Study Title	A Randomized, Placebo-Controlled Pilot Study of Genistein Supplementation in Pediatric Cancer Patients Receiving Myelosuppressive Chemotherapy
Protocol Number	UVA-Gen001
Study Intervention	Genistein
Indication Studied	Pediatric Cancer
Development Phase of Study	Pilot
Study Sponsor	University of Virginia
NCT #	NCT02624388
IND #	122755
Protocol Version	3.0
Amendment	4.0
Protocol Date	30Jun2017
GCP Statement	This study is to be performed in full compliance with acceptable Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality	This document is confidential and the property of the University of Virginia. No part of it may be transmitted, reproduced, published, or used by other persons without prior written authorization from the study sponsor.

Study Chair

William Petersen, Jr., MD (UVa PI)
Assistant Professor, Division of Hematology/Oncology
Department of Pediatrics
P.O. Box 800386
Charlottesville, VA 22908
P: 434-924-8499
F: 434-982-3509
wcp3g@virginia.edu

Biostatistician

Gina Petroni, PhD
Professor, Division of Translation Research and Applied Statistics
Department of Public Health Sciences
grp4c@virginia.edu

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Changes from the previous version are listed below. The affected sections are listed in parentheses.

- Version and date updated throughout
- Study inititation specified (Synopsis)
- Repaired formatting error in Inclusion Criteria, resulting in renumbering of list (3.1)
- Complete blood count with differential collected during Baseline (Days -7 to 1) and removed from Cycle 1 Day 1 assessments (6.1, 6.2)
- Cytokine panel removed from baseline assessments and added to Cycle 1 Day 1 assessments (6.1, 6.3)
- Acceptable window for visits and assessment indicated for Treatment Phase Assessments (6.3)
- AE details no longer required for antineoplastic agent dose modifications, antineoplastic agent treatment delays, or antimicrobial agent use (6.3)
- Data reporting for concomitant medications revised and clarified (6.3)
- Clarification of reporting for soy-based products (6.3)
- Expectedness clarified for reporting purposes (9.2.1, 9.2.2)
- Target AE subsection (9.2.3.1) added to Additional Reporting Requirements and other subsections renumbered
- Excluded certain toxicities from single-event FDA IND safety reporting (9.2.3.3, Appendix C)
- DSMC review changed from unblinded to blinded (10.2)
- Addition of scheduled AE review by study staff (10.3)

PROTOCOL SIGNATURE PAGE

A Randomized, Placebo-Controlled Pilot Study of Genistein in Pediatric Cancer Patients Receiving Myelosuppressive Chemotherapy

INVESTIGATORS' AGREEMENT

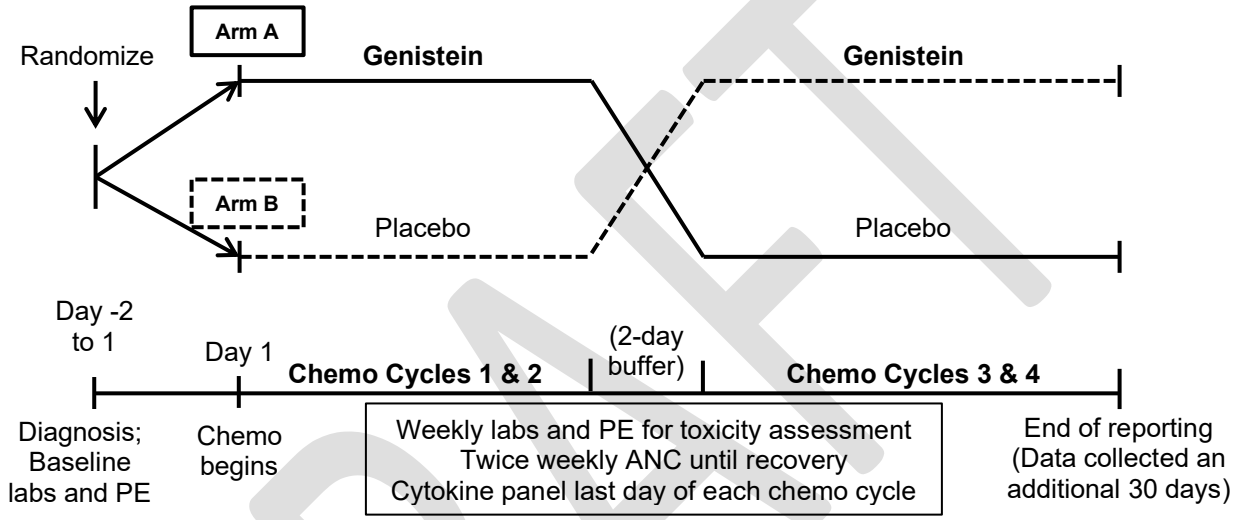
I confirm that I have read this protocol and agree to conduct the study as outlined herein. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations.

Signature:	_____	_____
	William Petersen, Jr, MD Study Chair	Date

Site Name:	_____	
Principle Investigator:	_____	_____
	Signature	Date
	_____	
	Printed Name	

Instructions to the Investigator: Please sign and date this signature page. File the original signature page in the study file at the site and send a copy of the signed and dated page to the Study Manager.

STUDY DESIGN SCHEMATIC



Chemo: chemotherapy
PE: physical exam
ANC: absolute neutrophil count

SYNOPSIS

Title of Study: A Randomized, Placebo-Controlled Pilot Study of Genistein Supplementation in Pediatric Cancer Patients Receiving Myelosuppressive Chemotherapy

Study Chair/ UVa Principal Investigator (PI): William Petersen, Jr., M.D.

Study center(s): University of Virginia Cancer Center (coordinating center) and participating US sites

Phase of study: Pilot	**Study Initiation:** August 2016

Objectives:

Primary:

- To estimate the effect of supplementation with genistein on the time to neutrophil count recovery following myelosuppressive chemotherapy

Secondary:

- To estimate the effect of supplementation with genistein on short-term side effects of myelosuppressive chemotherapy
- To estimate levels of the serum markers of inflammation during cycles of chemotherapy given in conjunction with genistein supplementation versus placebo

Methodology: This is a multi-center, randomized, double-blind, placebo-controlled crossover study to evaluate the effect of the isoflavone genistein on the short-term untoward effects of myelosuppressive chemotherapy used to treat pediatric cancers. Newly diagnosed cancer patients aged 1 - 21 years will be registered to the study and informed consent will be obtained prior to any study-related procedures. Stratification will be based on length of chemotherapy cycles: 14 days or 21 days. Subjects will be randomized 1:1 to one of two schedules within each stratum:

Arm A: Subjects will receive genistein daily throughout chemotherapy Cycles 1 and 2, and placebo during chemotherapy Cycles 3 and 4

Arm B: Subjects will receive placebo daily throughout chemotherapy Cycles 1 and 2, and genistein during chemotherapy Cycles 3 and 4

The safety and efficacy of genistein will be assessed during each cycle through clinical laboratory tests, cytokine panels, and physical exams. Study supplement compliance will be monitored by use of a subject diary, drug reconciliation, and serum isoflavone levels. Adverse events will be monitored starting on Cycle 1 Day 1 through 30 days following the last day of study supplementation (genistein/placebo). Serious adverse events will be collected through 6 months post-study intervention.

Number of subjects (planned): Up to 50 subjects will be accrued to obtain 44 eligible subjects.

Main Eligibility Requirements:

Inclusion criteria:

1. New diagnosis of a solid tumor or lymphoma, with histologic verification of malignancy
2. Age 1 - 21 years at the time of diagnosis
3. Able to tolerate enteral medication administration
4. Performance score minimum requirement ≥ 50 on Karnofsky/Lansky scale
5. Planned chemotherapy regimen involves at least four consecutive cycles of chemotherapy that is known to be myelosuppressive

Exclusion criteria:

1. Known allergy to soy or any soy-based food or supplement
2. Pre-existing neutropenia or neutrophil qualitative or quantitative disorder
3. Pre-existing cytopenia or bone marrow failure syndrome
4. Subject will not receive myelosuppressive chemotherapy
5. Current acute or chronic leukemia diagnosis
6. Enrolled on another therapeutic or supportive care clinical trial within the last 30 days
7. Secondary malignancy

Investigational intervention:

- Genistein: 30 mg/day, oral tablets
- Placebo: oral tablets

Both genistein and placebo tablets will be provided by DSM Nutritional Products Europe Ltd, Switzerland.

Other study intervention(s): The chemotherapeutic regimen for each subject will be determined by the treating physician and must contain a combination of at least two agents from the following list during each of the four cycles administered in this study: actinomycin, carboplatin, cisplatin, cyclophosphamide, daunorubicin, doxorubicin, etoposide, ifosfamide, topotecan.

Criteria for evaluation (i.e. endpoints):

Efficacy: To evaluate the effectiveness of genistein administration during myelosuppressive chemotherapy, the following endpoints will be compared between genistein cycles and placebo cycles:

Primary endpoint:

- Duration of grade 4 neutropenia, defined as an absolute neutrophil count (ANC) of < 500 cells/µl

Secondary endpoints (per cycle):

- Severity of neutropenia
- Duration of grade 4 neutropenia during hospital admissions for febrile neutropenia
- Frequency and duration of unplanned hospital admissions due to (an) adverse event(s)
- Days with fever (temperature > 101.5° F, or > 100° F more than once in a 24-hour period)
- Incidence and severity of infections
- Duration of antimicrobial agent use
- Duration and severity of oral mucositis
- Duration and severity of peripheral motor neuropathy (in subjects receiving vincristine)
- Incidence and severity of hearing impairment and tinnitus (in subjects receiving a platinum-based chemotherapy agent)
- Number of days delayed and percent reduction of full, planned doses of anti-neoplastic agents due to (an) adverse event(s)
- Incidence of primary and secondary G-CSF use
- Number of required blood product transfusions
- Cytokine, growth factor, C-reactive protein, and homocysteine levels as well as erythrocyte sedimentation rates

Safety: Safety will be assessed by incidence and severity of AEs and changes in physical examinations.

Statistical methods:

Graphical and repeated measure models will be used to describe the complete pattern of ANC over all four cycles. Between group (e.g. Cycles 1 & 2) and crossover differences (Cycles 1 - 4) form the structure for treatment comparisons. Repeated measure models will be used to assess differences in raw ANC, daily ANC, days with fever, duration of hospitalization, and duration of antimicrobial use for subjects admitted with febrile neutropenia. The Cochran–Mantel–Haenszel test statistics will be used in the analysis of stratified categorical data. The Cochran–Mantel–Haenszel test will be used to compare grade and repeated measure models for duration of mucositis between cycles containing genistein versus placebo. Safety data will be summarized and compared during genistein versus placebo cycles.

TABLE OF CONTENTS

1 BACKGROUND AND RATIONALE

1.1 Study Synopsis

Toxicities related to pediatric cancer treatment can lead to significant illness, organ damage, treatment delays, increased health care cost, and decrease in quality of life. Such toxicities are largely due to tissue damage sustained by chemotherapy, and strategies designed to limit such cellular damage to normal tissues may reduce therapy-related morbidity and mortality. In addition to their *in vitro* and *in vivo* anti-cancer effects, naturally occurring soy isoflavones have anti-inflammatory and anti-oxidant properties, and have been shown to reduce side effects of therapy in adult oncology clinical trials. This study will examine the effect of genistein, the major isoflavone component in soybeans and the most extensively studied of the soy isoflavones, on short-term side effects of myelosuppressive chemotherapy in pediatric cancer patients. Subjects will be randomized to receive either: a) 30 mg genistein daily throughout chemotherapy Cycles 1 and 2 and placebo during chemotherapy Cycles 3 and 4; or b) placebo daily during chemotherapy Cycles 1 and 2 and 30 mg genistein daily during chemotherapy Cycles 3 and 4. We hypothesize that subjects will have fewer short-term therapy-related side effects during cycles of chemotherapy given in conjunction with genistein supplementation than cycles given with placebo.

1.2 Background

1.2.1 Toxicities Associated With Chemotherapy for Pediatric Cancers

While cure rates for pediatric cancers have steadily improved over the last several decades, toxicities associated with cancer therapy continue to cause significant morbidity and mortality [1, 2]. Serious side effects of chemotherapy and radiation are common and are thought to be due to a variety of factors, including depletion of glutamine and glutathione, free radical generation, cytokine release, and oxidative damage [1, 3-9]. Unlike certain targeted anti-cancer agents, most chemotherapeutic drugs have nonspecific mechanisms of action that damage both normal tissue and cancer cells [1]. Similarly, the mechanism of action of radiation is nonspecific and can cause oxidative DNA damage to normal tissues that are within the radiation field [1]. These nonspecific effects of chemotherapy and radiation tend to be more severe in tissues that contain rapidly dividing, mitotically active cells such as those found in the bone marrow [1]. Myelosuppressive regimens cause a predictable decline in peripheral blood cell counts, usually 7 - 10 days after exposure to therapy. Highly-suppressed absolute neutrophil counts during this period put patients at an elevated risk for serious infection [10]. The standard of care at most institutions is to admit neutropenic patients with fever to the hospital and treat with empiric intravenous broad-spectrum antibiotics until their febrile neutropenia resolves. This is due to the high mortality associated with serious bacterial infections in this population, reported to be around 1% [11, 12]. Such patients also often require packed red blood cell and platelet transfusions for chemotherapy-induced anemia and thrombocytopenia, respectively, which are

associated with hemolytic transfusion reactions and transfusion-transmitted infections. Other common acute toxicities due to cancer treatment include mucositis caused by chemotherapy and radiation as well as neurotoxicity due to vincristine and other tubulin-inhibiting chemotherapeutic agents [13-15].

Many long-term side effects of therapy cause significant morbidity and mortality [2]. One problematic long-term side effect of therapy is the irreversible ototoxicity due to platinum-based chemotherapy [16, 17] that is estimated to occur in up to 61% of patients receiving cisplatin and postulated to be due to cochlear oxidative damage [3-5, 16]. Ototoxicity negatively impacts patients' quality of life by impairing their social and cognitive function and overall development [5]. It can also indirectly lead to increased risk of cancer recurrence if the cumulative dose of cisplatin is significantly reduced due to ototoxicity [5]. Cardiac toxicity caused by anthracycline-induced oxidative damage is another common dose-limiting side effect of therapy [18, 19]. Up to 40% of patients who receive anthracyclines will have an abnormal echocardiogram and survivors of childhood cancers who were treated with anthracyclines have a 15-fold increased relative risk of congestive heart failure compared to adults who were not treated for a childhood cancer [2]. Such therapy-related toxicities significantly impact patients' quality of life and cause treatment-related mortalities. Therapies that limit normal tissue damage without negatively impacting the therapeutic effects of chemotherapy and radiation are needed to improve outcomes and quality of life for childhood cancer patients.

1.2.2 Anti-cancer/Anti-Inflammatory Effects of Soy Isoflavones

Soy isoflavones are naturally-occurring components of soybeans that have both anti-neoplastic and antioxidant properties. Their *in vitro* and *in vivo* anti-cancer effects have been tested in varied cancer model systems and include apoptotic induction [20, 21], growth inhibition [22-24], cell cycle regulation [25], and sensitization to chemotherapy [26, 27] and radiation [28]. Soy isoflavones inhibit growth in preclinical studies of multiple pediatric solid tumors, including Wilms, rhabdoid renal tumors, and neuroblastoma [20-22, 24], as well enhance the cytotoxicity of chemotherapy in medulloblastoma cells [27].

