HUMANETICS CORPORATION
Non-Small Cell Lung Cancer (NSCLC)

A Phase I/II Clinical Study Evaluating the Safety and Effectiveness of BIO 300 Oral Suspension in Patients Receiving Chemoradiation Therapy for Non-Small Cell Lung Cancer (NSCLC)

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Sponsor
Humanetics Corporation
[redacted]

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GLOSSARY

4-D CT	4D Computed Tomography
AE	Adverse Event
AFRRI	Armed Forces Radiobiology Research Institute
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area under the plasma concentration versus time curve
BARDA	Biomedical Advanced Research and Development Authority
BMI	Body Mass Index
BP	Blood Pressure
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C	Centigrade
CBC	Complete Blood Count
cc	cubic centimeters
CFR	Code of Federal Regulations
CGE	Cobalt Gray Equivalent
Cmax	Maximum (peak) plasma concentration
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
D(d)	Day
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ER	Estrogen Receptor
F	Fahrenheit
FACT-TOI	Functional Assessment of Cancer Therapy – Trial Outcome Index
FDA	Food and Drug Administration
FDG	Fludeoxyglucose
FEV1	Forced Expiration Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GTV	Gross Tumor Volume
Gy	Gray
H(h)	Hour
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HRQOL	Health-Related Quality of Life
IL	Interleukin

IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
Kg	Kilogram
L	Liter
LBBB	Left Bundle Branch Block
mg	Milligram
MIP	Maximum Intensity Projection
mL	Milliliter
MPS	Mucopolysaccharidoses
MRI	Magnetic Resonance Imaging
msec	Millisecond
MTD	Maximal Tolerated Dose
NA	Not Available
NCI	National Cancer Institute
NDA	New Drug Application
ng	Nanogram
NIH	National Institutes of Health
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
OHRP	Office of Human Research Protection
OS	Overall Survival
P	Pulse
PD	Pharmacodynamic
PET	Positron Emission Tomography
PFS	Progression Free Survival
PFT	Pulmonary Function Test
PK	Pharmacokinetic
PLT	Platelet
PSA	Prostate-Specific Antigen
PVC	Premature Ventricular Contractions
QC	Quality Control
QOL	Quality of Life
QT	Time from ECG Q wave to the end of the T wave
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiotherapy
SOP	Standard Operating Procedure
T	Temperature
T½	Half-life of elimination
TA	Test Article
TBD	To be determined
TGF	Transforming Growth Factor

Tmax	Time to maximum (peak) plasma concentration
TNF	Tumor Necrosis Factor
UCSD-SOB	University of California, San Diego – Shortness of Breath Questionnaire
ULN	Upper Limit of Normal
V#	Visit Number
WBC	White Blood Cell
β hCG	Beta Human Chorionic Gonadotropin

PROTOCOL SYNOPSIS

Protocol Title	A Phase I/II Clinical Study Evaluating the Safety and Effectiveness of BIO 300 Oral Suspension in Patients Receiving Chemoradiation Therapy for Non-Small Cell Lung Cancer (NSCLC)
Protocol Number	CL-0101-01
Sponsor	Humanetics Corporation [redacted]
Study Phase	Phase I/II
Name of Study Drug	BIO 300 Oral Suspension (325 mg/mL)
Investigational Sites	Multiple sites within the United States
Study Objectives	*Primary Objective* The primary objective is to describe any dose limiting toxicities of the combination of BIO 300 with chemoradiotherapy in subjects with NSCLC and to determine the recommended dose (the optimal dose) of this combination. *Secondary Objectives* • To describe the overall adverse event profile of the combination of BIO 300 and chemoradiotherapy in the target patient population • To determine the pharmacokinetics of BIO 300 and the chemotherapy components of the regimen (paclitaxel and carboplatin) when given in combination • To determine the pharmacodynamic effects of BIO 300 in combination with chemoradiotherapy by the determination of certain serum protein and cytokine levels • To report local progression rate as defined per RECIST (1.1) criteria (see Appendix 4). Surgical patients pathological response will be evaluated as defined in Appendix 10. • Pulmonary function test (PFT) and quality of life (QOL) measures (FACT-TOI, USCD-SOB, and swallowing diary) • To study the effect of BIO 300 on the incidence of pulmonary fibrosis following chemoradiotherapy in the target population as assessed by 4D CT scanning • To determine overall survival (OS) and progression free survival (PFS) in the study population

Study Design	This is an open-label, single-arm, ascending dose Phase I/II study of BIO 300 given orally in combination with paclitaxel/carboplatin and radiotherapy in subjects with stage II, III, or IV NSCLC who are candidates for combined chemoradiotherapy. ***Phase I/II – Ascending Dose Evaluation of BIO 300 (3 dose levels)*** A minimum of 6 subjects will be accrued sequentially at each dose of BIO 300. BIO 300 will be administered daily for the entire course of concurrent chemoradiotherapy, a minimum of 6 weeks; chemotherapy will be administered weekly for 6 weeks and radiotherapy will be administered daily (M-F) for approximately 6-7 weeks. The initial dose of BIO 300 will be 500 mg/d; subsequent doses will be 1000 mg/d and 1500 mg/d. Paclitaxel and carboplatin will be administered intravenously weekly, paclitaxel in a dose of 45 mg/m^2 and carboplatin in a dose sufficient to achieve an AUC of 2 mg*min/mL. Radiotherapy will be administered 5 days a week (M-F) for approximately 6-7 weeks in a daily fraction of 1.8-2.0 Gy to a total dose of 60-70 Gy. The initial dose of BIO 300 will be administered on Day 1, Visit 2, in which safety data (adverse events, ECGs, results of safety laboratory determinations), pharmacokinetic (PK) and pharmacodynamic (PD) data will be collected. PK data will be collected from a minimum of six (6) study participants from each study cohort. Blood samples for PD data collection will be collected prior to and post BIO 300 dosing (2 hr) from all subjects in each study cohort. Day 1 of *chemotherapy* may be scheduled at the discretion of the investigator provided the subject has completed a minimum of 1 day of BIO 300 dosing. BIO 300 will be administered in combination with the chemotherapy components of the protocol therapy (paclitaxel and carboplatin). During the first or second chemotherapy infusion, as before, additional safety, PK and PD data will be collected. Blood samples for PD data collection will be collected prior to and post BIO 300 dosing (2 hr) from all subjects in each study cohort. Day 1 of *radiation therapy* (RT) may be scheduled at the discretion of the investigator provided the subject has completed a minimum of 2 days of BIO 300 dosing. BIO 300 will continue to be administered daily; paclitaxel and carboplatin will be administered weekly and radiotherapy will be administered daily as described above until a total dose of 60-70 Gy has been administered. During the period of

	combined BIO 300 and chemoradiotherapy (approximately 6-7 weeks), additional safety, PK and PD data will be collected weekly. Trough levels for BIO 300, paclitaxel, and carboplatin will be collected weekly. Blood samples for PD data collection will be collected weekly during the combined BIO 300 and chemoradiotherapy period at the same time as the trough levels, just prior to that week's chemotherapy treatment and that days' BIO 300 dose. Total duration of BIO 300 treatment will be a minimum of 6 weeks. Blood samples for PD data will also be collected at the end of the consolidation phase, and at the 3 and 6 months follow up visits. Following accrual of 6 subjects at a particular BIO 300 dose level, dose escalation may occur when a cohort has completed concurrent chemoradiotherapy with fewer than 33% DLTs attributed to BIO 300 Oral Suspension. Interim data analysis will be completed once the highest cohort concludes chemoradiation therapy, in an effort to determine the optimal biological dose. Following analysis, there will be an option to enroll up to an additional 12 subjects at the optimal biological dose. At the conclusion of the study, data will be analyzed from all cohorts to determine the oncologic response, safety of BIO 300, and a recommended BIO 300 dose. Reporting of local progression rate as defined per RECIST (1.1) criteria will be done for all subjects in each of the cohorts (see Appendix 4). Surgical patients pathological response will be evaluated as defined in Appendix 10. In addition, quality of life will be assessed using the Functional Assessment of Cancer Therapy – Trial Outcome Index (FACT-TOI). The rate of FACT-TOI decline at 3 months post concurrent chemoradiation therapy completion will be measured. Additional quality of life measures will also be used, including a swallowing diary and the University of California – San Diego (UCSD) shortness of breath (SOB) questionnaire. Subjects will undergo long-term follow-up after the completion of therapy to determine overall survival (OS), progression free survival (PFS), and the effect of BIO 300 on pulmonary fibrosis.
Inclusion Criteria	*Subjects must fulfill all of the following inclusion criteria:* 1) Age $\geq$ 18 2) Histological or cytological confirmation of NSCLC (sputum cytology will not be adequate evidence of malignancy) 3) Subjects diagnosed with stage II, III, or IV (oligometastatic) NSCLC for whom radiation

