these analyses. Order of priority in choosing a transformation will be to satisfy the 1) linearity assumption, 2) homogeneity of variances assumption, and 3) normality assumption. We will also quantify the number of days of ARI by month, which will allow us to assess treatment differences over time and the time by treatment interaction using a repeated measures analysis of variance. These analyses will also be used to assess the effect of COLD-fX on the number of antibiotic use days, serum IgG levels, and CD4 counts.

Chi-squared tests will be used to assess unadjusted treatment differences in the binomial responses such as the proportion of patients experiencing ARI-related symptoms, toxicities or adverse events. Logistic regression will be used to assess differences in these outcomes after adjustment for baseline covariates. Poisson regression will be used to assess the effect of COLD-fX on the respiratory infection rate and the overall infection rate adjusting for stratification factors and patient characteristics. A negative binomial generalized linear model will be considered in

case of overdispersion. Cox's proportional hazards model will be used to assess the effect of treatment on the risk of respiratory infections over time. The counting process notation as discussed by Therneau and Grambsch (2002) will be used to account for multiple infections and time dependent covariates.

Little is known about the acute respiratory infection rate, the number of ARI days, the number of antibiotic days, or any of the other outcome measures mentioned above among untreated CLL patients. Estimates for these measures will all be obtained as part of the comparison between the COLD-fX and placebo groups, providing much needed data for future trials in this patient population.

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