One mechanism by which soy isoflavones exert a protective effect is by inhibiting oxidative damage in healthy cells [29-31]. Oxidative DNA damage is significantly reduced in men and women who receive soy milk supplementation, as determined by 8-isoprostane plasma levels and DNA strand breakage [32-34], which is consistent with *in vitro* and *in vivo* experiments demonstrating antioxidant properties of isoflavones [35-37]. Isoflavones also reduce hydrogen peroxide-induced DNA damage in sperm [38] and neutrophils [39].

Of the three main soy compounds, genistein, daidzein, and glycitein, the major component in soybeans (about 50%) and the most extensively studied of the soy isoflavones is genistein [40]. Genistein has been shown *in vitro* to increase antioxidant gene expression in colon cancer [41] and inhibit induced oxidative stress in epidermal

carcinoma [37, 42] and terminally differentiated leukemia [37]. It also inhibits oxidation of low density lipoprotein in the presence of copper ions and superoxide free radicals, and protects vascular endothelial cells from damage by oxidized lipoproteins [43]. In an experimental model of acute liver damage, genistein-treated rats had lower liver tissue malondialdehyde levels, higher levels of glutathione, and reduced inflammation and necrosis compared to rats that were not exposed to genistein. The protective effect correlated with reduced markers of lipid peroxidation, suggesting that genistein inhibits reactive oxygen species-induced membrane damage [44]. Genistein administration is associated with increased activity of several antioxidant enzymes, including superoxide dismutase, glutathione peroxidase, glutathione reductase, catalase, and glutathione-S-transferase in a mouse model [45]. Additionally, in a guinea pig asthma model, genistein treatment was associated with fewer total white blood cells (WBCs) and eosinophils in bronchoalveolar lavage fluid and reduced airway eosinophilia. Subsequent experiments demonstrated decreased eosinophil peroxidase activity and epidermal growth factor-induced tyrosine phosphorylation, suggesting mechanisms for genistein-mediated inhibition of inflammation [46]. Interestingly, several preclinical studies suggest that genistein may have opposing mechanisms of action and biological effects on some paired normal and malignant cell lines. For example, it has little impact on the generation of reactive oxygen species in astrocytes or hyperdiploidy in normal breast cell models, but they increase in paired malignant cell lines [37, 47]. These and other paired *in vitro* models show a minimal or pro-survival impact of genistein in non-malignant cells but poorer survival in their cancerous counterparts [47-52].

While genistein may promote inflammatory processes, including increased IFN-γ secretion, in the context of some cancers [62-64], data suggest that soy isoflavone consumption may lower pro-inflammatory proteins in non-malignant cells. *In vitro* studies suggest a mechanism whereby genistein may attenuate homocysteine inflammatory signaling through IL-1β, reactive oxygen species, and NF-κB, thereby inhibiting expression of C-reactive protein and its downstream effectors, IL-6 and TNF-α [53-56]. Supporting this, genistein supplementation was associated with reduced serum IL-6 and IFN-γ in a mouse autoimmune encephalitis model [57]. Soy intake inversely correlated with serum TNF- α, IL-6, and IL-1β levels in rats [58], which is consistent with data showing lower serum IL-6 and TNF-α levels in Chinese women who consumed soy-rich diets [59]. Serum CRP and homocysteine levels have been found to be inversely related to soy isoflavone intake in U.S. adults [60, 61]; CRP also inversely correlates with serum genistein levels in adults receiving flavonoid supplementation [60]. Inhibition of cytokine production may be another mechanism by which soy isoflavones, and specifically genistein, reduce inflammation in healthy tissues.

1.2.3 Genistein Reduces Chemotherapy-Induced Side Effects

Genistein's anti-inflammatory and antioxidant properties may counteract the oxidative damage and inflammation induced by anti-neoplastic therapy in healthy tissues, thereby reducing untoward toxicities. Adult men with localized prostate cancer who received 200 mg daily soy isoflavone supplementation (including about 96 mg genistein per day)

concomitant with their radiation therapy had reduced urinary, intestinal, and sexual adverse effects compared to subjects treated with placebo. Compliance was 100% with the study tablets and no side effects from soy supplementation were reported [28]. A small pediatric pilot study found a similar reduction in chemotherapy and radiation therapy-related toxicities with genistein supplementation [65]. In this study, eight solid tumor and brain tumor patients received the first course of therapy without soy supplementation and then received a 0.3 g tablet containing 82% soy isoflavone extract and 2.7% (8 mg) genistein daily with subsequent courses of chemotherapy. No isoflavone-related toxicities were noted and none of the children stopped taking the supplement. While these data were not statistically significant, subjects receiving genistein in conjunction with chemotherapy appeared to have less myelosuppression, less mucositis, shorter durations of antimicrobial therapy, and fewer blood product transfusions compared to cycles of chemotherapy without genistein. Furthermore, subjects who received abdominal radiation reported less pain and diarrhea while taking the genistein supplement, although this was also not statistically significant. While encouraging, these data are preliminary and additional randomized trials are needed to evaluate genistein's effect on anti-neoplastic therapy-related toxicities.

1.3 Study Design and Rationale

Although recent studies have demonstrated the ability of genistein supplementation to reduce chemotherapy-related acute toxicities in a limited number of pediatric cancer patients, data regarding safety and efficacy of soy isoflavones in pediatric cancer patients are scant. The purpose of this study is to evaluate the efficacy and safety of genistein supplementation in pediatric cancer patients receiving myelosuppressive chemotherapy. The study plans to accrue 44 eligible subjects at University of Virginia (coordinating center) and additional participating sites (affiliates).

Genistein safety, efficacy, pharmacokinetics, and pharmacodynamics have been determined in adult clinical trials [66,67]. While much of the soy isoflavone data does not specify which of the soy components are responsible for the clinical effects seen, genistein is known to be the major component in soybeans (about 50%) and the most extensively studied of the soy isoflavones [40]. This study will employ purified genistein rather than a mixture of soy components so as to more clearly define genistein's safety and efficacy in the context of myelosuppressive chemotherapy and a pediatric population.

A dose of 30 mg purified genistein was chosen for this clinical trial based on prior safety and efficacy studies in pediatric and adult populations. In a study of eight solid and brain tumor pediatric patients, subjects received a 0.3 g tablet containing 82% soy isoflavone extract and 2.7% (8 mg) genistein daily [65], which corresponded to a daily genistein dose of approximately 130 mg. No isoflavone-related toxicities were observed and no subjects discontinued supplementation during that study. The findings support the safety of genistein supplementation at a dose up to 130 mg in a pediatric population. In addition, De Ruijter and colleagues [68] recently studied the effects of genistein in 30

subjects with Sanfillipo disease with a median age of 11 – 13 years. They demonstrated that genistein could be administered in this population at doses of 10 mg/kg/day with no observed treatment-related adverse events (AEs). The safety of soy isoflavones in the pediatric population has been evaluated by researchers studying the effects of soy formula intake in infants. Infants who were exposed to an estimated 4 to 16 mg/kg/day of soy isoflavones (approximately 2 to 8 mg/kg/day of genistein, which is equal to about 32 mg daily for a 4 kg infant) in soy formula during their first 4 months of life had no evidence of any significant short- or long-term deleterious effects, including no differences in puberty or fertility compared to infants receiving cow's milk formulas [71]. A dose of 30 mg genistein has been established as a minimal effective dose in adults; it demonstrated elevated serum levels of genistein and was associated with reduced prostate-specific antigen levels in adults with prostate cancer [69, 70]. Most AEs were mild and significant events were rare in those studies. Together, toxicity data do not suggest a need for a dose-finding pediatric trial or that the dose of purified genistein selected for this study will compromise the safety of pediatric subjects. As a reference, two eight-ounce glasses of soy milk contain roughly 30 mg of genistein.

Eligibility is limited by a patient's intended chemotherapeutic regimen. Qualifying regimens must be known to be myelosuppressive and have at least four cycles (14 or 21-day cycles). The sequence of protocol therapy will be randomized in a double-blind fashion to control for bias. This study will also employ a crossover design to limit any period effects and to allow for intra-subject comparisons. Efficacy will be retrospectively evaluated using clinical laboratory results and the incidence of pre-specified AEs. Subjects will be monitored for safety starting on Cycle 1 Day 1 through 30 days following the last day of genistein supplementation.

2 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 To estimate the effect of supplementation with genistein on the time to neutrophil count recovery following myelosuppressive chemotherapy

2.2 Secondary Objectives

2.2.1 To estimate the effect of supplementation with genistein on short-term side effects of myelosuppressive chemotherapy

2.2.2 To estimate levels of the serum markers of inflammation during cycles of chemotherapy given in conjunction with genistein supplementation versus placebo

3 SUBJECT ELIGIBILITY

Eligibility must be reviewed and confirmed by a study investigator prior to subject enrollment.

3.1 Inclusion Criteria

[1] Newly diagnosed solid tumor or lymphoma with histological verification

[2] Age 1 - 21 years at time of diagnosis

[3] Karnofsky/Lanksy performance score of ≥ 50

[4] Able to tolerate enteral medication administration

[5] Planned chemotherapeutic regimen for a patient must meet **all** of the following criteria:

a. A known myelosuppressive regimen which includes at least two of the following agents: actinomycin, carboplatin, cisplatin, cyclophosphamide, daunorubicin, doxorubicin, etoposide, ifosfamide, topotecan

b. At least four consecutive cycles

c. Cycle length is either 14 or 21 days

d. Regimen **must either alternate myelosuppressive chemotherapeutic agents in an X-Y-X-Y format**, such that the same chemotherapy is given every other cycle (e.g. vincristine/doxorubicin/cyclophosphamide | ifosfamide/etoposide), **or repeat the same chemotherapeutic agents each cycle in an X-X-X-X format** (e.g. repeated cycles of cisplatin/etoposide/bleomycin). Courses eligible for this trial may occur at any time during treatment provided that they are consecutive and follow the one of the described patterns. Non-myelosuppressive anti-neoplastic treatments will not be considered for the purposes of determining eligibility. Questions regarding whether or not a patient's chemotherapy plan meets inclusion criteria will be decided by the Study Chair.

[6] Informed consent or parental permission and assent obtained prior to trial-related activities (Section 4.3)

[7] Able and willing to comply with all study related procedures

[8] Women of childbearing potential must agree to use adequate contraception 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 Exclusion Criteria

[1] Known allergy to soy or any soy-based food or supplement

[2] Unable or unwilling to discontinue consuming prohibited soy-based food or supplements while participating in this study (Section 4.8.1)

[3] Pre-existing neutropenia or neutrophil qualitative or quantitative disorder (Section 6.3)

[4] Pre-existing cytopenia or bone marrow failure syndrome

[5] History of gastric or duodenal ulcers or hyperacidity syndromes

[6] History of Human Immunodeficiency Virus (HIV)

[7] Has an active infection requiring systemic therapy

[8] Planned treatment does not include myelosuppressive chemotherapy

[9] Enrolled on a therapeutic or supportive care clinical trial within the last 30 days

[10] Current acute or chronic leukemia diagnosis

[11] Requires medication dosing via an enteral feeding tube that terminates in the duodenum or jejunum. (Enteral feeding tubes that terminate in the stomach are acceptable for study medication delivery.)

[12] Pregnant or breastfeeding woman

[13] Incarceration

[14] Secondary malignancy, i.e. the cancer for which the patient is presently or will be receiving treatment may not be a malignancy related to prior cancer therapy

[15] Any condition which might be worsened by estrogen, such as breast cancer, uterine cancer, ovarian cancer, endometriosis or uterine fibroids

[16] Any condition, in the investigator's opinion, that would compromise patient safety or study outcomes

[17] Anyone who, in the investigator's discretion, would be unwilling or unable to comply with study procedures

3.3 Enrollment Exceptions

An enrollment exception is the sponsor's prospective approval for the enrollment of a single research subject that fails to meet current approved protocol inclusion criteria or satisfies protocol exclusion criteria. Enrollment exceptions will not be granted on this study.

4 TREATMENT PLAN

4.1 Subject Status Definitions

Enrolled: All subjects who sign an informed consent will be considered enrolled on the study.

Screen Failure: A subject who is withdrawn or discontinues from the study prior to receiving any protocol therapy (genistein or placebo) is considered a screen fail. Screen failures do not count toward accrual and will be replaced.

On Study: An enrolled subject is considered on-study/registered when a site investigator has determined that the subject has met all of the inclusion and none of the exclusion criteria, and the Study Chair, Study Research Coordinator, or designee has confirmed the eligibility. The on study date is the date that eligibility is confirmed at UVa.

Randomized: A subject that has been assigned to an arm is considered randomized.

On Treatment: A subject is considered on-treatment on the date that the protocol therapy (genistein/placebo) is initiated (i.e. Cycle 1 Day 1).

Off Treatment: The off-treatment date is the date that the subject, for any reason, is no longer receiving protocol therapy (genistein or placebo). It begins the day after the last dose of study supplement.

On Follow-up: A subject is considered on follow-up on the date that the protocol therapy is completed or discontinued for any reason listed in Section 4.9. The on follow-up date is described below.

- Protocol therapy completed per protocol: date after Cycle 4 Last Day, same as off-treatment date
- Early discontinuation of protocol therapy: same as off-treatment date
- Screen failure: date determined to be ineligible

Off Follow-up: A subject is considered off follow-up when he or she has completed the follow-up period or the last date of follow-up if withdrawn during this period

Off-Study: A subject is considered off-study if he or she is removed from the study for any of the reasons listed in Section 4.10 or if he or she has completed follow-up. It begins the date that the subject's participation in protocol activities has ended and typically coincides with the off-follow-up date.

- Follow-up period completed per protocol: date of six months post-treatment review
- Screen failure: date determined to be ineligible
- Withdrawn from study: date withdrawn

4.2 Recruitment

Recruitment will be managed by each site's local Institutional Review Board (IRB) with oversight by the Sponsor. See Procedure Manual for additional information.

4.3 Informed Consent

In obtaining and documenting informed consent, the investigator must comply with the applicable regulatory requirement(s), and must adhere to all ICH E6 principles, Good Clinical Practice (GCP), and ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject and/or his or her parent(s)/guardian(s) will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject/parent(s)/guardian(s) and the investigator is assured that the subject/parent(s)/guardian(s) understand(s) the implications of participating in the study, the adult subject will be asked to give consent or parent(s)/guardian(s) to provide permission to participate in the study by signing an IRB-approved consent form.

Prior to a subject's participation in the trial, the written informed consent form must be signed and personally dated by the subject/parent(s)/guardian(s) and by the person who conducted the informed consent discussion.

Oral assent will be obtained from minor subjects ≥ 7 years old, unless more stringent requirements are imposed by a site's IRB. In addition, consent must be requested from subjects who become pregnant during the course of the study for the purposes of following the subject and fetus. The format of consent from a pregnant subject will determined by the site's IRB policies. The Sponsor will provide oversight of all consent/permission/assent activities (see Protocol Section 3.1 criterion #6, Procedure Manual).

4.4 Registration

Subjects who have consented to the study must be registered in OnCore (an online clinical trials management system) in accordance with the UVa Cancer Center OnCore standard operating procedures, which can be found on the UVa OnCore Resources webpage (see the OnCore Help tab). General guidelines are provided in the Procedure Manual for reference, but registration must follow the OnCore SOP in case of any discrepancy.

Subject eligibility must be confirmed by the site PI and the eligibility packet must include at a minimum the informed consent and eligibility worksheet. All sites will then submit an

eligibility packet for each eligible subject to the Study Manager for review (Procedure Manual).