	therapy of 60-70 Gy and concurrent weekly paclitaxel/carboplatin is recommended as part of potentially curative therapy either alone or preoperatively. 4) Up to three small (≤ 3 cm each) lung oligometastases will be allowed and/or one oligometastasis at any other/or site in the body. These could be treated with focused SBRT (Stereotactic Body RT). 5) ECOG PS of 0 or 1 (Appendix 6) 6) FEV1: best value obtained pre- or post-bronchodilator must be ≥ 1.0 liters/second or > 50% predicted value 7) Adequate bone marrow reserve based on a. WBC ≥ 3,000/μL b. ANC ≥ 1,500/μL c. PLT ≥ 100,000/μL d. HGB ≥ 9 g/dL 8) Adequate hepatic reserve as evidenced by ALT/AST ≤ 3X ULN for the reference lab and bilirubin ≤ 1.5 mg/dL (except in subjects with known Gilbert's syndrome, where the bilirubin may be ≤ 2.0 mg/dL) 9) Adequate renal function as evidenced by a serum creatinine ≤ 1.5 X ULN for the reference laboratory OR a calculated creatinine clearance of ≥ 60 mL/min by the Cockroft-Gault equation 10) Female subjects of childbearing potential must have a negative pregnancy test within 72 hours of the start of treatment 11) Female subjects of childbearing potential and male subjects with female sexual partners of childbearing potential must agree to use an effective method of contraception (e.g., oral contraceptives, double-barrier methods such as a condom and a diaphragm, intrauterine device) during the study and for 90 days following the last dose of study medication or to abstain from sexual intercourse for this time; a woman not of childbearing potential is one who has undergone bilateral oophorectomies or who is post-menopausal, defined as no menstrual periods for 12 consecutive months 12) Ability to read and provide written informed consent
Exclusion Criteria	*Subjects may not have any of the following exclusion criteria:*

	1) Weight loss greater than 10% in prior 4 weeks 2) Prior malignancy in which they received any thoracic radiotherapy unless the treating physician considers it unlikely to impact the clinical outcome of the patient. 3) Patients with concurrent invasive malignancy other than non-melanoma skin cancer or cervical intraepithelial neoplasia unless the treating physician considers it unlikely to impact the clinical outcome of the patient. 4) An active infection or with a fever ≥ 38.5°C within 3 days of the first scheduled day of dosing 5) Poorly controlled intercurrent illnesses, such as uncontrolled hypertension; poorly controlled diabetes mellitus, defined as the need for hospitalization 2 or more times in the preceding 12 months. Patient may not have had any of the following within 6 months prior to study entry: unstable angina; history of myocardial infarction, acute coronary syndrome; history of congestive heart failure; cardiac arrhythmias requiring medical therapy or a pacemaker; cerebrovascular events. 6) Patients with a prior thoracotomy within 1 week of study registration. 7) Chronic Obstructive Pulmonary Disease (COPD) exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration 8) Patients with any of the following are not eligible; a. Previous history of QTc prolongation resulting from medication that required discontinuation of that medication; b. Congenital long QT syndrome, or 1st degree relative with unexplained sudden death under 40 years of age; c. Presence of left bundle branch block (LBBB); d. QTc with Fridericia's correction that is unmeasurable, or ≥ 480 msec on screening ECG. The average QTc from the screening ECG (completed in triplicate) must be < 480 msec in order for the patient to be eligible for the study; e. Subjects taking any concomitant medication that may cause QTc prolongation, induce Torsades de Pointes (see Appendix 2) are not eligible if QTc ≥ 460 msec.

	9) Patients must not have had a clinically significant cardiac event such as myocardial infarction (within 6 months prior to the first dose of the study treatment); uncontrolled/symptomatic congestive heart failure (New York Heart Association (NYHA) classification of heart disease, Class III or IV, see Appendix 3) within 6 months before entry; or the presence of any other uncontrolled cardiovascular conditions (hypertension or arrhythmia, unstable angina pectoris, or severe valvular heart disease, etc.) that, in the opinion of the Investigator, increases the risk of ventricular arrhythmia. 10) Patients with a history of arrhythmia (multifocal premature ventricular contractions (PVCs), bigeminy, trigeminy, ventricular tachycardia, or uncontrolled atrial fibrillation) which is symptomatic or requires treatment (CTCAE Grade 3) or asymptomatic sustained ventricular tachycardia are not eligible. Patients with atrial fibrillation with well-controlled ventricular rate on medication, are eligible. 11) Psychiatric conditions, social situations or substance abuse that precludes the ability of the subject to cooperate with the requirements of the trial and protocol therapy 12) Grade 2 or higher peripheral neuropathy 13) Known history of HIV/AIDS, hepatitis B or C. Note, however, that HIV or hepatitis testing is not required for entry into this protocol. The need to exclude patients with AIDS, hepatitis B or C from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients. 14) Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be teratogenic. 15) Women who are breastfeeding are not eligible for this study.
Number of Subjects	Up to thirty-six (36) male and female subjects who give informed consent and fulfill the selection criteria will be

	enrolled into the trial. Three cohorts will be completed sequentially; each will accrue a minimum of 6 subjects. Once the third cohort has completed chemoradiation therapy and interim data analysis has determined the optimal biological dose of BIO 300, up to an additional 12 subjects will be enrolled at that dose.
Dose Escalation Criteria	A minimum of 6 subjects will be treated per dose level. Dose escalation may occur when a cohort has completed concurrent chemoradiotherapy with less than 33% DLTs attributable to BIO 300 Oral Suspension. If one or fewer DLTs occur, the dose will be escalated to the next cohort of 6 subjects. If 2 DLTs occur (2/6 subjects), an additional 2 subjects will be treated with the same dose. If no additional DLTs occur (2/8 subjects), dose escalation may proceed. If 1 additional DLT occurs (3/8 subjects), an additional 2 subjects will be treated at the same dose for a total of 10 subjects. If no additional DLTs occur (3/10 subjects), dose escalation may proceed. The study sponsor will temporarily cease enrollment for evaluation if in any given cohort 4 subjects (out of a total of 10) experience DLTs attributable to BIO 300 Oral Suspension as the MTD will have been exceeded.
Protocol Therapy	BIO 300 will be administered once daily orally as an aqueous nanosuspension at the dose currently open to enrollment. Paclitaxel will be administered intravenously weekly during radiotherapy in a dose of 45 mg/m^2. Carboplatin will be administered intravenously weekly during radiotherapy in a dose designed to achieve an AUC of 2 mg*min/mL. Radiotherapy will be administered 5 days a week (M-F) in fractions of 1.8-2.0 Gy to total dose of 60-70 Gy over approximately 6-7 weeks. Following completion of the protocol prescribed chemoradiotherapy, subjects with unresectable/medically inoperable disease will receive consolidation chemotherapy consisting of an additional 2 cycles of paclitaxel 200 mg/m^2 and carboplatin administered to achieve an AUC of 6 mg*min/mL on Day 1 of a 3-week cycle. Subjects with potentially resectable disease will be evaluated for surgery and restaged. If the patient is deemed fit and an appropriate candidate for surgery, surgery will occur approximately 6-12 weeks post concurrent chemoradiation with consolidation chemotherapy scheduled 6-12 weeks following surgery.
Duration of Study Treatment	BIO 300 treatment will be approximately 6-7 weeks in duration, in combination with chemoradiotherapy. BIO 300