4.5 Randomization or Arm Assignment

Following completion of subject registration as described in Section 4.4, the subject will be randomized by the Study Manager at UVa using custom randomization software developed at UVa. The software incorporates the randomization scheme generated by the Biostatistician and assigns the subject to one of the two arms. The arm assignment will only be available to unblinded site personnel for the purposes of dispensing protocol therapy, the Core Investigational Pharmacist, Study Manager, and Biostatistician. See the Procedure Manual for additional information.

Randomization must occur within the 2 days prior to the anticipated Cycle 1 Day 1.

4.6 Unblinding

Subjects and the study team, with the exception of the site Investigational Pharmacist or designee, will be blinded to the randomization assignment. In the event that an Investigator believes that for the safety of the subject the blind must be broken, the Investigator may contact the site Investigational Pharmacist or designee to unblind the subject. When a subject unblinding occurs, the Study Chair, Biostatistician, and Study Manager must be notified in writing within 5 business days, and the reason must be fully documented and recorded on a Case Report Form (CRF).

Unblinded subjects must immediately discontinue protocol therapy (Section 4.9) and will be considered to be in Follow-up.

4.7 Dosage and Administration

4.7.1 Chemotherapeutic Regimen

The chemotherapeutic regimen must meet the inclusion criteria described in Section 3.1. Administration of anti-neoplastic therapy must follow standard clinical practices, including dosing delays and dose modifications to anti-neoplastic therapy. See Section 4.7.3 for information pertaining to treatment delays.

If the pre-treatment audiogram for subjects scheduled to receive platinum-based chemotherapy is indicative of severe hearing loss, the chemotherapeutic dose should be adjusted according to standard clinical practices. Any change(s) to the anticipated cancer treatment regimen must be captured in OnCore.

4.7.2 Genistein/Placebo Supplementation

For the purposes of this study, the duration of treatment cycles will coincide exactly with chemotherapy cycles. “Cycle 1” here refers to the first chemotherapy cycle during which the subject receives genistein or placebo, though this may not be the actual first cycle of the subject’s chemotherapeutic treatment.

Subjects will receive 30 mg genistein (Arm A) or placebo (Arm B) daily throughout Cycles 1 & 2, beginning on the first day of the first cycle of chemotherapy coinciding with this study (Cycle 1 Day 1) and ending two days prior to the predicted start date of Cycle 3. Following a 2-day washout, subjects will then receive placebo (Arm A) or 30 mg genistein (Arm B) throughout chemotherapy Cycles 3 & 4, beginning on the first day of Cycle 3 and ending on the last day of Cycle 4. **The treatment schedule is summarized on Roadmaps, located in the Procedure Manual appendices**. For the purposes of this clinical trial, "study supplement" will refer to both genistein and placebo.

The study supplement will be delivered orally by the subject or a parent, and a diary will be kept to document dose administration. For doses given at home, subjects and parents will be instructed to bring unused pills to study visits. For children who are unable to swallow tablets, instructions for crushing and administering will be given to the families (Procedure Manual). Tablets may be crushed and delivered via feeding tube only if subjects are unable to take the medication orally and the feeding tube terminates in the stomach. Delivery to the duodenum or jejunum may alter genistein pharmacokinetics.

Subjects will record study treatments on a daily Pill Diary to indicate number of doses and time of dosing (Procedure Manual). If a subject misses a dose by less than 12 hours, he or she must be instructed to take the missed dose. If a subject misses a dose by more than 12 hours, he or she must be instructed to skip the missed dose and continue with regular dosing schedule. However, he or she must redose if vomiting occurs within the first 20 minutes after study supplement ingestion. Redosing may occur only once per 24 hour period.

4.7.3 Treatment Delays

A treatment delay is when scheduled therapy is postponed, typically due to toxicity or scheduling difficulties. This trial contains no scheduled treatment delays. Subjects must continue to take the genistein/placebo supplementation if an anti-neoplastic treatment delay occurs, except in the following circumstance: If the anti-neoplastic treatment delay occurs after the subject has stopped taking the study supplement because of the scheduled washout between Cycles 2 and 3, then genistein/placebo must be held until Cycle 3, Day 1.

See Section 6.3 for additional information on study assessments during treatment delays.

4.7.4 Dose Modifications

Dose modifications for AEs which are at least possibly treatment-related are must follow Table 1. Dose modifications for reasons other than treatment-related AEs are not permitted. See Section 9 for information pertaining to the severity and attribution of AEs.

Table 1. Dose Modifications by Adverse Event Grade for Initial Presentation

Grade	Action
Grade 0 - 1	No change
Grade 2	Reduce dose of the study supplement to 50% (½ tablet)
Grade 3 - 4	Suspend treatment

Return to prior dose after three consecutive days of resolution/baseline grade, or the beginning of Cycle 3. If the rechallenge results in toxicity possibly/probably/definitely attributed to the study supplement, reduce the supplement to 50% of full dose (grade 2) or discontinue treatment (grades 3 – 4) until the start of Cycle 3 or the end of Cycle 4, whichever comes first.

The study supplement must be started at the full dose at the beginning of Cycle 3, regardless of any dose modifications during Cycles 1 and 2. This is because the agent used during Cycles 1 and 2 differs from that which is used during Cycles 3 and 4.

Table 2. Dose Modifications by Adverse Event Grade Following Rechallenge

Grade	Action
Grade 0 - 1	No change
Grade 2	Reduce study supplement dose to 50% (½ tablet) until the start of Cycle 3 or the end of Cycle 4, whichever comes first
Grade 3 - 4	Suspend treatment until the start of Cycle 3 or the end of Cycle 4, whichever comes first

If treatment-related AEs are concurrent, modify the dose based upon the highest grade demonstrated. Rechallenge with the previous dose only after all treatment-related AEs have resolved or returned to baseline.

Pill splitting may be necessary and will not alter genistein pharmacokinetics. The Procedure Manual contains further information about pill splitting.

4.8 Concomitant Medications/Treatments

4.8.1 Prohibited Medications

Over-the-counter soy-based foods, drinks, and supplements are not permitted for consumption during this study as they may confound study results. Any subject consuming soy-based food or supplements as part of his or her daily diet must discontinue consumption prior to taking protocol therapy on Cycle 1 Day 1. The study team will provide guidance to the subject to help determine whether his or her diet is consistent with this requirement of the study. **A subject handout summarizing prohibited food and drinks can be found in the Procedure Manual appendices**.

Soy consumption prior to and during treatment must be reported according to Section 6.2 and 6.3. Consumption of prohibited soy products during the treatment period constitutes a protocol deviation and must be handled according to the Procedure Manual

and site IRB policy. Subjects will receive a "warning" and additional education for a first offense; ingestion a second time will result in discontinuation of protocol therapy (Section 4.9).

4.8.2 Concomitant Medications

For the purposes of this study, anti-neoplastic agents (i.e. chemotherapy, hormonal therapy, immunotherapy, other small molecule inhibitors, and gene therapy), antimicrobials (i.e. antibiotics, antifungals, antivirals), transfused blood products, G-CSF, and soy products will be the only collected concomitant medications. Antimicrobial agent use will be designated as prophylactic or for the treatment of a presumed or known infection. See Section 6 for additional information about what data will be collected during the trial.

A platelet or packed red blood cell transfusion must be provided if any of the below criteria are met:

- Hemoglobin of < 7 g/dl or if symptomatic
- Platelets of < 10,000 cells/µl or abnormal bleeding
- Treating physician determines it is in the subject's best clinical interest

4.9 Discontinuation of Protocol Therapy

Subjects will receive genistein or placebo for four 14- or 21-day cycles of chemotherapy, depending upon chemotherapeutic regimen, or until any of the following occur:

- Development of a secondary condition which, in the investigator's opinion, would compromise patient safety or study results
- A female subject becomes pregnant
- Non-compliance with study procedures or protocol therapy (missing more than 20% of prescribed doses of genistein/placebo) since the first dose of study supplement treatment
- Consumption of prohibited soy-based products more than once during the Treatment Phase (Section 4.8.1)
- Unacceptable AE(s). Subjects who experience National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4 grade 3 or higher AE that is possibly, probably, or definitely related to the genistein/placebo during Cycle 3 or 4
- Chemotherapy regimen is altered such that it no longer meets Inclusion Criterion #5 (Section 3.1)
- Subject's treatment assignment is unblinded (Section 4.6)
- Subject decides to discontinue protocol therapy

If a subject discontinues protocol therapy for any of the above reasons, the subject will be considered "Off-treatment" and the subject will be "On Follow-Up". Subjects removed

from protocol therapy for (an) unacceptable AE(s) will be followed until resolution or stabilization of the AE.

Should a pregnant subject consent, the subject will also be followed to determine the outcome of her pregnancy (including any premature termination of the pregnancy). Generally, follow-up will be requested by the Sponsor no longer than 8 weeks following the delivery or termination date.

4.10 Withdrawal from Study

Subjects may withdraw or be withdrawn from study at any time for any of the following reasons:

- Subject decides to withdraw from study
- Discretion of the investigator
- Death

The primary reason for discontinuation or withdrawal from protocol therapy or study must be recorded in both the study and medical records, including an explanation if removed due to an investigator's discretion. All subjects that discontinue or withdraw from the study will continue to receive standard of care treatment.

A subject's participation is considered completed when the subject has received all study procedures and has completed all follow-up visits. Subjects that discontinue from the study prior to receiving any dose of protocol therapy (genistein or placebo) will be replaced. A subject who is withdrawn or discontinues from the study after receiving protocol therapy (genistein/placebo) is considered a discontinuation and will not be replaced.

5 SUPPLEMENT INFORMATION

5.1 Genistein

5.1.1 Chemical Name

5, 7-dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one

5.1.2 Other Names

i-cool tablets containing 30 mg geniVida™ TG (Product code 5011590)

5.1.3 Classification

Plant derived estrogen-like compound, Isoflavone

5.1.4 Molecular Formula

$C_{15}H_{10}O_5$

5.1.5 Manufacturer

DSM Nutritional Products Europe Ltd, Switzerland.

5.1.6 Dosage and Administration

A dose is one tablet (30 mg genistein) per oral daily. Subjects or parents/guardians will be instructed to bring in unused pills to study visits. For children who are unable to swallow tablets, instructions for crushing and administering will be given to a caregiver (Procedure Manual). Tablets may be crushed and delivered via feeding tube only if subjects are unable to take the medication orally and the feeding tube terminates in the stomach. Delivery to the duodenum or jejunum may alter genistein pharmacokinetics.

Refer to the Procedure Manual for additional administration instructions and Section 4.7.4 for dose modification instructions.

5.1.7 Expected Adverse Events

The side effects of usage of genistein reported in the literature are mild. The most common effect is abdominal pain (≤ grade 2). This is the only AE that will be considered to be expected for the purposes of this study.

Genistein may have estrogenic properties. Therefore any condition which might be worsened by estrogen, such as breast cancer, uterine cancer, ovarian cancer, endometriosis or uterine fibroids, may also be worsened by administration of genistein. The effect of genistein in someone who is pregnant or breast-feeding is not known.

5.2 Placebo

5.2.1 Formulation

The formulation includes: microcrystalline cellulose, dicalcium phosphate, and magnesium stearate in a ratio of 10:20:1. Tablets will weigh about 300 mg.

5.2.2 Manufacturer

DSM Nutritional Products Europe Ltd, Switzerland.

5.2.3 Dosage and Administration

Subjects will take one tablet per oral daily. Tablets are approximately 260 mg of placebo (cellulose).

Refer to the Procedure Manual for additional administration instructions and Section 4.7.4 for dose modification instructions.

5.2.4 Expected Adverse Events

None.

5.3 Clinical Supplies/Study Supplement Ordering

Genistein and placebo tablets will be provided to the Core Investigational Pharmacy by DSM Nutritional Products. The Core Investigational Pharmacy will supply each site with full bottles of 100 tablets to be dispensed in smaller quantities as defined in the Procedure Manual based upon cycle length. Site pharmacies must distribute the study supplement in accordance to institutional and state regulations.

Undispensed clinical supplies, including missed doses, must be returned to the Core Investigational Pharmacy. Bottles must not be transferred from one subject to another subject or from one protocol to another protocol.

Details regarding study supplement ordering are provided in the Procedure Manual.

5.4 Storage and Stability

The study supplement may be stored for up to 36 months from the date of manufacture at < 25 ºC. Keep container tightly closed. See the Procedure Manual for directives should a temperature excursion occur.

5.5 Agent Accountability

Subject Pill Diaries must be collected and study medication reconciled at the end of each cycle. Record agent accountability on the Investigational Agent Accountability Record. Both forms are located in the Procedure Manual appendices.

Each site will be responsible for providing periodic study supplement reconciliation reports to the Study Manager.

6 EVALUATIONS AND ASSESSMENTS

6.1 Study Procedures and Assessments Table

Table 3: Schedule of Events

Assessment[1]	Pre-Treatment	Treatment Phase				Follow-up[2]
	Day -28 to Day 1[3]	Cycle 1 Day 1[3,4]	Cycles 1 - 4 Weekly[5]	Cycles 2 - 4 Day 1	Cycle 4 Last Day[6]	
Informed Consent	X					
Eligibility Determination	X					
Baseline[7] and Demographic[8] Data	X					
Randomization[9]	X					
Medical History/Baseline Condition	X					
Physical Exam[10]	X	X	X	X		
Height and Weight		X		X		
Chemistry/Metabolic Panel[11]	X	X		X		
CBC with Differential[12]	X		X	X		
CRP, ESR, and Homocysteine[13]	X			X	X	
Cytokine and Isoflavone Panels[14]		X		X	X	
Audiogram[15]	X			X	X	
Concomitant Medications Review[16]	X[17]	X	X	X	X	
Adverse Events Review		X	X	X	X	X
Study Medication Dispensing		X		X		
Subject Pill Diary[18]		X	X	X	X	
Study Medication Reconciliation				X	X	

[1] All visits and assessments must be completed within ± 72 hours of the milestone date unless otherwise specified.
[2] Subjects must be followed for 30 days following the last study intervention for AEs and for 6 months for SAEs, unless consent is withdrawn.
[3] Cycles begin on Day 1. There is no Day 0.
[4] Cycle 1 Day 1 assessments do not need to be repeated if completed in the 7 days prior (i.e. Day -7 to Day 1) unless otherwise stated.
[5] Weekly visits are to occur at 7-day intervals between Day 1 and the cycle's last day.
[6] The last day of a cycle corresponds to the Day 1 of the next cycle. The last day's number will vary by cycle length.
[7] Diagnosis, stage, grade, site(s) of disease, anti-neoplastic treatment +/- radiation regimen
[8] Age, sex, race, and ethnicity
[9] Randomization must occur within the 2 days prior to the anticipated Cycle 1 Day 1. (Section 4.5)
[10] Full physical exam at the beginning of each cycle of chemotherapy, and a symptom-directed physical exam at each of the weekly treatment visits. Collect height, weight and BSA on Day 1 of each cycle.
[11] Chemistry labs to assess for general safety must be conducted on Day 1 of each cycle. They must include serum creatinine, total bilirubin, AST, and ALT.
[12] CBC must be collected once during Baseline (Day -7 to 1), and then Day 1 of Cycles 2, 3, and 4, and Day 8 of Cycles 1, 2, 3, and 4. Once ANC begins to decrease each cycle, obtain twice a week until ANC recovery (see Section 7.1 for definition of ANC recovery). CBC must include the following: hemoglobin, hematocrit, platelet count, total white blood cell count and automated differential (manual differential if automated not available).
[13] Blood sample must be drawn at Baseline (Day -7 to Day 1), Day 1 of Cycles 2, 3, and 4, and the last day of Cycle 4.
[14] Blood sample must be drawn on Day 1 of Cycles 1, 2, 3, and 4, and the last day of Cycle 4.
[15] In subjects receiving platinum based chemotherapy only, an audiogram must be resulted at baseline (Day -7 to Day 1) and again 0 - 4 days prior to Day 1 of Cycles 2, 3, 4, and the last day of Cycle 4. If hearing loss is detected then adjust dose per Section 4.7.4.
[16] G-CSF, antimicrobials, blood product transfusions, anti-neoplastic agents, and soy-based products (Section 4.8 and 6.4)
[17] Concomitant medications used in the 28 days prior to the initiation of the study intervention
[18] Dispense Day 1 of each cycle. Weekly review recommended but not required. Collect and review on the last day of each cycle.

6.2 Pre-treatment Assessments

Informed consent will be obtained from a parent or guardian of eligible minor subjects, or the patient if ≥ 18 years old. Oral assent will be obtained from minor subjects ≥ 7 years old, unless more stringent requirements are imposed by a site's IRB. Consent and assent must be obtained prior to any study-related procedures. (Section 4.3, Procedure Manual)

Subject eligibility must be confirmed prior to subject enrollment using the inclusion and exclusion criteria (Section 3.1 – 3.2). The following data must also be collected pre-treatment:

- Clinical data: diagnosis, stage, grade, site(s) of disease
    - Stage (extent of spread): *in situ*, localized, regional, distant, unknown
    - Grade (differentiation level): well differentiated/low grade, moderately differentiated/moderate grade, poorly differentiated/high grade, undifferentiated/highest grade
- Anticipated anti-neoplastic treatment regimen for courses coinciding with this trial: therapeutic agents (i.e. chemotherapy, hormonal therapy, immunotherapy, other small molecule inhibitors, gene therapy), doses expressed per kilogram body weight, duration of cycle (14 or 21 days), radiation dose and number of fractions (if applicable)
- Demographic data: date of birth, sex, race, and ethnicity
- Blood sample collection for serum homocysteine, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), and complete blood count (CBC) with differential must be drawn at baseline (Day -7 to Day 1). Raw data will be reported.
    - CBC with differential must include hemoglobin, hematocrit, platelet count, total white blood cell count and automated white blood cell differential (manual differential if automated not available) (Procedure Manual).
- Medical history and physical exam for the purpose of establishing baseline conditions (Section 6.2.1)
- Audiogram on Day -7 to Day 1 for subjects receiving platinum-based chemotherapy
- Use of the following concomitant medications in the 28 days prior to the anticipated Cycle 1 Day 1: G-CSF, antimicrobials, blood product transfusions, anti-neoplastic agents, and soy-based products. See Sections 4.8, 6.3, and the Procedure Manual for additional details on concomitant medications.

In addition, the following **target AEs** must be assessed during the Pre-treatment Period. Use assessment closest to Cycle 1 Day 1 if more than one assessment is done during the Pre-treatment period.

- Neutropenia
- Febrile neutropenia, with temperature
- Fever for temperatures > 101.5° F, or > 100° F more than once in a 24-hour period
- Infections and Infestations: Maximum grade for any AE listed in this CTCAE category. Infections meeting the AE reporting threshold must be listed in the medical history.
- Oral mucositis
- Tinnitus (subjects receiving platinum-based chemotherapy only)
- Hearing impairment (subjects receiving platinum-based chemotherapy only)
- Peripheral motor neuropathy (subjects receiving vincristine only)

6.2.1 Medical History and Physical Examination

A medical history must be obtained and physical exam performed during the Pre-treatment Assessment to establish baseline medical condition(s) (Section 6.2). Medical history includes clinically significant diseases, history of cancer (including date of diagnosis, location of disease, stage, grade, biopsies, resections, prior cancer therapies and procedures), and selected medications (anti-neoplastic agents, blood products, soy products, antimicrobials, and G-CSF) used by the patient within 28 days prior to protocol therapy (genistein/placebo).

A full physical examination will be performed at the Pre-treatment Assessment and Day 1 of each cycle (Sections 6.2 and 6.3). Physical examinations will include examination of the following body systems: general appearance/constitution (including height and body weight), skin, neck, HEENT (head, ears, eyes, nose and throat), cardiovascular system (auscultation of heart sounds), lungs/chest (auscultation of lung fields), abdomen palpation, genitourinary system (auscultation of bowel sounds), lymph nodes, extremities, and nervous system.

An abbreviated, symptom-directed physical exam will be performed at all other visits (Section 6.3). This must also be conducted in such a way to assess for incidence of secondary conditions listed as endpoints (i.e., infection, mucositis, etc.) In addition, any clinically significant abnormal finding which was not noted at the baseline assessment must be reported as an AE, provided it also meets the reporting criteria in Section 9.

Baseline conditions and AEs must be reported as diagnoses, when possible. Laboratory value abnormalities present at the time of enrollment must be reported as baseline conditions according to their CTCAE classifications. The baseline onset and severity of all grades of all target AEs defined in Section 6.2 must be reported, as well as any other

non-target baseline condition if its severity is greater than or equal to grade 3 (Section 9.1.8). The outcome of baseline conditions and resolution dates, when applicable, must be reported at the end of the follow-up period.

6.3 Treatment Phase Assessments (Cycles 1 – 4)

Investigators should maintain good clinical practice and perform standard of care assessments and procedures per local institutional guidelines. In addition, the following list of study-specific assessments must be performed once a patient enters the Treatment Phase. All visits and assessments must be completed within ± 72 hours of the milestone date unless otherwise specified.

- The following will be performed for the purposes of assessing clinically significant AEs. AEs found prior to the first study supplement dose must be reported as baseline conditions. See Section 9 and the Procedure Manual for more information about AE reporting.
    - Chemistry/metabolic liver function labs on Day 1 of each cycle: must include serum creatinine, total bilirubin, AST, and ALT (Procedure Manual)
    - CBC with differential on Day 1 of Cycles 2, 3, and 4, and at weekly visits: must include hemoglobin, hematocrit, platelet count, total white blood cell count and automated white blood cell differential (manual differential if automated not available) (Procedure Manual). See below for additional requirements for ANC reporting.
    - Full physical exam on Day 1 of each cycle and a symptom-directed physical exam at each of the weekly visits (Section 6.2.1)
        - The Pre-treatment and Cycle 1 Day 1 physical exams may be combined performed ≤ 72 hrs. prior to Cycle 1 Day 1.
        - Subjects receiving vincristine must be assessed for vincristine toxicity in the form of peripheral motor neuropathy.
    - Audiograms for subjects receiving a platinum-based chemotherapy agent at 0 - 4 days prior to Day 1 of Cycles 2, 3, 4, and 0 - 4 days prior to the last day of Cycle 4. Assess hearing impairment and tinnitus.
- ANCs must be obtained as follows:
    - The ANC must include both neutrophils and bands. The following equation is recommended:

      ANC = WBC x 1000 (% Neutrophils + % Bands)
    - Obtain on Day 1 of Cycles 2, 3, 4 and at weekly visits

- Once ANC levels begin to decrease, ANC must be determined at least twice weekly (≤ 96 hours between blood collection) until ANC recovers to ≥ 500 cells/μL, then switch to weekly testing in the following situations:
  - If nadir is < 500 cells/μl, begin once ANC ≥ 500 cells/μl, OR
  - If nadir is ≥ 500 cells/μl, begin once ANC has increased by 50% above nadir
- If ANC is < 500 cells/μl at any point after beginning weekly testing, resume twice weekly testing until ANC ≥ 500 cells/μl.
- ANC will be obtained daily during any admission for febrile neutropenia.
- All ANC values will be reported.

- Serum CRP, homocysteine, and ESR: Report raw data collected on Day 1 of Cycles 2, 3, 4, and the last day of Cycle 4
- Cytokine Panel and Isoflavone Panels: Draw and process specimen per the Procedure Manual on Day 1 of Cycles 1, 2, 3, 4, and the last day of Cycle 4
- Weight and height on Day 1 of each cycle
- The following **target AEs** must be assessed and the maximum grade reported for each cycle in addition to standard AE/SAE reporting (Section 9):
  - Neutropenia
  - Febrile neutropenia, with maximum associated temperature per cycle
  - Fever, including number of days per cycle, for temperatures > 101.5° F, or > 100° F more than once in a 24-hour period (report maximum temperature)
  - Infections and Infestations: Maximum grade for any AE listed in this CTCAE category. Infections meeting the AE reporting threshold must be listed individually.
  - Oral mucositis
  - Tinnitus (subjects receiving platinum-based chemotherapy only)
  - Hearing impairment (subjects receiving platinum-based chemotherapy only)
  - Peripheral motor neuropathy (subjects receiving vincristine only)
- Report per cycle:
  - Study supplement:
    - Total number of tablets taken

        - Subject compliance with study medication dosing as determined by self-reported administration reports and supplement reconciliation
        - Reason for dose change, if applicable. Any AE(s) precipitating a dose reduction must be reported even the minimum AE reporting threshold is not otherwise met (Section 9.2).
    - Anti-neoplastic treatment delay(s):
        - Total number of days delayed from planned schedule
        - Cause for delay: AE, or reason other than AE
    - Anti-neoplastic agent dose reduction(s):
        - Delayed agent(s)
        - Planned dose(s)
        - Actual dose(s)
        - Cause for dose change: AE, or reason other than AE
    - All unplanned or prolonged hospitalizations due to (an) AE(s) (Section 9.1.9):
        - Date of admission or start of prolongation and discharge date
        - Causes/diagnoses precipitating hospitalization or prolonged hospitalization
- Concomitant medication review at each scheduled visit for the following:
    - Soy-based products: Product, dates of use. Reporting is limited to the soy-containing products described in Section 4.8.1 and the patient handout in the Procedure Manual.
    - Antimicrobials: type (antibiotic, antifungal, antiviral, other); route of administration (IV, oral, other); dates of use; AE(s) precipitating use, prophylactic use, or the treatment of a presumed/known infection
    - Blood product transfusions: dates of use, blood product type (platelets, red blood cells, other), and indication (Section 4.8.2)
    - G-CSF: Number of days per cycle that G-CSF was administered, primary or secondary use (planned before the cycle began or in response to prolonged neutropenia, respectively)
- Date of disease recurrence or progression, description of recurrence/progression, and site(s) of disease
- Date of secondary malignancy diagnosis, description of secondary malignancy, and site(s) of disease

- Date of death due to any cause, and description of clinical scenario surrounding the subject's death.

The procedures and assessments schedule is summarized on the Roadmaps in the Procedure Manual appendices.

Day 8 assessments must be repeated at intervening/additional weekly visits resulting from an anti-neoplastic therapy treatment delay or any other factors that causes the prolongation of a course.

6.4 Post-Treatment/Follow-up Assessments

All subjects will be followed for a minimum of 30 days after the last dose of protocol therapy (genistein/placebo) to assess for AEs. If subjects complete all four cycles of anti-neoplastic therapy, this visit will occur at 35 ± 5 days following the last day of Cycle 4. If subjects are withdrawn or discontinued prior to completion of the anti-neoplastic therapy, this will occur at 35 ± 5 days following the last day the study supplement is administered.

All serious adverse events (SAEs), other grade 3 – 4 AEs that are believed to be related to the investigational intervention, cancer progressions and relapses (including date, description, and sites), secondary malignancies (including date, description, and sites), and deaths (with date and clinical narrative) must be reported until 6 months after the end of the study intervention. See Section 9.2 for additional information on AE and SAE reporting during this period.

7 EVALUATION CRITERIA

7.1 Primary Endpoint

The primary endpoint of this clinical trial is the average day of neutrophil count recovery following myelosuppressive chemotherapy. Neutropenia will be defined as ANC < 500 cells/µl (grade 4 neutropenia per CTCAE), and the "day of recovery" for each subject during each cycle of chemotherapy will be defined as the first post-nadir day of each cycle that the ANC is ≥ 500 cells/µl (i.e. ≤ grade 3). For example, if the ANC is 400 cells/µl on Day 12 and 600 cells/µl on Day 14, then the day of recovery will be Day 14. For subjects whose ANC nadir is ≥ 500 cells/µl, the day of recovery will be the day of the first ANC after their lowest ANC is obtained.

7.2 Secondary Endpoints (per cycle)

"Incidence" refers to both the frequency of an event per subject and the number of affected subjects in this study.

- **Severity of neutropenia**
- Duration of **grade 4 neutropenia during hospital admissions for febrile neutropenia**
- Frequency and duration of unplanned or prolonged **hospitalizations** due to (an) AE(s) (Section 9.1.9)
- Days with **fever** (temperature > 101.5° F, or > 100° F more than once in a 24-hour period)
- Incidence and severity of **infections**
- Duration of **antimicrobial use**
- Duration and severity of oral **mucositis**
- Duration and severity of **peripheral motor neuropathy** (in subjects treated with vincristine)
- Incidence and severity of **hearing impairment** and **tinnitus** (in subjects treated with a platinum-based chemotherapy agent)
- Number of days of **delays and percent reduction of full planned doses of anti-neoplastic agents due to (an) AE(s)**
- Incidence of primary and secondary **G-CSF use**
- Number and cause of required **blood product transfusions**
- **Serum cytokine levels**:
    - G-CSF, granulocyte-macrophage colony stimulating factor (GM-CSF), interferon-α (IFN-α), IFN-γ, IL-1β, IL-1 receptor antagonist (IL-1RA), IL-2 receptor (IL-2R), IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, TNF-α.

  - Chemokines: eotaxin, IFN-γ induced protein 10 (IP-10), monocyte chemotactic protein 1 (MCP-1), monokine induced by IFN-γ (MIG), macrophage inflammatory protein 1-α (MIP-1α), MIP-1β, Regulated upon Activation Normal T cell Expressed and presumably Secreted (RANTES).

- **Serum growth factor levels**: epidermal growth factor (EGF), fibroblast growth factor-basic (FGF-basic), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF)
- **Serum CRP levels**, **homocysteine levels, and ESRs**

7.3 Toxicity and Safety

Toxicity will be assessed in subjects randomized to both groups for 30 days following the last dose of protocol therapy (genistein/placebo), as indicated in Section 6.4. AEs will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4. See also Section 9.

8 STATISTICAL CONSIDERATIONS

8.1 Study Design

This is a multi-center, randomized, double-blind, placebo-controlled, stratified, two-arm trial with a cross-over component which results in both a between-group comparison (A vs B for Cycles 1 and 2 data) and a crossover within group difference comparison (genistein cycles minus placebo cycles data). Patterns of ANCs over time will be estimated and average day of recovery over the two cycles will be the primary comparison. Neutropenia is defined in Section 7.1. For each subject, two co-primary endpoints will be estimated; a) the average day to recovery during Cycles 1 and 2, and b) the difference in the average days during genistein cycles and the average days during placebo cycles.

In addition, the study is designed to capture other clinically-relevant short-term side effects of therapy that appear to be reduced by genistein supplementation. Secondary endpoints are listed in Section 7.2.

8.2 Sample Size and Accrual

This pilot study is designed to obtain preliminary data to describe the overall pattern of ANC over time during myelosuppressive chemotherapy, assess neutropenia, and to determine whether the data support a decrease in time to recovery of 3 days for the genistein group compared to placebo. Target sample size for this pilot study was based upon results from a chart review performed at UVa which found that the mean day of recovery for pediatric cancer patients receiving myelosuppressive chemotherapy was day 16.25. Group sample sizes of 22 eligible subjects per group achieves approximately 80% power to detect a difference of 3 days with a 5% one-sided Mann-Whitney-Wilcoxon Test. These results were based on 3000 Monte Carlo samples assuming a null Poisson (mean 16.25) distribution and an alternative Poisson (mean 13.25) distribution. ANC determination and neutropenia are defined in Sections 6.3 and 7.1. Adjusting for a 10% ineligibility/drop-out rate, approximately 49 - 50 subjects may need to be accrued to the study.