	treatment will be given daily until concurrent chemoradiation therapy is completed. Subjects will receive consolidation chemotherapy consisting of paclitaxel and carboplatin administration at the conclusion of the concurrent chemoradiation treatments or after surgery. Carboplatin will be given after paclitaxel, both will be administered by intravenous drip once every 21 days for two cycles.
Study Procedures	See Schedule of Assessments
Criteria for Evaluation	*Safety* Safety of the combination of BIO 300 and chemoradiotherapy will be based on the reporting of adverse events by study subjects; by findings on physical exam; by determination of vital signs (blood pressure, pulse, temperature, respiratory rate and weight); by findings on ECGs; and the results of safety laboratory tests (complete blood counts, serum chemistries, urinalyses). *Pharmacokinetics* The pharmacokinetics of BIO 300 and the chemotherapy agents that compose protocol therapy (paclitaxel and carboplatin) will be determined by measures of the serum levels of total genistein, free genistein, paclitaxel and carboplatin. Standard pharmacokinetic parameters (Cmax, Tmax, AUC, half-life, Vd, etc.) will then be derived from these measured serum levels. *Pharmacodynamics* The pharmacodynamic effect of BIO 300 alone and in combination with chemoradiotherapy will be determined by the measurement of certain serum protein and cytokine levels. Cytokine markers may include IL-6, IL-1α, IL-1β, IL-8, IL-10, TNFα, TGFβ1, TGFβ2, and TGFβ3. Potential serum proteins of interest include granulocyte colony stimulating factor (G-CSF), C-reactive protein, and prostaglandin E2. *Efficacy* The local progression rate as defined per the RECIST 1.1 criteria (Appendix 4) will be used to assess the near-term efficacy of the combination of BIO 300 and chemoradiotherapy. Surgical patients pathological response will be evaluated as defined in Appendix 10. In addition, PFTs and a swallowing diary will be used to assess safety of BIO 300 Oral Suspension. The longer-term efficacy of this combination will be based for the determination of overall and progression-free survival and for the incidence of pulmonary fibrosis as determined by 4D CT scanning. Quality of life

	assessments using the UCSD-SOB, swallowing diary, and FACT-TOI will be used to evaluate both the short-term and the long-term efficacy of the combined therapy.

1.0 INTRODUCTION

1.1 Disease Background

Lung cancer is the third most common cancer and the most common cause of cancer related mortality in the United States [1, 2]. It is estimated that 224,210 new cases of lung and bronchus cancer will be diagnosed in 2014 while it is estimated that 159,260 people die of the disease [2]. Approximately 75-80% of all lung cancer cases are non-small cell lung cancer (NSCLC). Approximately 55% of these cancer patients will receive some form of radiotherapy. Radiotherapy not only damages cancer cells but can also damage the healthy cells located near the tumor site resulting in side effects that are often dose limiting. Side effects from lung cancer radiation treatment include pneumonitis and lung fibrosis, each of which can diminish the quality of life following treatment.

1.2 Background of the Study Drug

The active pharmaceutical ingredient in BIO 300 Oral Suspension is unconjugated, synthetically prepared, highly pure form of genistein (5,7-dihydroxy-3-(4-hydroxyphenyl)-chromen-4-one) [redacted] Genistein was originally isolated by Perkin and Newbury in 1899 from Dyer's Broom (Genista tinctoria). This naturally derived compound is a member of the isoflavone branch of the flavonoid family of small molecules, which includes over 5,000 compounds. The isoflavones are structurally characterized by their 3-phenylchromen-4-one backbone, which consists of two benzene rings linked by a heterocyclic pyran ring. In addition to this heterocyclic core, genistein and its related isoflavone family members are polyphenols, in that they contain several hydroxyl groups attached to core phenyl rings. These phenols lend significant antioxidant activity to this class of compounds, exhibiting significant activity against free radicals in tissue [3]. Importantly, genistein is a recognized protein tyrosine kinase inhibitor [3]. Although this has not been proven, this activity is presumed to stem from genistein's C4′ phenolic group, which structurally resembles the phosphoacceptor moiety of tyrosine [4].

BIO 300 Oral Suspension is a unique nanoparticle suspension of genistein that is being developed for the protection of normal tissues and as an adjunctive treatment for solid tumor cancers in patients undergoing radiation or chemoradiation therapy. The radioprotective effects of genistein were discovered by researchers at the Armed Forces Radiobiology Research Institute (AFRRI) and subsequently licensed to Humanetics Corporation for commercial development (U.S. Patent 7,655,694). [redacted]

Table 1.2.1 BIO 300 Oral Suspension Formulation

BIO 300 Oral Suspension	Amount (mg/mL)	Function
Genistein (BIO 300)	325	Active Ingredient
Polysorbate 80	2	Wetting Agent
Povidone K25	50	Suspending Agent
Methylparaben	1.8	Preservative
Propylparaben	0.2	Preservative
Water for Irrigation	Q.S	Carrier/Vehicle

[redacted]

[redacted]

Published trials with related products have reported minimal toxicity. A clinical trial in children with mucopolysaccharidoses (MPS) disorders administered 150 mg/kg/day of geniVida® for up to two years and found no definite evidence of any serious toxicity based on either clinical or laboratory findings [5]. Fischer *et al.* reported administration up to 600 mg genistein a day for 84 days resulted in minor estrogenic effects including breast changes and hot flashes, in addition to constipation, edema, hypocalcemia, and elevated serum amylase [6] Pop *et al.* reported no clinically significant changes in estrogenic/antiestrogenic laboratory measurements and no changes in blood pressure after 600 mg of genistein for 84 days [7].

[redacted]

[redacted]

[redacted]

[redacted]

1.4 Rationale for Proposed Therapeutic Study

NSCLC is very difficult to cure and significant toxicities are associated with current chemotherapy and chemoradiotherapy treatment regimens. Chemoradiation-induced toxicities such as esophagitis and pneumonitis have the potential to negatively impact the quality of life following treatment and/or may even be dose-limiting. Late lung fibrosis following radiation-induced pneumonitis can be a significant side effect seen in lung cancer patients. These radiotoxicities are a major barrier to improving the cure rate and well-being of cancer patients, because these maladies can limit the effective radiation dose and diminish normal lung function. The currently accepted standard of care for patients with locally-advanced NSCLC is radiation plus chemotherapy followed by surgery in select patients. Common chemotherapy agents utilized in current chemoradiation treatment regimens include carboplatin and paclitaxel. In this study we aim to evaluate the safety and effectiveness of BIO 300 Oral Suspension in reducing the toxicities of chemotherapy and radiotherapy, and preventing tumor recurrence in patients with NSCLC. In addition, because BIO 300 has the potential to function as a radiosensitizer and radioprotectant, the study is being designed to assess those capabilities by including patients for whom radiation therapy of 60-70 Gy and concurrent weekly paclitaxel/carboplatin is recommended as part of potentially curative therapy either alone or preoperatively.

[redacted]

[redacted]

[redacted]

2.0 OBJECTIVES

2.1 Primary

The primary objective is to describe any dose limiting toxicities of the combination of BIO 300 Oral Suspension with chemoradiotherapy in subjects with NSCLC and to determine the recommended dose (the optimal dose) of this combination.

2.2 Secondary

To evaluate the pharmacokinetic (PK) profile of BIO 300 Oral Suspension, and carboplatin and paclitaxel when given in combination with BIO 300 Oral Suspension. The objective is to assess any drug-drug interactions between BIO 300 and the chemotherapeutics.

To describe the overall adverse event profile of the combination of BIO 300 Oral Suspension and chemoradiotherapy in the target patient population.

To describe the pharmacodynamic effects of BIO 300 Oral Suspension alone and in combination with chemoradiotherapy by the determination of certain serum protein and cytokine levels.