8.3 Stratification Factors/ Randomization

Stratification will be based on the length of chemotherapy cycles, between 14-day (i.e. Ewing sarcoma patients receiving interval compressed chemotherapy) and 21-day cycles (most others). Site will not be a stratification factor. Subjects will be randomized with equal allocation to each arm using a stratified block randomization scheme with varying block sizes (of size 2 - 4).

8.4 Data Analyses Plans

Graphical and repeated measure models will be used to describe the complete pattern of ANC over all four cycles. Between-group (Cycles 1 & 2) and crossover differences (Cycles 1 - 4) form the structure for treatment comparisons. Repeated measure models

will be used to assess differences in raw ANC, daily ANC, days with fever, duration of hospitalization, and duration of antimicrobial use for subjects admitted with febrile neutropenia. The Cochran–Mantel–Haenszel test statistics will be used in the analysis of stratified categorical data such as neutropenia grades (severe: ≤ 100 cells/μl; moderate: ≤ 500 cells/μl; mild: ≤ 1000 cells/μl) and filgrastim (G-CSF) usage. For duration and severity of mucositis and peripheral motor neuropathy, detailed physical examinations will be documented at each weekly physical exam. Grading (grade 1 - 5) will be performed according to the CTCAE guidelines, version 4.0. The Cochran–Mantel–Haenszel test will be used to compare grade and repeated measure models for duration of mucositis between cycles containing genistein versus placebo.

Number of subjects who experience hearing impairment and tinnitus will be summarized by treatment for each cycle. The number of required blood product transfusions, both packed red blood cells and platelets, will be documented and compared during genistein and placebo cycles using repeated measure models. Reporting will be in the form of total ml/kg body weight infused of red blood cells and platelets. Criteria for transfusion are listed in Section 4.8.2.

9 ADVERSE EVENTS AND REPORTING

After informed consent has been obtained but prior to initiation of investigational intervention, only SAEs caused by a protocol-mandated intervention must be reported (e.g. SAEs related to invasive procedures).

After initiation of the investigational study supplement dosing, all AEs must be collected as described in the following sections through 30 days after the last study supplement dose (Section 6). In addition, investigators must report any deaths, SAEs, other AEs of concern that are believed to be related to the investigational intervention, cancer progression, cancer relapse, and secondary malignancies through six months after the end of the study intervention. See the Procedure Manual for additional information on and resources for AE reporting.

All AEs, whether reported by the subject or noted by study personnel, must be recorded in the subject's medical and study records. AEs must be assessed for seriousness, severity, attribution and expectedness by the investigator. The following sections provide definitions for AE characteristics and reporting requirements.

AEs must be followed to resolution or stabilization, and reported as SAEs if they are or become serious. This also applies to subjects experiencing AEs that cause interruption or discontinuation of study intervention, or those experiencing AEs that are present at the end of their participation in the study. Such subjects should receive post-treatment follow-up as appropriate.

If an ongoing AE changes in its severity or in its perceived relationship to study intervention, a new AE entry for the event must be completed.

9.1 Definitions

9.1.1 Adverse Event [72]

An adverse event is any untoward medical occurrence in a subject who has received an investigational intervention, whether or not related to the investigational intervention(s). Medical conditions present before starting the investigational intervention (pre-existing conditions) will be considered AEs only if they worsen after starting the study supplement (Sections 6.3 and 9.1.6). AEs include unfavorable, harmful or pathological changes in the general condition of a subject; subjective or objective symptoms (spontaneously offered by the subject and/or observed by the Investigator or the study nurse); intercurrent events or exacerbation of pre-existing diseases which occurred after the administration of the study supplement; clinically significant changes in laboratory abnormalities; or any undesirable and unintended effect of research occurring in human subjects as a result of the collection of identifiable, private information for research purposes.

Only clinically significant AEs will be reported on this study. Reporting will include, at minimum, the dates of onset and resolution, severity, attribution to study intervention, expectedness, seriousness, and treatment (medication, transfusion, procedure, other, or none). AEs should be reported as diagnoses, when possible.

9.1.2 Persistent or Recurrent Adverse Events

A persistent AE is an event which extends continuously, without resolution, between assessments. This event must only be recorded once with the initial severity grade. If the severity of the event worsens, then the original event ends and a separate event is recorded at the greater grade or with an altered relationship to the study supplement.

A recurrent AE is an event which resolves between assessments and subsequently recurs. This must be recorded as a separate event for each recurrence.

9.1.3 Secondary Adverse Events

In general, events occurring secondary to other events (e.g., cascade events or clinical sequelae) must be considered a single event identified by the primary cause. However, a secondary event must be listed as an independent event if it meets one of the following criteria:

- Severe
- Serious
- Separated in time from the primary event

If it is not clear as to whether events are dependent, then record as separate AEs.

9.1.4 Abnormal Laboratory Values/Clinical Assessments

It is the responsibility of the investigator to review and document all laboratory findings and clinical assessments, which may include vital signs, physical exams and electrocardiograms (ECGs). Medical and scientific judgment must be exercised in deciding whether a laboratory abnormality or clinical finding must be classified as an AE. An abnormal laboratory test result or clinical finding must be considered as an AE if it meets at least one of the following criteria:

- Is associated with clinical symptoms
- Results in a change in study treatment (e.g., treatment modification, interruption or discontinuation)
- Requires a medical intervention or change in concomitant therapy
- Clinically significant in the investigator's judgment

9.1.5 Death

Death must be considered an outcome of an AE and not an independent AE. The event or condition that caused the death must be recorded as the AE with the outcome of

death. If the cause of death is unknown and cannot be ascertained at the time of reporting, then the event must be reported as a "death NOS". If the cause of death later becomes available (e.g., after autopsy), "death NOS" must be updated by the established cause of death.

9.1.6 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present during the pre-treatment screening assessments. These conditions must be noted as medical history as described in Section 6.2.1. Pre-existing medical conditions are not considered AEs unless any of the following characteristics worsen following initiation of any study-related procedure:

- Frequency
- Severity
- Character

If any of the above conditions apply, then this must be recorded as an AE. Convey that this is a change in a preexisting condition when describing the event.

9.1.7 Expectedness

The expectedness of the AE will be determined by the investigator based on current literature and the investigator's experience. The most common AE associated with genistein supplementation is grade 2 abdominal pain (Section 5.1.7).

SAEs will also take into consideration the expectedness of an AE within the study population, due to the underlying anti-neoplastic treatment regimen and/or underlying disease.

See Sections 9.2.1 and 9.2.2 for information on expectedness as it relates to required reporting.

9.1.8 Severity

The descriptions and grading scales found in the revised CTCAE version 4.0, dated 28May2009, will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov, Appendix A).

To assess severity of AEs not included in the CTCAE version 4.0, use Table 2 below.

Table 4. AE Grading Scale for AEs Not Specifically Listed in the NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
3	Severe or medically significant but not immediately life-threatening; hospitalization or

	prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE

[a]Instrumental activities of daily living (ADL) refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b]Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

9.1.9 Serious Adverse Event [72]

A serious adverse event or experience (SAE) or serious adverse drug reaction (ADR) is any AE temporally associated with the subject's participation in research that meets any of the following criteria:

- Fatal
- Life-threatening (places the subject at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization or prolongation of existing hospitalization*
- Results in a congenital anomaly/birth defect
- Results in a persistent or significant disability/incapacity
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the subject safety and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization or prolonged hospitalization must be documented and reported as a SAE, except if the hospitalization meets at least one of the following criteria:

- The hospitalization is less than 24 hours and without an admission
- Hospitalization for respite care
- Planned hospitalization required for or related to anti-neoplastic treatment (e.g. for anticipated procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery)
- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
    - The subject has not suffered a causative AE.

If the hospitalization meets any of these criteria, then it is not considered a SAE.

SAEs are subject to both expedited and routine reporting. See Section 9.2.3.2 and the Procedure Manual for additional information on expedited reporting requirements for SAEs.

9.1.10 Attribution Assessment

The investigator will evaluate all AEs and to assess the attribution, if any, to study supplement. The following criteria will define the attribution [72]:

Definite: The AE *is clearly related* to the investigational intervention

Probable: The AE *is likely related* to the investigational intervention

Possible: The AE *may be related* to the investigational intervention

Unlikely: The AE *is doubtfully related* to the investigational intervention

Unrelated: The AE *is clearly NOT related* to the investigational intervention

9.2 Required Reporting

9.2.1 UVa Cancer Center DSMC Reporting Requirements

All AEs must be reported into UVa Cancer Center OnCore database within the time frame specified below. All timeframes are expressed in (calendar) days from the first point at which any member of the study team learned of the event.

For the purposes of reporting AEs for DSMC review, expectedness is defined in relationship to treatment with the investigational agent. I.e. Is the AE in question expected when undergoing genistein treatment? See Sections 5.1.7 and 5.2.4 for the expected AE. AEs meeting the thresholds below require additional reporting in OnCore beyond the routine data capture associated with a reporting period.

Target AEs do not need to be reported apart from routine data capture unless they meet the criteria below. Progressions, recurrences, and secondary malignancies must be reported within 30 days of the end of the reporting period during which they occurred, or the next quarterly deadline, whichever comes last. See the Procedure Manual for additional information pertaining to data capture.

Table 5. DSMC reporting requirements for AEs that occur during Cycles 1 – 4

<table>
<tr><th rowspan="3">Attribution to Study Supplement</th><th colspan="2">Grades 1 & 2</th><th colspan="2">Grade 3</th><th>Grade 4</th><th>Grade 5</th></tr>
<tr><th colspan="2">Expected & Unexpected</th><th colspan="2">Expected & Unexpected</th><th rowspan="2">Unexpected</th><th rowspan="2">Unexpected</th></tr>
<tr><th>Target AEs[1]</th><th>All other:</th><th>Target AEs[1]</th><th>All other:</th></tr>
<tr><td>Unrelated
Unlikely</td><td rowspan="2">OnCore:
30 days/
quarterly[3]</td><td rowspan="2">Not required</td><td rowspan="2">OnCore:
30 days/
quarterly[3]</td><td>Not required</td><td>OnCore:
30 days/quarterly[3]</td><td rowspan="2">See SAE</td></tr>
<tr><td>Possible
Probable
Definite</td><td>OnCore:
30 days from
end of Cycle</td><td>OnCore:
15 days from
end of Cycle</td></tr>
<tr><td>SAE[4]</td><td colspan="6">OnCore: (24-hrs), 7 days[2]</td></tr>
<tr><td colspan="7">[1] Target AEs: Neutrophil count decreased, infection (any), mucositis oral, febrile neutropenia, fever, tinnitus & hearing impaired (subjects on platinum-based chemotherapy only), peripheral</td></tr>
</table>

motor neuropathy (subjects on vincristine only).
[2] Enter into Cancer Center database within 24 hours and submit supporting documentation within 7 days.
[3] Data to be entered within 30 days of the end of the reporting period or the next quarterly deadline, whichever comes last. Deadlines are Jan. 31, Apr. 31, July 31, and Oct. 31.
[4] Any AE that is an SAE must be reported using the SAE timeline regardless of grade or attribution.

Less stringent reporting is required during the follow-up period.

Table 6. DSMC reporting requirements for AEs that occur after the subject's last cycle taking the study supplement until 6 months post-treatment (i.e. follow-up)

Attribution to Study Supplement	Grades 1 & 2	Grade 3	Grade 4	Grade 5
	Expected & Unexpected	Expected & Unexpected	Unexpected	Unexpected
Unrelated Unlikely	Not required	Not required	OnCore: 30 days/quarterly[2]	See SAE
Possible Probable Definite		OnCore: 30 days from end of Reporting Period[3]	OnCore: 15 days from end of Reporting Period[3]	
SAE[4]	OnCore: (24-hrs), 7 days[1]			

[1] Enter into Cancer Center database within 24 hours and submit supporting documentation within 7 days.
[2] Data to be entered within 30 days of the end of the reporting period or the next quarterly deadline, whichever comes last. Deadlines are Jan. 31, Apr. 31, July 31, and Oct. 31.
[3] Reporting is not required if AE onset is > 30 days after the last dose of study supplement
[4] Any AE that is an SAE must be reported using the SAE timeline regardless of grade or attribution.

9.2.2 IRB Reporting Requirements

Serious and unexpected AEs must be submitted to the site IRB according to the participating site institutional policies.

For the UVa clinical site, the PI or designee is responsible for reporting AEs and unanticipated problems to the UVa Institutional Review Board for Health Sciences Research (UVa IRB-HSR) according to the following guidelines.

For the purposes of reporting to UVa IRB-HSR, expectedness is defined in relationship to the patient population. I.e. Is the AE in question expected given the characteristics of the population being studied or in terms of the nature, severity or frequency given the research procedures described in the protocol?

Table 7. IRB Reporting Requirements for UVa

Type of Event	To whom will it be reported:	Time Frame for Reporting	How reported?
Any internal event resulting in death that is deemed DEFINITELY related to (caused by) study participation *An internal event is one that occurs in a subject enrolled in a UVa protocol*	IRB-HSR	Within 24 hours	IRB Online and phone call www.irb.virginia.edu/
Internal, Serious, Unexpected AE *See also OnCore reporting requirement (Section 9.2.3.2, Procedure Manual).*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event. *Timeline includes submission of signed hardcopy of AE form.*	IRB Online www.irb.virginia.edu/
External, Serious, Unexpected AE that results in a change to the risk section of the consent and/or modification to the protocol	IRB-HSR		IRB Online www.irb.virginia.edu/
Unanticipated Problems that are not AEs or protocol violations *This would include a Data Breach.*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Unanticipated Problem report form. *http://www.virginia.edu/vprgs/irb/HSR_docs/Forms/Reporting_Requirements-Unanticipated_Problems.doc*
Protocol Violations (*The IRB-HSR only requires that MAJOR violation be reported, unless otherwise required by your sponsor, if applicable.)*	IRB-HSR	Within 7 calendar days from the time the study team received knowledge of the event.	Protocol Violation and Enrollment Exception Reporting Form *http://www.virginia.edu/vprgs/irb/hsr_forms.html*
Data Breach	The UVa Corporate Compliance and Privacy Office ITC: if breach involves electronic data UVa Police if breach includes such things as stolen computers.	As soon as possible and no later than 24 hours from the time the incident is identified. As soon as possible but no later than 24 hours from the time the incident is identified. IMMEDIATELY.	UVa Corporate Compliance and Privacy Office: (434) 924-9741 **ITC:** Information Security Incident Reporting procedure, *http://www.itc.virginia.edu/security/reporting.html* Phone: (434) 924-7166

Table 8. DSMC Reporting Requirements

INDEPENDENT DSMB/DSMC			
DSMB/DSMC Reports	IRB	15 calendar days of the study team receiving the report	Copy of DSMB/ DSMC report

9.2.3 Additional reporting Requirements

9.2.3.1 Target Adverse Events

Target AEs are AEs of special interest and will be collected throughout the treatment phase, regardless of expectedness, severity, or attribution. They are listed in Section 6.3. Target AEs will not be collected during the follow-up reporting periods unless the AEs otherwise meet the DSMC or IRB reporting requirements outlined in Sections 9.2.1 and 9.2.2.

9.2.3.2 Additional Reporting Requirements for Affiliate Sites

In addition to reporting in OnCore, all SAEs must be reported by facsimile within 24 hours of the event to the Sponsor (UVa) as outlined in the Procedure Manual. Any SAEs that occur in the 30 days following the last dose of protocol therapy must be reported. After that time, only SAEs that are related to protocol therapy are required to be reported. For every SAE which occurs, affiliates must send an SAE report with the following information:

- Safety reporting cover sheet (Procedure Manual appendices)
- Relevant hospital case records and autopsy reports (where applicable)

9.2.3.3 Reporting to the FDA

The Study Chair or designee is responsible for providing safety updates to the FDA per the following guidelines. The reporting times refer to the time the study team received knowledge of the AE.

Table 9. FDA Reporting Requirements

UVa PI HELD IND			
Type of Event	**To whom will it be reported:**	**Time Frame for Reporting**	**How reported?**
Life-threatening and/or fatal unexpected events related or possibly related to the use of the investigational agent.*	FDA	Within 7 calendar days of the study team learning of the event	Form FDA 3500A (MedWatch) or narrative
Serious, unexpected and related or possibly related AEs*	FDA	Within 15 calendar days after the study team receives knowledge of the event	Form FDA 3500A (MedWatch) or narrative
All AEs	FDA	Annually	IND annual report

*Applies to AEs/SAEs not identified in Appendix C

Certain anticipated SAEs will not be reported individually to the FDA in an expedited fashion due to their frequency in the study population independent of study supplement exposure. The events listed in Appendix C are common in patients receiving the chemotherapeutic agents listed in Section 3.1 and so will instead be reported in aggregate to the FDA using an IND safety report should analysis indicate that the toxicities are occurring more frequently in patients taking genistein.

The Study Chair may also choose to refrain from single-event IND safety reporting should an AE/SAE be related to the subject's underlying disease. These events are not included in Appendix C due to the wide range of cancers that may participate in this study. As above, such AE/SAEs will be reported using an IND safety report should aggregate analysis demonstrate increased toxicity associated with genistein treatment.

Single-event IND safety reports submitted to the FDA will be blinded, per permission granted by the agency on 19May2017.

Annual reports to the FDA will include AEs and SAEs collected as described in Section 9.2.1, with the exception of target AEs collected solely for the purposes endpoint analysis. Those target AEs are non-serious grades 1 and 2, any attribution to the study supplement, and non-serious grade 3 with an unrelated or unlikely relationship to the study supplement.

9.2.3.4 Reporting to Participating Sites

The Study Chair or designee is responsible for providing safety updates to all participating sites per the following guidelines:

Table 10. Required Reporting to Participating Sites

UVa PI of MULTI-SITE TRIAL			
Type of Event	**To whom will it be reported:**	**Time Frame for Reporting**	**How reported?**
Serious, unexpected and related or possibly related AEs	All Research Sites	Within 15 calendar days after the Study Chair receives knowledge of the event	IND Safety Report (Cover letter, copy of MedWatch or narrative)
Unanticipated Problem	All Research Sites	Within 15 calendar days from the time the Study Chair receives knowledge of the event.	Letter to Site PIs, Copy of MedWatch or narrative

10 DATA SAFETY MONITORING PLAN

The Study Chair will provide continuous monitoring of subject safety in this trial with periodic reporting to the UVa Data Safety Monitoring Committee (DSMC).

10.1 Data Collection/CRF Completion

All data must be entered into OnCore in accordance the University of Virginia Cancer Center OnCore standard operating procedure (SOP), which can be found on the OnCore Resources page (see the OnCore Help tab). AEs must be entered into OnCore as described in Section 9.2 and in the Procedure Manual. All other study specific data must be entered into OnCore in the timeframes specified in the SOP. Sample CRFs are available in the Procedure Manual appendices.

10.2 UVa Cancer Center Data Safety Monitoring Committee

The UVa Cancer Center (CC) Data and Safety Monitoring Committee (DSMC) will provide oversight of the conduct of this study. The CC DSMC will report to the UVa Protocol Review Committee (PRC). These reports will also be provided to participating sites for submission to their IRBs.

The DSMC will review the following data in blinded format:

- All AEs
- Audit results
- Application of study designed stopping/decision rules
- Whether the study accrual pattern warrants continuation/action
- Protocol violations

The CC DSMC will meet every month for aggregate review of AE data. Tracking reports of the meetings are available to the Study Chair for review. Issues of immediate concern by the DSMC are brought to the attention of the Study Chair (and if appropriate to the PRC and IRB) and a formal response from the Study Chair is requested. Per the CC NIH-approved institutional plan this study will be audited approximately every 6 or 12 months.

10.3 Review of Adverse Events by the Study Team

Individual AEs will be reviewed by the treating physician and/or principal investigator, and the clinical research coordinator(s) (CRC). Additional staff on the research team may also review AEs.

SAEs will be reviewed by the Study Chair and Study Statistician at least once every six months after the first subject's first dose with study supplement. Those present at the meeting may include the Study Chair, PIs at other sites, sub-investigators, protocol

development staff, biostatisticians, research nurses, research coordinators, laboratory specialists, and laboratory research managers. These meetings also include the review of individual participants to assess whether they are protocol candidates, whether AEs warrant discontinuation, and whether the existing protocol should be continued, amended, or closed.

11 STUDY MANAGEMENT

11.1 IRB Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. Each site's IRB must approve the consent form(s) and protocol. All initial and amendment approvals, annual renewals, and IRB-stamped consent forms must be submitted to the Study Manager (Procedure Manual).

Section 4.3 outlines expectations for properly obtaining and documenting informed consent.

11.2 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol. The UVa IRB-HSR will approve all aspects of this study, including the clinical trial protocol, informed consent documents, and subject materials. Modifications to the protocol or consent form will be reviewed and approved by the UVa IRB-HSR prior to implementation, except when necessary to eliminate apparent immediate hazards to the study participants. The study will undergo continuing IRB review based on the level of risk as assessed by the IRB. This review will take place no less than annually. Participating sites will be responsible for ensuring their consent forms are written in accord with 21 CFR 50.

Affiliate sites must submit this study for the review of their local site IRBs in accordance with local policies. At a minimum, all consent forms, the protocol (all versions from the time of affiliate start-up), annual renewals, and study closure must be approved by the site IRB. See the Procedure Manual for further details.

11.2.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval/favorable opinion, if permitted by the site's IRB.

For any such emergency modification implemented at UVa, an IRB modification form must be completed by study personnel within five (5) business days of making the change.

11.2.2 Protocol Deviations/Violations

Protocol Deviations: A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants

- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

Study personnel will record the deviation, and report to the Sponsor or DSMC in accordance with their policies. Deviations must be summarized and reported to the site IRB at the time of continuing review or according to site IRB's policy.

Protocol Violations: An unplanned protocol variance is considered a violation if the variance:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or institutional policies.

Violations must be reported by study personnel to the site IRB in accordance with the site IRB's policy and to the Sponsor as outlined in the Procedure Manual.

11.3 Record Retention

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g. protocol and amendments, IRB correspondence and approvals/acknowledgements, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents must be kept on file until six years after the completion and final study report of this investigational study. Completion is defined as study closure through the UVa IRB-HSR.

11.4 Obligations of Investigators

The PI is responsible for the conduct of the clinical trial at their site in accordance with Title 21 of the Code of Federal Regulations, all applicable local regulatory laws and regulations and/or the Declaration of Helsinki. The PI is responsible for personally

overseeing the treatment of all study subjects at his or her site and must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion. It is the responsibility of the PI to ensure that all study site personnel are aware that the study protocol and all data generated is confidential and not disclosed to third parties (with the exception of local and national regulatory bodies which require access for oversight purposes).

The PI at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the CRFs. Periodically, monitoring visits will be conducted and the PI will provide access to his or her original records to permit verification of proper entry of data. At the completion of the study, all CRFs will be reviewed by the PI and will require his or her final signature to verify the accuracy of the data.

12 REFERENCES

1. Hoekman, K., W.J. van der Vijgh, and J.B. Vermorken, *Clinical and preclinical modulation of chemotherapy-induced toxicity in patients with cancer.* Drugs, 1999. **57**(2): p. 133-55.
2. Oeffinger, K.C., et al., *Chronic health conditions in adult survivors of childhood cancer.* N Engl J Med, 2006. **355**(15): p. 1572-82.
3. Rybak, L.P. and S. Somani, *Ototoxicity. Amelioration by protective agents.* Ann N Y Acad Sci, 1999. **884**: p. 143-51.
4. Rybak, L.P., C. Whitworth, and S. Somani, *Application of antioxidants and other agents to prevent cisplatin ototoxicity.* Laryngoscope, 1999. **109**(11): p. 1740-4.
5. Brock, P.R., et al., *Platinum-induced ototoxicity in children: a consensus review on mechanisms, predisposition, and protection, including a new International Society of Pediatric Oncology Boston ototoxicity scale.* J Clin Oncol, 2012. **30**(19): p. 2408-17.
6. Lopez, I., et al., *[Treatment of mucositis with vitamin E during administration of neutropenic antineoplastic agents].* Ann Med Interne (Paris), 1994. **145**(6): p. 405-8.
7. Griggs, J.J., *Reducing the toxicity of anticancer therapy: new strategies.* Leuk Res, 1998. **22 Suppl 1**: p. S27-33.
8. Gaurav, K., et al., *Glutamine: A novel approach to chemotherapy-induced toxicity.* Indian J Med Paediatr Oncol, 2012. **33**(1): p. 13-20.
9. Rubin, P., et al., *A perpetual cascade of cytokines postirradiation leads to pulmonary fibrosis.* Int J Radiat Oncol Biol Phys, 1995. **33**(1): p. 99-109.
10. Macher, E., et al., *Predicting the risk of severe bacterial infection in children with chemotherapy-induced febrile neutropenia.* Pediatr Blood Cancer, 2010. **55**(4): p. 662-7.
11. Hann, I., et al., *A comparison of outcome from febrile neutropenic episodes in children compared with adults: results from four EORTC studies. International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC).* Br J Haematol, 1997. **99**(3): p. 580-8.
12. Ammann, R.A., et al., *Predicting adverse events in children with fever and chemotherapy-induced neutropenia: the prospective multicenter SPOG 2003 FN study.* J Clin Oncol, 2010. **28**(12): p. 2008-14.
13. Jackson, D.V., et al., *Amelioration of vincristine neurotoxicity by glutamic acid.* Am J Med, 1988. **84**(6): p. 1016-22.
14. Weiss, H.D., M.D. Walker, and P.H. Wiernik, *Neurotoxicity of commonly used antineoplastic agents (first of two parts).* N Engl J Med, 1974. **291**(2): p. 75-81.
15. Cheng, K.K., et al., *Oral mucositis in pediatric and adolescent patients undergoing chemotherapy: the impact of symptoms on quality of life.* Support Care Cancer, 2012. **20**(10): p. 2335-42.
16. Knight, K.R., D.F. Kraemer, and E.A. Neuwelt, *Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development.* J Clin Oncol, 2005. **23**(34): p. 8588-96.
17. Ilveskoski, I., et al., *Ototoxicity in children with malignant brain tumors treated with the "8 in 1" chemotherapy protocol.* Med Pediatr Oncol, 1996. **27**(1): p. 26-31.
18. Lipshultz, S.E., et al., *The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphoblastic leukemia.* N Engl J Med, 2004. **351**(2): p. 145-53.
19. Brown, T.R., et al., *Anthracycline induced cardiac toxicity in pediatric Ewing sarcoma: a longitudinal study.* Pediatr Blood Cancer, 2013. **60**(5): p. 842-8.

20. Mohan, N., et al., *Bcl-2 inhibitor HA14-1 and genistein together adeptly down regulated survival factors and activated cysteine proteases for apoptosis in human malignant neuroblastoma SK-N-BE2 and SH-SY5Y cells.* Brain Res, 2009. **1283**: p. 155-66.
21. Karmakar, S., et al., *Combination of N-(4-hydroxyphenyl) retinamide and genistein increased apoptosis in neuroblastoma SK-N-BE2 and SH-SY5Y xenografts.* Neuroscience, 2009. **163**(1): p. 286-95.
22. Naraghi, S., et al., *Receptor tyrosine kinase inhibition suppresses growth of pediatric renal tumor cells in vitro.* J Pediatr Surg, 2000. **35**(6): p. 884-90.
23. Zhou, J.R., et al., *Soybean phytochemicals inhibit the growth of transplantable human prostate carcinoma and tumor angiogenesis in mice.* J Nutr, 1999. **129**(9): p. 1628-35.
24. Li, H., et al., *Genistein demethylates the promoter of CHD5 and inhibits neuroblastoma growth in vivo.* Int J Mol Med, 2012. **30**(5): p. 1081-6.
25. Choi, Y.H., et al., *Genistein-induced G2/M arrest is associated with the inhibition of cyclin B1 and the induction of p21 in human breast carcinoma cells.* Int J Oncol, 1998. **13**(2): p. 391-6.
26. Li, Y., et al., *Antitumor and antimetastatic activities of docetaxel are enhanced by genistein through regulation of osteoprotegerin/receptor activator of nuclear factor-kappaB (RANK)/RANK ligand/MMP-9 signaling in prostate cancer.* Cancer Res, 2006. **66**(9): p. 4816-25.
27. Khoshyomn, S., et al., *Synergistic action of genistein and cisplatin on growth inhibition and cytotoxicity of human medulloblastoma cells.* Pediatr Neurosurg, 2000. **33**(3): p. 123-31.
28. Ahmad, I.U., et al., *Soy isoflavones in conjunction with radiation therapy in patients with prostate cancer.* Nutr Cancer, 2010. **62**(7): p. 996-1000.
29. Adlercreutz, H., *Phytoestrogens: epidemiology and a possible role in cancer protection.* Environmental Health Perspectives, 1995. **103**(Suppl 7): p. 103-12.
30. Ruiz-Larrea, M.B., et al., *Antioxidant activity of phytoestrogenic isoflavones.* Free Radical Research, 1997. **26**(1): p. 63-70.
31. Stoll, B.A., *Macronutrient supplements may reduce breast cancer risk: how, when and which?* European Journal of Clinical Nutrition, 1997. **51**(9): p. 573-7.
32. Ryan-Borchers, T.A., et al., *Soy isoflavones modulate immune function in healthy postmenopausal women.* Am J Clin Nutr, 2006. **83**(5): p. 1118-25.
33. Mitchell, J.H. and A.R. Collins, *Effects of a soy milk supplement on plasma cholesterol levels and oxidative DNA damage in men--a pilot study.* Eur J Nutr, 1999. **38**(3): p. 143-8.
34. Djuric, Z., et al., *Effect of soy isoflavone supplementation on markers of oxidative stress in men and women.* Cancer Lett, 2001. **172**(1): p. 1-6.
35. Ruiz-Larrea, M.B., et al., *Antioxidant activity of phytoestrogenic isoflavones.* Free Radic Res, 1997. **26**(1): p. 63-70.
36. Arora, A., M.G. Nair, and G.M. Strasburg, *Antioxidant activities of isoflavones and their biological metabolites in a liposomal system.* Arch Biochem Biophys, 1998. **356**(2): p. 133-41.
37. Giles, D. and H. Wei, *Effect of structurally related flavones/isoflavones on hydrogen peroxide production and oxidative DNA damage in phorbol ester-stimulated HL-60 cells.* Nutr Cancer, 1997. **29**(1): p. 77-82.
38. Sierens, J., et al., *In vitro isoflavone supplementation reduces hydrogen peroxide-induced DNA damage in sperm.* Teratog Carcinog Mutagen, 2002. **22**(3): p. 227-34.
39. Wei, H., et al., *Inhibition of tumor promoter-induced hydrogen peroxide formation in vitro and in vivo by genistein.* Nutr Cancer, 1993. **20**(1): p. 1-12.