To report local progression rate as defined per RECIST (1.1) criteria (Appendix 4). Surgical patients will be evaluated as defined via pathological response (Appendix 10).

To measure pulmonary function (PFT) and QOL (swallowing diary, FACT-TOI and USCD-SOB).

To describe the effect of BIO 300 Oral Suspension on the incidence of pulmonary fibrosis following chemoradiotherapy in the target population as assessed by 4D CT scanning.

To determine overall and progression free survival (PFS) in the study population.

3.0 STUDY DESIGN

This study is an open label, dose escalation trial with sequential cohorts of subjects receiving BIO 300 Oral Suspension and chemoradiation therapy. Three doses of BIO 300 Oral Suspension (500 mg/d, 1000 mg/d, and 1500 mg/d) will be administered during the course of concurrent chemoradiation therapy. Each cohort will begin with a study of the pharmacokinetics of BIO 300 Oral Suspension followed by a pharmacokinetic study of BIO 300 Oral Suspension in combination with paclitaxel and carboplatin. This is to describe any potential drug-drug interactions of BIO 300 Oral Suspension with the chemotherapeutics. The subjects will complete six (6) weeks of concurrent chemoradiation therapy while continuing daily BIO 300 Oral Suspension dosing. Following chemoradiation therapy patients will complete consolidation therapy as described below. During consolidation therapy patients will not be dosed with the study drug.

3.1 Chemotherapy Dose Levels

Patients should be treated at the following dose levels:

Table 3.1.1 Paclitaxel and Carboplatin Dosing Scheme

Dose Levels of Paclitaxel and Carboplatin		
	Starting Dose	Dose Level -1
Concurrent Therapy[a]		
Paclitaxel	45 mg/m^2	NA
Carboplatin	AUC=2.0	NA
Consolidation Therapy[b]		
Paclitaxel	200 mg/m^2	150 mg/m^2
Carboplatin	AUC=6 mg*min/mL	AUC=5.0 mg*min/mL

[a] For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.
[b] For consolidation therapy, dose reductions of paclitaxel and carboplatin below the -1 dose level will not be allowed.

3.2 Consolidation Treatment

Patients will receive consolidation chemotherapy consisting of paclitaxel and carboplatin. Following completion of the protocol prescribed chemoradiotherapy, subjects with unresectable/medically inoperable disease will receive consolidation chemotherapy within the one-month post completion of concurrent chemoradiation. Subjects with potentially resectable disease will be evaluated for surgery and restaged. If the patient is deemed fit and an appropriate candidate for surgery, consolidation chemotherapy will be scheduled 6-12 weeks following surgery.

1) To begin consolidation chemotherapy, all previous toxicities including neuropathy must have resolved to < grade 2, CTCAE, v4.03.
2) If the patient is unable to initiate consolidation chemotherapy at the specified time points, the chemotherapy may be delayed up to an additional 4 weeks. If the chemotherapy cannot be given during this time interval, protocol treatment will be discontinued.
3) Carboplatin will be given after paclitaxel. Both paclitaxel and carboplatin will be administered by intravenous drip q 21 days x 2.
4) Carboplatin, AUC=6 mg*min/mL, will be given over approximately 30 minutes with standard anti-emetics.
5) Paclitaxel, 200 mg/m^2, will be given over approximately 3 hours with standard premedication, such as consisting of diphenhydramine 25-50 mg, an H2-blocker, and dexamethasone (oral or intravenous is acceptable according to local custom) at least 30 minutes prior to paclitaxel.

3.3 Study Overview - Phase I/II Dose Escalation Trial

Table 3.3.1 Treatment Overview

Concurrent Therapy	Dose	Schedule
Paclitaxel	45 mg/m^2 weekly	Weekly, wk 1-6
Carboplatin	AUC = 2 mg*min/mL	Weekly, wk 1-6
Radiation	60-70 Gy (1.8-2.0 Gy per fraction) 5X per week for approximately 6-7 weeks	Daily, 5d/wk, wk 1-6 or 7
BIO 300 Oral Suspension	Cohort 1: 500 mg/d Cohort 2: 1000 mg/d Cohort 3: 1500 mg/d Cohort 4: optimal dose TBD mg/d*	Daily, 7d/wk, (day 1 through conclusion of RT)

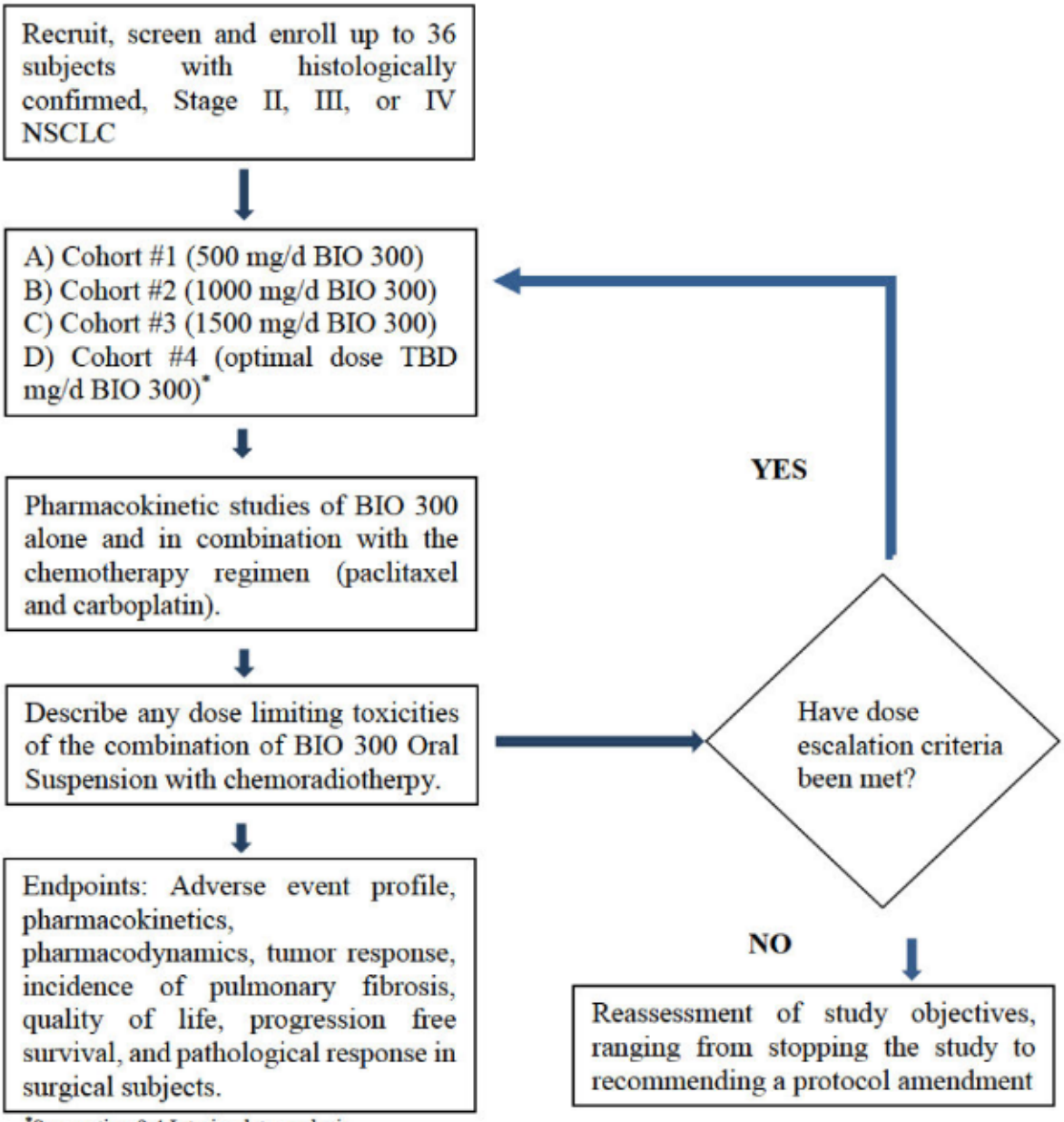
*See Section 9.4 Interim data analysis.