40. Sarkar, F.H. and Y. Li, *The role of isoflavones in cancer chemoprevention.* Front Biosci, 2004. **9**: p. 2714-24.
41. Kameoka, S., et al., *Expression of antioxidant proteins in human intestinal Caco-2 cells treated with dietary flavonoids.* Cancer Lett, 1999. **146**(2): p. 161-7.
42. Chan, W.H. and J.S. Yu, *Inhibition of UV irradiation-induced oxidative stress and apoptotic biochemical changes in human epidermal carcinoma A431 cells by genistein.* J Cell Biochem, 2000. **78**(1): p. 73-84.
43. Kapiotis, S., et al., *Genistein, the dietary-derived angiogenesis inhibitor, prevents LDL oxidation and protects endothelial cells from damage by atherogenic LDL.* Arterioscler Thromb Vasc Biol, 1997. **17**(11): p. 2868-74.
44. Kuzu, N., et al., *Protective role of genistein in acute liver damage induced by carbon tetrachloride.* Mediators Inflamm, 2007. **2007**: p. 36381.
45. Cai, Q. and H. Wei, *Effect of dietary genistein on antioxidant enzyme activities in SENCAR mice.* Nutr Cancer, 1996. **25**(1): p. 1-7.
46. Duan, W., et al., *Antiinflammatory effects of genistein, a tyrosine kinase inhibitor, on a guinea pig model of asthma.* Am J Respir Crit Care Med, 2003. **167**(2): p. 185-92.
47. Upadhyay, S., et al., *Differential sensitivity of normal and malignant breast epithelial cells to genistein is partly mediated by p21(WAF1).* Clin Cancer Res, 2001. **7**(6): p. 1782-9.
48. Das, A., N.L. Banik, and S.K. Ray, *Flavonoids activated caspases for apoptosis in human glioblastoma T98G and U87MG cells but not in human normal astrocytes.* Cancer, 2010. **116**(1): p. 164-76.
49. Seo, H.S., et al., *Induction of apoptotic cell death by phytoestrogens by up-regulating the levels of phospho-p53 and p21 in normal and malignant estrogen receptor alpha-negative breast cells.* Nutr Res, 2011. **31**(2): p. 139-46.
50. Li, Y., et al., *Epigenetic regulation of multiple tumor-related genes leads to suppression of breast tumorigenesis by dietary genistein.* PLoS One, 2013. **8**(1): p. e54369.
51. Kingsley, K., et al., *Soy protein extract (SPE) exhibits differential in vitro cell proliferation effects in oral cancer and normal cell lines.* J Diet Suppl, 2011. **8**(2): p. 169-88.
52. Chen, F.P. and M.H. Chien, *Phytoestrogens induce differential effects on both normal and malignant human breast cells in vitro.* Climacteric, 2014. **17**(6): p. 682-91.
53. Bai, Y.P., et al., *Rosiglitazone attenuates NF-kappaB-dependent ICAM-1 and TNF-alpha production caused by homocysteine via inhibiting ERK1/2/p38MAPK activation.* Biochem Biophys Res Commun, 2007. **360**(1): p. 20-6.
54. Pang, X., et al., *Homocysteine induces the expression of C-reactive protein via NMDAr-ROS-MAPK-NF-kappaB signal pathway in rat vascular smooth muscle cells.* Atherosclerosis, 2014. **236**(1): p. 73-81.
55. Thaler, R., et al., *Homocysteine suppresses the expression of the collagen cross-linker lysyl oxidase involving IL-6, Fli1, and epigenetic DNA methylation.* J Biol Chem, 2011. **286**(7): p. 5578-88.
56. Wenzel, U., D. Fuchs, and H. Daniel, *Protective effects of soy-isoflavones in cardiovascular disease. Identification of molecular targets.* Hamostaseologie, 2008. **28**(1-2): p. 85-8.
57. Castro, S.B., et al., *Immunomodulatory effects and improved prognosis of experimental autoimmune encephalomyelitis after O-tetradecanoyl-genistein treatment.* Int Immunopharmacol, 2012. **12**(2): p. 465-70.
58. Hsu, A., et al., *Dietary soy and tea mitigate chronic inflammation and prostate cancer via NFkappaB pathway in the Noble rat model.* J Nutr Biochem, 2011. **22**(5): p. 502-10.
59. Wu, S.H., et al., *Soy food intake and circulating levels of inflammatory markers in Chinese women.* J Acad Nutr Diet, 2012. **112**(7): p. 996-1004, 1004 e1-4.

60. Chun, O.K., et al., *Serum C-reactive protein concentrations are inversely associated with dietary flavonoid intake in U.S. adults.* J Nutr, 2008. **138**(4): p. 753-60.
61. Floegel, A., et al., *Antioxidant intake from diet and supplements and elevated serum C-reactive protein and plasma homocysteine concentrations in US adults: a cross-sectional study.* Public Health Nutr, 2011. **14**(11): p. 2055-64.
62. Mansour, A., et al., *Genistein induces G2 arrest in malignant B cells by decreasing IL-10 secretion.* Cell Cycle, 2004. **3**(12): p. 1597-605.
63. Ghaemi, A., et al., *Genistein induces a protective immunomodulatory effect in a mouse model of cervical cancer.* Iran J Immunol, 2012. **9**(2): p. 119-27.
64. Guo, T.L., et al., *Genistein modulates immune responses and increases host resistance to B16F10 tumor in adult female B6C3F1 mice.* J Nutr, 2001. **131**(12): p. 3251-8.
65. Tacyildiz, N., et al., *Soy isoflavones ameliorate the adverse effects of chemotherapy in children.* Nutr Cancer, 2010. **62**(7): p. 1001-5.
66. Fischer, L., et al., *Clinical characteristics and pharmacokinetics of purified soy isoflavones: multiple-dose administration to men with prostate neoplasia.* Nutr Cancer, 2004. **48**(2): p. 160-70.
67. Takimoto, C.H., et al., *Phase I pharmacokinetic and pharmacodynamic analysis of unconjugated soy isoflavones administered to individuals with cancer.* Cancer Epidemiol Biomarkers Prev, 2003. **12**(11 Pt 1): p. 1213-21.
68. de Ruijter, J., et al., *Genistein in Sanfilippo disease: a randomized controlled crossover trial.* Ann Neurol, 2012. **71**(1): p. 110-20.
69. Lazarevic, B., et al., *Efficacy and safety of short-term genistein intervention in patients with localized prostate cancer prior to radical prostatectomy: a randomized, placebo-controlled, double-blind Phase 2 clinical trial.* Nutr Cancer, 2011. **63**(6): p. 889-98.
70. Lazarevic, B., et al., *The effects of short-term genistein intervention on prostate biomarker expression in patients with localised prostate cancer before radical prostatectomy.* Br J Nutr, 2012. **108**(12): p. 2138-47.
71. Strom, B.L., et al., *Exposure to soy-based formula in infancy and endocrinological and reproductive outcomes in young adulthood.* JAMA, 2001. **286**(7): p. 807-14.
72. *NCI Guidelines: Adverse Event Reporting Requirements for NCI Investigational Agents*. 2012, National Cancer Institute: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

13 APPENDICES

APPENDIX A: CTCAE

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4

An electronic pdf copy of the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 may be obtained from the CTEP website. The web address is:
http://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf

An online version of the current version of the CTCAE may be accessed at: https://safetyprofiler-ctep.nci.nih.gov/. Please note that searches in the online Safety Profiler must utilize the "literal" button rather than keyword" or enter.

APPENDIX B: STUDY MEDICATION INFORMATION

Product Information

Product Data Sheet

geniVida™ TG

Description

geniVida™ TG is a granular powder. It contains a minimum of 95% genistein, an isoflavone, granulated with pectin.

Product identification

Product code: 50 1159 0

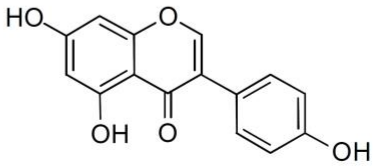
Chemical name: 5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one

Synonyms: genistein

CAS No: 446-72-0

Empirical formula: $C_{15}H_{10}O_5$

Molecular mass: 270.25 g/mol



Specifications

Appearance:	granular powder
Colour:	off-white to pale yellowish or pale orange
Fineness (US standard sieves):	min. 95% through sieve No. 20 max. 40% through sieve No. 100
Identity:	corresponds
Loss on drying:	max. 0.6%
Heavy metals:	max. 10 ppm
Arsenic:	max. 3 ppm
Assay:	min 95% genistein
Microbiological purity:	
• Total aerobic microbial count	max. 10^3 CFU/g
• Total combined yeast/moulds count	max. 10^2 CFU/g
• Enterobacteria	< 10 CFU/g
• Escherichia coli	negative in 10 g
• Salmonella spp.	negative in 25 g
• Staphylococcus aureus	negative in 10 g
• Pseudomonas aeruginosa	negative in 10 g

Stability and storage

geniVida™ TG may be stored for at least 36 months from the date of manufacture in the unopened original container and at a temperature below 25 °C. The 'best use before' date is printed on the label. Keep container tightly closed. Once opened, use contents quickly.

Product Information

Product Data Sheet

geniVida™ TG

Uses

Especially suited for use in capsules and for direct compression of tablets.

Safety

This product is safe for the intended use. Avoid ingestion, inhalation of dust or direct contact by applying suitable protective measures and personal hygiene.

For full safety information and necessary precautions, please refer to the respective DSM Material Safety Data Sheet.

Legal notice

The information given in this publication is based on our current knowledge and experience, and may be used at your discretion and risk. It does not relieve you from carrying out your own precautions and tests. We do not assume any liability in connection with your product or its use. You must comply with all applicable laws and regulations, and observe all third party rights.

DSM Nutritional Products Ltd Product Management Building 241 PO Box 2676 CH-4002 Basel Switzerland	Tel.: +41 (0) 61 815 8899 Fax: +41 (0) 61 815 8390 Internet www.dsmnutritionalproducts.com

DSM Nutritional Products North America 45 Waterview Boulevard Parsippany, NJ 07054-1298	Tel.: +1 (800) 526 0189 (Human Nutrition, Personal Care) Tel.: +1 (800) 451-8325 (Animal Nutrition) Fax: +1 (973) 257 8420 Internet www.unlimitednutrition-na.dsm.com
DSM Nutritional Products Europe AG PO Box 2676 CH-4002 Basel Switzerland	Tel.: +41 (0) 61 815 7777 Fax: +41 (0) 61 815 7770 Internet www.unlimitednutrition-eu.dsm.com
DSM Nutritional Products Asia Pacific Pte Ltd 2 Havelock Road #04-01 Singapore 059763	Tel.: + (65) 66326500 Fax: + (65) 66326600 Internet www.dsmnutritionalproducts.com
DSM Nutritional Products China No. 476, Li Bing Road Zhangjiang High-Tech Park Pudong Area, Shanghai 201203 P.R. of China	Tel.: + 86 (0)21 6141 8188 Fax: + 86 (0)21 6141 8088 Internet www.dsmnutritionalproducts.cn
DSM Produtos Nutricionais Brasil Ltda Caixa Postal 3003 06210-970 São Paulo SP Brasil	Tel.: + 55 (11) 3760-6300 Fax: + 55 (11) 3760-6492 Internet www.dsmnutritionalproducts.com

SAFETY DATA SHEET
according to Regulation (EC) No. 1907/2006

DSM

geniVida™ TG **5011590**

Version 1.1 Revision Date 14.01.2013 Print Date 14.01.2013

1. Identification of the substance/mixture and of the company/undertaking

1.1 Product identifier

Trade name : geniVida™ TG

1.2 Relevant identified uses of the substance or mixture and uses advised against

Use of the Substance/Mixture : Ingredient for capsules and/or tablets

1.3 Details of the supplier of the safety data sheet

Company : DSM Nutritional Products Ltd.
PO Box 2676
CH-4002 Basel
Telephone : +41618158888
Telefax : +41618157253
E-mail address : sds.nutritionalproducts@dsm.com
Responsible/issuing person

1.4 Emergency telephone number

+41 62 866 2314

2. Hazards identification

2.1 Classification of the substance or mixture

Classification (REGULATION (EC) No 1272/2008)

Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.

Classification (67/548/EEC, 1999/45/EC)

Not a hazardous substance or mixture according to EC-directives 67/548/EEC or 1999/45/EC.

2.2 Label elements

Labelling (REGULATION (EC) No 1272/2008)

Not a hazardous substance or mixture according to Regulation (EC) No. 1272/2008.

2.3 Other hazards

Risk of dust explosion.

3. Composition/information on ingredients

Synonyms : genistein

Brief description of the product : Mixture (preparation) containing active ingredient and auxiliary substance

3.2 Mixtures

Remarks : No dangerous ingredients according to Regulation (EC) No. 1907/2006

Further ingredients

Chemical Name	CAS-No.	Classification	GHS Classification	Concentration [%]

6. Accidental release measures

6.1 Personal precautions, protective equipment and emergency procedures

Use personal protective equipment.
Avoid dust formation.

6.2 Environmental precautions

Try to prevent the material from entering drains or water courses.

6.3 Methods and materials for containment and cleaning up

Sweep up and shovel.

6.4 Reference to other sections

For personal protection see section 8.
For disposal considerations see section 13.

7. Handling and storage

7.1 Precautions for safe handling

Advice on safe handling : For personal protection see section 8.
No special handling advice required.

Advice on protection against fire and explosion : Avoid dust formation.
Provide appropriate exhaust ventilation at places where dust is formed.
Take precautionary measures against static discharges.

7.2 Conditions for safe storage, including any incompatibilities

Requirements for storage areas and containers : Keep container tightly closed and dry.

Advice on common storage : No special restrictions on storage with other products.

Storage temperature : < 25 °C

7.3 Specific end use(s)

Specific use(s) : not applicable

8. Exposure controls/personal protection

8.1 Control parameters

Components	CAS-No.	Value (Form of exposure)	Control parameters	Update	Basis
5,7-dihydroxy-3-(4-hydroxyphenyl)-4-benzopyrone	446-72-0	TWA	0,25 mg/m3		DSM Internal Limit

8.2 Exposure controls

Personal protective equipment

Respiratory protection	:	No personal respiratory protective equipment normally required. In case of high dust concentration use a dust mask applicable to local conditions.
Hand protection	:	Glove material: for example nitrile rubber
Eye protection	:	Safety glasses
Skin and body protection	:	Protective suit
Hygiene measures	:	General industrial hygiene practice.

9. Physical and chemical properties

9.1 Information on basic physical and chemical properties

Appearance	:	granular, powder
Colour	:	off-white - pale yellow
Odour	:	No information available.
Odour Threshold	:	No information available.
pH	:	no data available
Melting point/range	:	not determined
Boiling point/boiling range	:	not determined
Flash point	:	not applicable
Flammability (solid, gas)	:	Not classified as flammable as defined by the transport regulations.
Vapour pressure	:	not applicable
Relative vapor density	:	not applicable
Density	:	not determined
Water solubility	:	practically insoluble
Partition coefficient: n-octanol/water	:	log Pow 1,7 (24,5 °C; OECD Test Guideline 117) Information refers to the main component.
Auto-ignition temperature	:	No self ignition observed in the Grewer oven at temperatures below melting point.
Thermal decomposition	:	Not relevant
Explosive properties	:	no data available
Oxidizing properties	:	no data available

9.2 Other information

Combustibility index for deposited dust	:	1 (ca. 21 °C)
Minimum ignition temperature of a dust/air mix	:	> 540 °C determined in the BAM oven

10. Stability and reactivity

10.1 Reactivity

No hazards to be specially mentioned.

10.2 Chemical stability

Stable under recommended storage conditions.

10.3 Possibility of hazardous reactions

Dust may form explosive mixture in air.

10.4 Conditions to avoid

Heat.

10.5 Incompatible materials

Strong acids and strong bases
Strong oxidizing agents

10.6 Hazardous decomposition products

No decomposition if used as directed.

11. Toxicological information

11.1 Information on toxicological effects

Acute oral toxicity	:	LD50 (rat): > 2 000 mg/kg (calculated from LD50 of components)
Skin corrosion/irritation	:	None of the components is classified as an irritant.
Serious eye damage/eye irritation	:	None of the components is classified as an irritant.
Respiratory or skin sensitization	:	None of the components is classified as a sensitiser.
Germ cell mutagenicity		
Genotoxicity in vitro	:	no data available
Carcinogenicity	:	This information is not available.
Reproductive toxicity	:	This information is not available.
STOT - repeated exposure	:	This information is not available.

12. Ecological information

12.1 Toxicity

Toxicity to fish	:	Cyprinus carpio (Carp) LC50 (96 h) > 100 mg/l (nominal concentration) Information refers to the main component. (OECD Test Guideline 203)
Toxicity to algae	:	Scenedesmus capricornutum (fresh water algae) EbC50 (72 h) 3,8 mg/l (OECD Test Guideline 201)
	:	ErC50 (72 h) 9,4 mg/l Information refers to the main component.

12.2 Persistence and degradability

Biodegradability	:	Readily biodegradable. 91 % (28 d) (OECD Test Guideline 301B) Information refers to the main component.

12.3 Bioaccumulative potential

Bioaccumulation	:	no data available
Partition coefficient: n-octanol/water	:	log Pow 1,7 (24,5 °C ; OECD Test Guideline 117) Information refers to the main component.

12.4 Mobility in soil

Distribution among environmental compartments	:	no data available

12.5 Results of PBT and vPvB assessment

Assessment	:	This mixture contains no substance considered to be persistent, bioaccumulating nor toxic (PBT).
	:	This mixture contains no substance considered to be very persistent nor very bioaccumulating (vPvB).

12.6 Other adverse effects

Additional ecological information	:	There is no data available for this product.

13. Disposal considerations

13.1 Waste treatment methods

Product	:	Offer surplus and non-recyclable solutions to a licensed disposal company.
Contaminated packaging	:	Empty containers should be taken to an approved waste handling site for recycling or disposal.

14. Transport information

14.1 UN number

ADR
Not dangerous goods
RID
Not dangerous goods
IMDG
Not dangerous goods
IATA
Not dangerous goods

14.2 Proper shipping name

ADR
Not dangerous goods
RID
Not dangerous goods
IMDG
Not dangerous goods
IATA
Not dangerous goods

14.3 Transport hazard class

ADR
Not dangerous goods
RID
Not dangerous goods
IMDG
Not dangerous goods
IATA
Not dangerous goods

14.4 Packing group

ADR
Not dangerous goods
RID
Not dangerous goods
IMDG
Not dangerous goods
IATA
Not dangerous goods

14.5 Environmental hazards

ADR
Not dangerous goods
RID
Not dangerous goods
IMDG
Not dangerous goods
IATA
Not dangerous goods

14.6 Special precautions for user

Not classified as dangerous in the meaning of transport regulations.

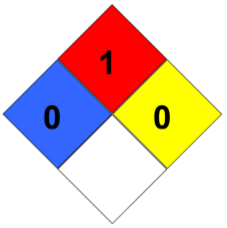
14.7 Transport in bulk according to Annex II of MARPOL 73/78 and the IBC Code

no data available

15. Regulatory information

15.1 Safety, health and environmental regulations/legislation specific for the substance or mixture

NFPA Classification : Health hazard: 0
Fire Hazard: 1
Reactivity Hazard: 0



15.2 Chemical Safety Assessment

not applicable

16. Other information

The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text.

Abbreviations: 67/548/EEC= Dangerous Substances Directive. 1999/45/EC= Dangerous Preparations Directive. Regulation (EC) No. 1272/2008= Regulation on classification, labelling and packaging of substances and mixtures. DNEL= Derived No-Effect Level. PNEC= Predicted No-Effect Concentration. NFPA= National Fire Protection Association (USA). IATA= International Air Transport Association. IMDG= International Maritime Dangerous Goods. RID= International Rule for Transport of Dangerous Substances by Railway; ADR= European Agreement concerning the International Carriage of Dangerous Goods by Road. TWA= Time Weighted Average. STEL= Short term exposure limit.

Genistein Fact Sheet

Protocol Title: A Randomized, Placebo-Controlled Pilot Study of Genistein Supplementation in Pediatric Cancer Patients Receiving Myelosuppressive Chemotherapy (UVa-Gen001)

NOTE: *THIS INFORMATION IS FOR CONFIDENTIAL REVIEW BY HOUSESTAFF AND NURSES ADMINISTERING INVESTIGATIONAL MEDICATION*

NAME AND SYNONYMS:
Chemical Name: 5, 7-dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one
Other Names: i-cool tablets containing 30 mg geniVida™ TG (Product code 5011590)

FORM(S) AND STRENGTH(S):
30 mg/tablet

USUAL DOSE RANGE, SCHEDULE AND ROUTES OF ADMINISTRATION:
Genistein is the main isoflavone component in dietary soy[1]. The genistein concentration of 30 mg is roughly the equivalent of two cups of soy milk. See protocol section 1.3 for more information regarding genistein as a component of dietary soy intake, including safety data.

Concentrations of purified genistein used in adult clinical trials have ranged from 30 – 600 mg/day. Data on the use of purified genistein in pediatric populations is limited. A recent study on children with Sanfilippo disease administered a genistein-rich soy isoflavone extract containing 10 mg/kg/day genistein[2] and a trial on children and adults with lymphoid malignancies used 0.1 – 0.18 mg/kg of an immunoconjugated genistein[3].

1. Sarkar, F.H. and Y. Li, The role of isoflavones in cancer chemoprevention. Front Biosci, 2004. 9: p. 2714-24.
2. de Ruijter J, Valstar MJ, Narajczyk M, Wegrzyn G, Kulik W, Ijlst L, Wagemans T, van der Wal WM, Wijburg FA. Genistein in Sanfilippo disease: a randomized controlled crossover trial. Ann Neurol. 2012 Jan;71(1):110-20. doi: 10.1002/ana.22643.
3. Chen CL, Levine A, Rao A, O'Neill K, Messinger Y, Myers DE, Goldman F, Hurvitz C, Casper JT, Uckun FM. Clinical pharmacokinetics of the CD19 receptor-directed tyrosine kinase inhibitor B43-Genistein in patients with B-lineage lymphoid malignancies. J Clin Pharmacol. 1999 Dec;39(12):1248-55.

OBJECTIVE:
See Protocol Section 2

PROTOCOL DESIGN:
See Protocol Sections 1.1, 4.7.2

PROTOCOL DOSAGE RANGE:
See Protocol Sections 4.7.2 and 5.1.6

PHARMACOLOGY:
Genistein is an isoflavonoid that preferentially binds to estrogen receptor-β, but uses both estrogen receptors α and β to modulate gene expression[1,2]. It inhibits protein-tyrosine kinase and topoisomerase-II. It has been shown to cause G2 phase arrest in human and murine cell lines and displays antineoplastic and antitumorigenic activity[3].

Genistein has a low oral bioavailability due to its extensive metabolism in the intestine and liver[4]. Acid hydrolysis or intestinal microflora-mediated hydrolysis releases ingested genistein from the glucoside genistein. It can then be absorbed or further metabolized to dihydrogenistein or 5-hydroxy-equol[5]. A 50 mg/kg purified genistein dose given to six human subjects resulted in a plasma concentration of 1.26 ± 0.27 μm, a T_{max} of 5.2 hr., and an elimination half-life of 6.8 hr[4].

Genistein's predominate distribution site is controversial. Rat studies have shown higher concentrations of the compound in the intestines, stomach, kidney, liver, lung, heart, brain, plasma, reproductive organs, and brain. The excretion pathways for genistein and its metabolites are intestinal, biliary, and renal[4].

In vivo animal studies have shown that the pharmacokinetics for this compound may be gender-dependent[4].

1. Henley DV, Korach KS. Physiological effects and mechanisms of action of endocrine disrupting chemicals that alter estrogen signaling. Hormones (Athens). 2010 Jul-Sep;9(3):191-205.
2. Rietjens IM1, Sotoca AM, Vervoort J, Louisse J. Mechanisms underlying the dualistic mode of action of major soy isoflavones in relation to cell proliferation and cancer risks. Mol Nutr Food Res. 2013 Jan;57(1):100-13.
3. NIH U.S. National Library of Medicine TOXNET Toxicology Data Network ChemIDplus. "Genistein." Accessed September 22, 2014. http://chem.sis.nlm.nih.gov/chemidplus/rn/446-72-0
4. Yang Z1, Kulkarni K, Zhu W, Hu M. Bioavailability and pharmacokinetics of genistein: mechanistic studies on its ADME. Anticancer Agents Med Chem. 2012 Dec;12(10):1264-80.
5. Behloul N1, Wu G. Genistein: a promising therapeutic agent for obesity and diabetes treatment. Eur J Pharmacol. 2013 Jan 5;698(1-3):31-8.

ADVERSE EFFECTS:

See Protocol Sections 4.7.4, 5.1.7, and genistein safety data sheet section 11.1

By way of comparison, the safety profiles of two commercially-available genistein-containing supplements are listed below.

Fosteum PLUS[1]

"FOSTEUM® PLUS Capsules
calcium compounds (dicalcium malate and pentacalcium hydroxide triphosphate) (500 mg)
phosphate (70 mg)
genistein aglycone (27 mg)
citrated zinc bisglycinate (20 mg)
trans-menaquinone-7 (90 µg)
cholecalciferol (400 IU)

"Recommended dosage: 1 capsule q12 hours (54 mg genistein/day)

"Toxicity:
Genistein showed no toxicity in rats following acute dosing up to 2000 mg/kg. Long-term toxicity studies up to 52 weeks duration using oral administration of 0-500 mg/kg/day in rats and dogs showed minimal adverse effects. From these studies, the no observed adverse effect level (NOAEL) for genistein in rats was determined to be 50 mg/kg/day and in dogs >500 mg/kg/day. These intake levels are at least 50-fold greater than the recommended human dose of the genistein in FOSTEUM PLUS on a mg/kg basis.

"Adverse Events from Fosteum Plus:

In a three-year clinical trial[2], 389 subjects were randomized to either genistein plus calcium and vitamin D3 (n = 198) or calcium and vitamin D3 alone (n=191). A total of 52 subjects in both groups discontinued due to adverse events. Study discontinuation in these subjects was due to gastrointestinal symptoms, including abdominal and epigastric pain, dyspepsia, vomiting and constipation. Discontinuation was reported in both groups. The incidence of adverse events was statistically higher in the genistein group throughout the study. The major adverse events are shown in the table below without attribution of causality.

Adverse Events	Year 1		Year 2		Year 3	
	Genistein +Ca/D3 (n=178)	**Ca/D3 (n=172)**	**Genistein +Ca/D3 (n=150)**	**Ca/D3 (n=154)**	**Genistein +Ca/D3 (n=71)**	**Ca/D3 (n=67)**
Abdominal Pain	4 (2.2%)	2 (1.1%)	2 (1.3%)	1 (0.6%)	1(1.4%)	1(1.5%)
Dyspepsia	2 (1.1%)	1 (0.6%)	7 (4.7%)	2 (1.3%)	2(2.8%)	1(1.5%)
Constipation	5 (2.8%)	3 (1.7%)	8 (5.3%)	3 (1.9%)	2(2.8%)	1(1.5%)

"Some of these adverse event occurrences may be attributable to the intake of 1,000 mg per day of calcium carbonate by subjects in both groups. Taking FOSTEUM PLUS with food may reduce or eliminate some gastrointestinal symptoms."

Citracal Plus[3]
Contents per serving:

Vitamin D	400 IU
Calcium	600 mg
Magnesium	50 mg
Zinc	7.5 mg
Copper	1 mg
Manganese	2 mg
Molybdenum	75 mcg
Genistein	27 mg

1. FosteumPLUS. "Package insert." Accessed September 22, 2014. http://www.fosteumplus.com/professionals/package-insert.php
2. Herbert Marini, MD; Letteria Minutoli, MD; Francesca Polito, PhD; Alessandra Bitto, MD; Domenica Altavilla, PhD; Marco Atteritano, MD; Agostino Gaudio, MD; Susanna Mazzaferro, MD; Alessia Frisina, MD; Nicola Frisina, MD; Carla Lubrano, MD; Michele Bonaiuto, MD; Rosario D'Anna, MD; Maria Letizia Cannata, MD; Francesco Corrado, MD; Elena Bianca Adamo, MD; Steven Wilson, PhD; and Francesco Squadrito, MD. Effects of the Phytoestrogen Genistein on Bone Metabolism in Osteopenic Postmenopausal Women. Ann Intern Med. 2007;146:839-847.
3. CITRACAL® Plus Bone Density Builder. "Supplement facts." Accessed September 22, 2014. http://labeling.bayercare.com/omr/online/citracal-plus-bone-density-builder.pdf

CONTRAINDICATIONS:
Soy allergy

ADMINISTRATION AS PER STUDY:
See Protocol Section 5.1.6

STORAGE AND STABILITY (in vial and infusion form):

See Protocol Section 5.4

PREPARED PER GMP GUIDELINES (suitable for human use): Yes

APPENDIX C: TOXICITIES EXCLUDED FROM SINGLE-EVENT IND SAFETY REPORTING TO THE FDA

See Section 9.2.3.3 for additional information about the submission of these toxicities to the FDA.

Adverse Events	Actinomycin	Carboplatin	Cisplatin	Cyclophosphamide	Daunorubicin	Doxorubicin	Etoposide	Ifosfamide	Topotecan	Vincristine
Myelosuppression	X	X	X	X	X	X	X	X	X	
Anemia	X	X	X	X	X	X	X	X	X	
Leukopenia	X	X	X	X	X	X	X	X	X	X
Neutropenia	X	X	X	X	X	X	X	X	X	
Thrombocytopenia	X	X	X	X	X	X	X	X	X	X
Febrile Neutropenia	X	X	X	X	X	X	X	X	X	
Infection	X	X	X	X	X	X	X	X	X	X
Nausea	X	X	X	X	X	X	X	X	X	X
Vomiting	X	X	X	X	X	X	X	X	X	X
Diarrhea	X	X		X	X	X	X		X	X
Abdominal Pain	X			X	X	X	X		X	X
Anorexia	X			X			X		X	
Mucositis		X			X	X				
Hypersensitivity Reaction		X								
Cardiotoxicity				X	X	X				
Ototoxicity		X	X							
Nephrotoxicity		X	X					X		
Hepatotoxicity	X						X			
Hypomagnesmia		X	X	X						
Hypokalemia		X	X							
Hypocalcemia		X	X							
Hyponatremia		X	X							
Neurotoxicity		X	X					X		X
Neuropathy		X	X							X
Alopecia	X			X	X	X	X	X	X	X