3.3.1 Schema of Trial Design

A Phase I/II Clinical Study Evaluating the Safety and Effectiveness of BIO 300 Oral Suspension in Patients Receiving Chemoradiation Therapy for Non-Small Cell Lung Cancer (NSCLC)

BIO 300 Oral Suspension Dose Escalation (3 cohorts with a minimum of 6 subjects per cohort)

Figure 3.3.1 Schema of Trial Design



*See section 9.4 Interim data analysis

4.0 SUBJECTS

4.1 Number of Subjects

Up to thirty-six (36) male and female subjects who give informed consent and fulfill the selection criteria will be recruited and enrolled into the trial. Three cohorts will be completed sequentially; each will accrue a minimum of 6 subjects. Once the third cohort has completed chemoradiation therapy and interim data analysis has determined the optimal biological BIO 300 dose, there will be an option to enroll up to an additional 12 subjects at that dose (see section 9.4 for selection of optimal dose).

4.2 Subject Eligibility

Prior to enrollment into the study, subjects must meet all inclusion criteria and not meet any of the exclusion criteria. If the Principal Investigator has any questions on a subject's eligibility, the sponsor will contact the Medical Monitor to review and to make a final determination of eligibility.

4.2.1 Inclusion Criteria

1) Age ≥ 18.
2) Histological or cytological confirmation of NSCLC (sputum cytology will not be adequate evidence of malignancy).
3) Patients diagnosed with stage II, III, or IV (oligometastatic) NSCLC for whom radiation therapy of 60-70 Gy and concurrent weekly paclitaxel/carboplatin is recommended as part of potentially curative therapy either alone or preoperatively. If a pleural effusion is present, the following criteria must be met to exclude malignant involvement (incurable M1a disease):
    a) When pleural fluid is visible on both the CT scan and on a chest x-ray, a pleuracentesis is required to confirm that the pleural fluid is cytologically negative, unless the effusion is minimal and/or too small to safely tap.
4) Patients may have ≤ 3 lung oligometastases (each ≤ 3cm) and/or 1 oligometastasis at any other site in the body, based upon the following minimum acceptable diagnostic workup:
    a) History/physical examination within 10 weeks prior to registration
    b) Computed tomographic (CT)/MRI imaging of the lung within 10 weeks prior to registration (NOTE: If a whole body PET/CT was done, a separate CT scan of the chest is not required)
    c) Whole-body FDG-PET or PET/CT; or if no PET is available, a bone scan is required within 10 weeks prior to registration (and CT or MRI must include the liver)
    d) MRI (or CT) imaging of the brain within 10 weeks prior to registration

    Oligometastases may be treated at the discretion of the treating physician.
5) ECOG Performance Status 0-1 (Appendix 6).
6) FEV1: best value obtained pre- or post-bronchodilator must be ≥ 1.0 liters/second or > 50% predicted value.
7) CBC/differential obtained within 4 weeks prior to starting treatment, with adequate bone marrow function defined as follows:
    a) WBC ≥ 3,000/μL

b) Absolute neutrophil count (ANC) ≥ 1,500 cells/μL
c) Platelets ≥ 100,000 cells/μL
d) Hemoglobin ≥ 9.0 g/dL (Note: The use of transfusion or other intervention to achieve HGB ≥ 9.0 g/dL is acceptable.)

8) Adequate hepatic reserve as evidenced by ALT/AST ≤ 3X ULN for the reference lab and bilirubin ≤ 1.5 mg/dL (except in subjects with known Gilbert's syndrome, where the bilirubin may be ≤ 2.0 mg/dL)
9) Adequate renal function as evidenced by a serum creatinine ≤ 1.5X ULN for the reference laboratory OR a calculated creatinine clearance of ≥ 60 mL/min by the Cockroft-Gault equation.
10) Female subjects of childbearing potential must have a negative pregnancy test within 72 hours of the start of treatment.
11) Female subjects of childbearing potential and male subjects with female sexual partners of childbearing potential must agree to use an effective method of contraception (e.g., oral contraceptives, double-barrier methods such as a condom and a diaphragm, intrauterine device) during the study and for 90 days following the last dose of the study medication or to abstain from sexual intercourse for this time; a woman not of childbearing potential is one who has undergone bilateral oophorectomies or who is post-menopausal, defined as no menstrual periods for 12 consecutive months.
12) Patient must be able to read and sign the study specific informed consent prior to study entry.

4.2.2 Exclusion Criteria

1) Weight loss greater than 10% in the prior 4 weeks.
2) Prior malignancy in which they received any thoracic radiotherapy unless the treating physician considers it unlikely to impact the clinical outcome of the patient.
3) Patients with concurrent invasive malignancy other than non-melanoma skin cancer or cervical intraepithelial neoplasia unless the treating physician considers it unlikely to impact the clinical outcome of the patient.
4) An active infection or with a fever ≥ 38.5°C within 3 days of the first scheduled day of dosing.
5) Poorly controlled intercurrent illnesses, such as;
   a) uncontrolled hypertension;
   b) poorly controlled diabetes mellitus, defined as the need for hospitalization 2 or more times in the preceding 12 months.
   c) unstable angina; history of myocardial infarction or acute coronary syndrome within 6 months prior to study entry;
   d) history of congestive heart failure within 6 months of study entry;
   e) cardiac arrhythmias requiring medical therapy or a pacemaker; cerebrovascular events within 6 months prior to study entry;
6) Patients with a prior thoracotomy within 1 week of study registration.
7) Chronic Obstructive Pulmonary Disease (COPD) exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before starting treatment.

8) Patients with any of the following are not eligible;
   a) Previous history of QTc prolongation resulting from medication that required discontinuation of that medication;
   b) Congenital long QT syndrome, or 1st degree relative with unexplained sudden death under 40 years of age;
   c) Presence of left bundle branch block (LBBB);
   d) QTc with Fridericia's correction that is unmeasurable, or ≥ 480 msec on screening ECG. The average QTc from the screening ECGs (completed in triplicate) must be < 480 msec in order for the patient to be eligible for the study;
   e) Subjects taking any concomitant medication that may cause QTc prolongation, induce Torsades de Pointes (see Appendix 2) are not eligible if QTc ≥ 460 msec.
9) Patients must not have had a clinically significant cardiac event such as myocardial infarction (within 6 months prior to the first dose of the study treatment); uncontrolled/symptomatic congestive heart failure (New York Heart Association (NYHA) classification of heart disease, Class III or IV, see Appendix 3) within 6 months before entry; or the presence of any other uncontrolled cardiovascular conditions (hypertension or arrhythmia, unstable angina pectoris, or severe valvular heart disease, etc.) that, in the opinion of the Investigator, increases the risk of ventricular arrhythmia.
10) Patients with a history of arrhythmia (multifocal premature ventricular contractions (PVCs), bigeminy, trigeminy, ventricular tachycardia, or uncontrolled atrial fibrillation) which is symptomatic or requires treatment (CTCAE Grade 3) or asymptomatic sustained ventricular tachycardia are not eligible. Patients with atrial fibrillation with well-controlled ventricular rate on medication, are eligible.
11) Psychiatric conditions, social situations or substance abuse that precludes the ability of the subject to cooperate with the requirements of the trial and protocol therapy
12) Grade 2 or higher peripheral neuropathy
13) Known history of HIV/AIDS, hepatitis B or C. Note, however, that HIV or hepatitis testing is not required for entry into this protocol. The need to exclude patients with AIDS or hepatitis B or C from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
14) Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be teratogenic.
15) Women who are breastfeeding are not eligible for this study.

4.3 Subject Withdrawal and Replacement

4.3.1 Subject Withdrawal

Subject retention will be determined as the number of subjects who successfully complete the study protocol (this number will include subjects who have inadvertent protocol deviations). Subjects, who drop out, are lost to follow up, or who need to be withdrawn from the study, will be identified and the reason will be coded in the case report form.

4.3.2 Subject Replacement

Subjects that present with an unrelated medical condition (e.g. stroke, myocardial infarction) that is not attributable to the investigational drug will be replaced. Subjects that are unable or unwilling to complete at least 2 weeks of concurrent chemoradiation therapy plus the investigational drug of the study protocol will be replaced. If these subjects have completed through the BIO 300 + Chemo PK visit, the replacement subjects will be assigned to the non-PK subgroup. Additional subjects will be enrolled as needed to fulfill dose escalation criteria (see section 5.5 Dose Escalation Criteria).

4.3.3 Potential Reasons for Subject Attrition

For any subject leaving the study early, the final study measurements will be performed at the time of departure (or as shortly thereafter as possible).

4.3.3.1 Drug-Related Reasons

1) Subject experiences an adverse reaction and does not wish to remain in the trial.
2) Subject experiences a serious adverse reaction or a specific adverse reaction that requires discontinuation according to the protocol as determined by the investigator.
3) Clinical trial is terminated prematurely because of unacceptable safety concerns (risks) of the supplement being tested.

4.3.3.2 Clinical-Trial-Related Reasons

1) Subject indicates the requirements are too onerous, or too long, or loses interest; or refuses to participate.
2) Clinical trial is terminated at a preset date and some subjects are not completed.

4.3.3.3 Subject-Related Reasons Determined by the Investigator

1) Subject fails to maintain adequate compliance with one or more aspects of the protocol or subject fails to cooperate adequately during clinical visits.
2) Subject found not to meet or no longer meets the original entry requirements.
3) Subject has used a non-approved medicine or treatment during the trial.
4) Subject who at the Investigator's discretion feels that continuing in the study would not be in their best interest.
5) Subject becomes pregnant (observation and follow-up procedures must be initiated).
6) Subject withdraws informed consent.

4.3.3.4 Other Reasons

1) Subject refuses to state reasons for dropping out.
2) Subject develops an intercurrent illness and is unable or unwilling to continue in a clinical trial; however, Investigator did not wish to discontinue the subject.
3) Subject's personal situation changes: e.g. more work responsibility/travel or home changes (moves, marries, family) and subject has less time/motivation to participate.
4) Other issues requiring withdrawal of the subject from the trial.

4.3.3.5 Lost to Follow-up

Subject's reasons are unknown because subject does not return for scheduled visits and is inaccessible after three separate attempts to contact. If this occurs, all attempts to locate the subject must be documented in the subject's chart.

4.3.3.6 Death

Efforts will be made to ascertain the cause of death, and to secure appropriate autopsy/pathology reports.

4.4 Criteria for Discontinuation of Subjects from the Trial

Protocol treatment may be discontinued for any of the following reasons:

1) At the discretion of the Investigator, atypical progression of disease;
2) If 40% or more of subjects (4 out of a total of 10) in a cohort experience a DLT attributable to BIO 300 Oral Suspension, the MTD will have been exceeded and enrollment into that cohort and any higher-dose cohort currently open to enrollment will cease (see section 8.5, Dose Limiting Toxicities (DLTs).
3) A delay in protocol treatment of greater than 3 weeks during the concurrent phase and more than 4 weeks in the consolidation chemotherapy phase.
4) Any one of the Dose Limiting Toxicities listed in section 8.5, Dose Limiting Toxicities (DLTs).
5) If protocol treatment is discontinued due to delay or dose limiting toxicity (DLT), at the discontinuation visit, CBC with differential and serum chemistries will be completed for safety reporting. At the discretion of the Investigator, additional follow-up blood work may be requested.
6) If protocol treatment is discontinued for any other reason, at the discretion of the Investigator, CBC with differential and serum chemistries may be requested for safety reporting purposes.

5.0 STUDY DRUG

5.1 Description of Study Drug

5.2 Drug Doses

A fixed daily dose of BIO 300 Oral Suspension, regardless of body surface area (BSA) and body mass index (BMI) will be evaluated in this study. The proposed dose escalation study will evaluate the safety of 500, 1000, and 1500 mg/day of BIO 300 Oral Suspension in the NSCLC patients. Patients will be provided BIO 300 Oral Suspension and oral syringes to dose themselves at home on all non-PK sampling days. Study subjects will be trained on proper dosing and will be provided with written instructions. During clinic visits when PK sampling is required, designated research staff will ensure BIO 300 dose is consumed after blood sampling.

Table 5.2.1 BIO 300 Oral Suspension Dosing

Daily dose of BIO 300 Oral Suspension	Volume administered
500 mg	1.5 mL
1000 mg	3.0 mL
1500 mg	4.5 mL

5.3 Duration of Treatment

The proposed dosing regimen for the drug product is a single daily dose (including weekends) administered until completion of the entire course of concurrent chemoradiation therapy.

5.4 Contraindication

BIO 300 Oral Suspension is manufactured with synthetic genistein, genistein is a naturally occurring isoflavone found in soy. Because BIO 300 Oral Suspension is manufactured using synthetic genistein, it is ***not*** contraindicated for those hypersensitive to soy or those with documented soy allergies. Although teratology studies were negative, it is not known if BIO 300 Oral Suspension will cause harm when administered to pregnant women. If a patient becomes pregnant (or begins breastfeeding) while taking BIO 300 Oral Suspension, the patient is no longer eligible for this trial.

[redacted]

5.5 Criteria for Dose Escalation

A minimum of 6 subjects will be treated per dose level. Dose escalation may occur when a cohort has completed concurrent chemoradiotherapy with less than 33% DLTs (see section 8.5 Dose Limiting Toxicities (DLTs)). If one or fewer DLTs occur, the dose will be escalated to the next cohort of 6 subjects. If 2 DLTs occur (2/6 subjects), an additional 2 subjects will be treated with the same dose. If no additional DLTs occur (2/8 subjects), dose escalation may proceed. If 1 additional DLT occurs (3/8 subjects), an additional 2 subjects will be treated at the same dose for a total of 10 subjects. If no additional DLTs occur (3/10 subjects), dose escalation may proceed.

The study sponsor will temporarily cease enrollment in any given cohort if 4 subjects (out of a total of 10), experience DLTs attributable to BIO 300 Oral Suspension as the MTD

will have been exceeded. The sponsor's medical monitor will assess the safety data collected to date to determine if enrollment should permanently cease at that dose. If the decision is made to cease enrollment, the sponsor and the principal investigators will determine if the dose should cease or be modified for those subjects in that cohort who have not experienced DLTs. The study sponsor, together with the PI, may consider amending the protocol through a modification of the dosing regimen.

[redacted]

5.7 Drug Accountability

This trial will be conducted in compliance with the individual research site's SOP for all study activities. The study medication (BIO 300 Oral Suspension) will be distributed by study staff and recorded in the subject's source document (including the date and time given). The number of BIO 300 Oral Suspension vials distributed will also be recorded on a study drug accounting log as defined in the standard operating procedures.

6.0 CONCURRENT MEDICATIONS AND TREATMENTS

6.1 Paclitaxel

The following is a list of factors that may result in exposure changes in paclitaxel and should be considered prior to administration:

- Caution should be exercised when paclitaxel is concomitantly administrated with known substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelinavir, ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampin and carbamazepine) of CYP34A.
- Caution should be exercised when paclitaxel is concomitantly administered with know substrates (e.g., repaglinide and rosiglitazone), inhibitors (e.g., gemfibrozil), and inducers (e.g., rifampin) of CYP2C8.

Refer to the package insert for detailed pharmacologic, dosing, storage, and safety information.

6.2 Carboplatin

The following is a list of factors that may result in exposure changes in carboplatin and should be considered prior to administration:

- Bone marrow suppression is increased in patients who have received prior therapy, especially regimens including cisplatin
- Marrow suppression is also increased in patients with impaired kidney function such as the elderly

- Use of carboplatin in combination with other bone marrow suppressing therapies must be carefully managed with respect to dosage and timing in order to minimize additive effects
- Renal effects of nephrotoxic compounds may be potentiated by carboplatin
- Concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity, and caution must be exercised when a patient receives both drugs
- Carboplatin can induce emesis, which can be more severe in patients previously receiving emetogenic therapy
- Incidence of peripheral neurotoxicity is increased in patients older than 65 years and in patients previously treated with cisplatin
- Increased risk of allergic reactions including anaphylaxis in patients previously exposed to platinum therapy (platins).

Refer to the package insert for detailed pharmacologic, dosing, storage, and safety information.

6.3 Radiation Therapy

Radiation therapy will begin during week 1 of the study and after a minimum of 2 days of BIO 300 dosing. The type of radiation therapy (3D Conformal Radiation Therapy, Intensity Modulated Radiation Therapy or Proton Beam Radiation Therapy) will be at the discretion of the treating investigator. Patients will receive RT treatment 5 days per week, in once daily fractions, 1.8-2.0 Gy per fraction. The total dose will be 60-70 Gy (cobalt Gy equivalent (CGE)) in 30-35 fractions. There are typically no field reductions. All fields should be treated daily and the entire planning target volume should be treated daily. On days when chemotherapy is given concurrently with RT, chemotherapy should ideally be administered prior to RT.

6.3.1 Adverse Events Reported with Radiation Therapy

Bone marrow toxicity, skin pigmentation, esophagitis and radiation pneumonitis are expected side effects of radiation therapy. Radiation induced myocarditis or transverse myelitis rarely occur. Radiographic evidence of radiation change and subsequent fibrosis of the lung will occur within lung volume of some patients receiving ≥20 Gy, usually within the first six months after initiation of treatment; the incidence of radiation induced pneumonitis is about 15-20%. It is essential to spare as much normal lung as possible in order to avoid symptomatic lung injury.

Radiation pneumonitis is a lung toxicity that is a side effect of chemoradiotherapy for lung cancer. It is characterized by edema, diffuse alveolar damage, desquamation of the capillary endothelium, and the development of hyaline membranes. Symptoms include shortness of breath, cough, fatigue, and loss of appetite. The incidence of radiation pneumonitis typically peaks between 2 and 4 months following the completion of radiotherapy. The lung may recover, but pneumonitis increases the risk of developing subsequent pulmonary complications, including permanent scaring of the lungs (fibrosis). A CT scan is used to detect this type of radiation-induced lung injury. Common CT

findings include ground-glass opacities and consolidation of airspace. Pneumonitis will be scored and documented on the CRF based on the table described in Appendix 11.

Esophagitis, esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration and nutrition. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous Xylocaine, Carafate, or other medications should be used for symptomatic relief. Occasionally, narcotics may be required.

If Grade 4 esophagitis occurs, and a treatment interruption is being considered, every effort should be made to limit it to 3 treatment days or less. Patients requiring hospitalization because of esophagitis may have their treatment interrupted. In this event, the site will notify the study sponsor.

Esophagitis should be graded according to the CTCAE v4.03

Table 6.3.1.1 Esophagitis grading system

Grade	Clinical Scenario
1	Asymptomatic pathologic, radiographic, or endoscopic findings only
2	Symptomatic; altered eating/swallowing (e.g., altered dietary habits, oral supplements), IV fluids indicated <24 hrs
3	Symptomatic and severely altered eating/swallowing (e.g., inadequate oral caloric or fluid intake), IV fluids, tube feedings, or TPN indicated >24 hrs
4	Life-threatening consequences
5	Death

Treatment should be interrupted for grade 4 or greater dysphagia or odynophagia. Acute esophageal toxicity, which typically can occur within two weeks of the initiation of treatment and manifests as dysphagia, odynophagia, reflux symptoms, etc. should be pharmacologically managed with the following approach and should be initiated at the first signs or symptoms of esophageal toxicity. Recommended treatments are in Table 6.3.1.2.

Table 6.3.1.2 Suggestions for management of radiation esophagitis

	Treatment Course	Notes
1	Mixture of: 2% viscous lidocaine: 60 cc Mylanta: 30 cc sucralfate (1 gm/cc): 10 cc Take 15-30 cc PO q3-4 hrs prn.	*Contraindications: pts on Dilantin, Cipro, Digoxin*
2	Ranitidine 150 mg PO BID (or other H2 blocker or a proton pump inhibitor such as omeprazole) until the completion of radiation	
3	Grade 4 esophagitis: hold RT + chemotherapy until grade 2 or less. We expect a significant portion of patients will experience grade 3 esophagitis.	
4	Ketoconazole 200 mg PO q day	Consider as clinically indicated
5	Fluconazole 100 mg PO q day until the completion of radiation	Consider as clinically indicated

6.4 Concomitant Therapies and Medications

Though no data have shown that any concomitant medications will interfere with BIO 300 Oral Suspension, it is advisable that patients not take any other medication(s) 1 hour before or after a dose of BIO 300 Oral Suspension. Concomitant medications will be collected for all subjects from the screening visit through consolidation chemotherapy. Patients on concomitant medications (see Appendix 2) that may prolong QTc are prohibited if QTc ≥ 460 msec.

Co-administration of drugs that in some reports might be associated with Torsades de Pointes, but at this time lack substantial evidence, should be avoided if possible (see Appendix 2). However, these drugs will be allowed, at the discretion of the investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored including regular checks of QTc and electrolytes. The ECG must be checked within 24 hours of commencing the concomitant medication and then at least once per week while the patient remains on the medication. The frequency of ECG monitoring could revert to the standard schedule if no ECG prolongation has been noted during the first two (2) weeks of co-administration of a drug that may cause QTc prolongation (see Appendix 2). Electrolytes should be maintained within the normal range using supplements if necessary.

Permitted supportive therapy

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

Nausea, vomiting or both may be controlled with antiemetic therapy. 5HT-3 antagonists may prolong QTc interval risk with the use of Ondansetron. Increased monitoring is suggested.

Therapies not permitted

WBC growth factors (G-CSF/GM-CSF) will not be permitted during radiation. If a patient receives WBC growth factors during radiation, this constitutes a major protocol violation. WBC growth factors may be used during consolidation chemotherapy in accordance with ASCO guidelines, but should not be given prophylactically. Erythropoietin may be given at the treating physician's discretion in accordance with accepted guidelines.

High doses of glucocorticoids (e.g., > 20 mg of Prednisone/day or equivalence) and immunosuppressants should not be used.

Immunotherapy

Immunotherapies (*e.g.,* durvalumab, pembrolizumab or nivolumab) may be initated after the completion of concurrent chemoradiotherapy at the discretion of the treating physician. Immunotherapeutics will be not be collected on the Concomitant Medication CRF but instead will be documented separately on the Immunotherpy CRF. Data from the CRF will be verified against the subject medical chart for accuracy.

Soy products, supplements, and diet

Study subjects will be requested to maintain a low isoflavone diet for the duration of the study. Subjects will be provided a list of dietary requirements for the study and encouraged to maintain their diet in an acceptable range. Adherence will be monitored weekly.

Study subjects will not be permitted to take soy containing or genistein containing supplements during the course of the study.

6.5 Guidelines for Dose Delay and Dose Modification

The guidelines for dosing delay, and any dose modification, for the chemotherapeutics, radiation therapy, and the investigational drug are described in the section and outlines in the accompanying tables.

The criteria for trial discontinuation (Section 4.4) and dose escalation (Section 5.5) will be followed.

6.5.1 Concurrent Chemoradiation and BIO 300 Treatment

Adverse events that can be directly attributable to the investigational study drug will be scored using the NCI Common Toxicity Criteria, Version 4.03. There will be no dose reductions of chemotherapy for hematologic toxicity during concurrent chemotherapy/radiotherapy. If either the ANC or platelets fall below the levels outlined in this table, chemotherapy will be held until the levels return to ANC $\geq$ 1000 or Platelets $\geq$75,000. Missed doses of chemotherapy during RT will not be made up. The first cycle of consolidation chemotherapy can be held due to low blood counts up to 4 weeks, and then administered at full doses. CBC should be rechecked weekly. For grade 4 toxicity during the first cycle of consolidation chemotherapy, including febrile neutropenia, doses of both carboplatin and paclitaxel should be reduced 25% and chemotherapy resumed when all toxicities have returned to grade 2 or less. If chemotherapy is held more than 3 weeks, patient will not be administered their final consolidation treatment.

6.5.1.1 Chemotherapy/BIO 300/RT Dose Modification for Hematologic Toxicity

Table 6.5.1.1.1 Dose Modification for Hematologic Toxicity

Toxicity NCI CTCAE Grade (CTCAE, v4.03)	Paclitaxel dose at start of subsequent cycles of therapy[a]	Carboplatin dose at start of subsequent cycles of therapy[a]	BIO 300 dose at start of subsequent cycles of therapy[a]
Neutropenia			
1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
3 (500-999/mm^3)	Hold therapy[b]	Hold therapy[b]	Maintain (1wk) / Hold therapy[c]
4 (<500/mm^3)	Hold therapy[b]	Hold therapy[b]	Maintain (1wk) / Hold therapy[c]
Neutropenic fever	Hold therapy[b]	Hold therapy[b]	Maintain (1wk) / Hold therapy[c]
Thrombocytopenia			
1 (< LLN – 75,000/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
2 (50,000 – 74,999/mm^3)	Hold therapy[b]	Hold therapy[b]	Maintain (1wk) / Hold therapy[c]
3 (25,000 – 49,999/mm^3)	Hold therapy[b]	Hold therapy[b]	Maintain (1wk) / Hold therapy[c]
4 (<25,000/mm^3)	Hold therapy[b]	Hold therapy[b]	Maintain (1wk) / Hold therapy[c]

Other hematologic toxicities	There will be no dose modifications for changes in leukopenia or lymphopenia.

[a]Dose levels are relative to the starting dose in the previous cycle. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.
[b]Repeat lab work weekly and resume chemotherapy based on this table.
[c]If Paclitaxel and/or carboplatin chemotherapy is held due to toxicity, BIO 300 Oral Suspension dosing will be maintained for 1 week. If the toxicity does not resolve (improve) in that week then BIO 300 Oral Suspension dosing will be held until toxicity returns to grade 2 or lower. Chemotherapy will resume based on this table.

If paclitaxel and/or carboplatin doses must be withheld for greater than three consecutive weeks, the drug(s) will be held permanently for the duration of concurrent therapy.

Hold radiation therapy (RT) for grade 4 hematologic toxicity (ie, ANC <500/mm^3 or platelet count <25,000/mm^3) or neutropenic fever (ie, fever [≥38.5 degrees Celsius] and ANC <1000/mm^3). If RT is withheld, blood counts will be measured twice weekly and if ANC ≥500/mm^3 AND platelet count ≥25,000/mm^3 AND fever resolves (or there was no fever), RT will resume. If fever continues, RT may resume as clinically indicated if ANC ≥1000/mm^3 and patient is clinically stable.

6.5.1.2 Chemotherapy/BIO300 Dose Modifications for Non-Hematologic Toxicity

Table 6.5.1.2.1 Dose Modification for Non-Hematologic Toxicity

Worst Toxicity NCI CTCAE Grade (CTCAE. V4.03)[a,d]	Paclitaxel Dose At Start of Subsequent Cycles of therapy[b]	Carboplatin Dose At Start of Subsequent Cycles of therapy[b]	BIO 300 Dose At Start of Subsequent Cycles of therapy[b]
Neuropathy			
≤ Grade 1	Maintain dose level	Maintain dose level	Maintain dose level
Grade 2	Hold therapy until Grade ≤ 1; restart at full dose	Maintain dose level	Maintain dose level
Grade 3	Discontinue therapy	Maintain dose level	Maintain dose level
Paclitaxel Infusion Reaction[c]			
Grades 1, 2, 3	Premedicate 24 hours before and/or desensitization	Maintain dose level	Maintain dose level
Grade 4	Discontinue paclitaxel	Maintain dose level	Maintain dose level
Other non-hematologic toxicities			
≥ Grade 3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2

[a]For ≤ Grade 2 CTCAE, v4.03 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study. For neuropathy, follow the guidelines listed above.
[b]Dose levels are relative to the starting dose in the previous cycle. For concurrent therapy, paclitaxel and carboplatin doses will not be adjusted.
[c]Most patients with hypersensitivity reactions to paclitaxel can be successfully treated by administration of steroid, H1 and H2 blocker prophylaxis or increased infusion time. If the patient experiences repeated severe episodes (grade 3) then paclitaxel should be discontinued. Carboplatin, radiation, and BIO300 should be continued.

[d]Radiation therapy should continue to be delivered for ≤ Grade 3 non-hematologic toxicities in or outside the radiation treatment field. RT should be held for all Grade 4 non-hematologic toxicity and resumed only when toxicity is ≤ Grade 2.

6.5.1.3 Chemotherapy/RT Dose Modifications for RT Field, Non-Hematologic Toxicity During Concurrent Therapy

Table 6.5.1.3.1 Dose Modification for In-field non-Hematologic Toxicity

Treatment Modification for In-field Non-Hematologic Toxicity During Concurrent ChemoRT					
In-field	**CTCAE, Toxicity Grade**	**XRT**	**Paclitaxel**	**Carboplatin**	**BIO 300**
Esophagus/pharynx *(on day of XRT)*	4	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Maintain (1wk) / Hold treatment until ≤ Grade 2
Esophagus/pharynx *(on day of chemo)*	3	No change or hold ≤ 5 days	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Maintain (1wk) / Hold treatment until ≤ Grade 2
Esophagus/pharynx *(on day of chemo)*	2	No change	No change	No change	No change
Pulmonary	4	Discontinue	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Discontinue
Pulmonary	3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2
Skin	4	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2	Maintain (1wk) / Hold treatment until ≤ Grade 2
Skin	3	No change	No change	No change	No change

On day of chemotherapy administration during any treatment week, omit paclitaxel and carboplatin until toxicity resolves to ≤ grade 2 as detailed in the table above.

Radiotherapy should be interrupted for Grade 4 non-hematologic toxicity, including Grade 4 esophagitis or pulmonary toxicity and resumed according to the table. If treatment is interrupted for > 3 weeks, the patient should be removed from study treatment. If the patient experiences esophagitis so that IV fluid support is needed, insertion of a feeding tube should be considered.

In the event of acute onset of grade 3 or greater pulmonary symptoms, worsening of pulmonary symptoms not thought to be related to the underlying cancer, or pre-existing pulmonary disease, BIO300 therapy should be interrupted and a prompt investigation of these symptoms should occur.

In the event that radiation therapy and/or chemotherapy is interrupted for grade 4 esophagus/pharynx or grade 4 skin toxicity, BIO 300 Oral Suspension therapy will be maintained for 1 week. If the toxicity does not resolve (improve) in that week then BIO 300 Oral Suspension dosing will be held. Chemotherapy and/or radiation therapy will resume based on this table.

6.5.1.4 Carboplatin Dose Modifications for Renal Toxicity

A > 10% change in serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose.

6.5.1.5 Paclitaxel for Neuropathy

If paclitaxel doses must be withheld for greater than two consecutive weeks, the drug will be held permanently for the duration of concurrent therapy.

If there is a decline in ECOG performance status to greater than or equal to 2 for greater than 2 weeks while under treatment, RT should be held with no further chemotherapy administered (Appendix 6). Re-evaluate patient after one week for resumption of radiotherapy.

6.5.1.6 Carboplatin for Neuropathy

During concurrent chemoradiation therapy carboplatin dosing will be maintained. Of the routinely used chemotherapeutics, carboplatin is generally considered to possess low neurotoxicity. Grade 3 peripheral neuropathy is not usually associated with carboplatin, but rather the more toxic chemotherapeutic paclitaxel.

6.5.2 Dose Modifications During Consolidation Chemotherapy

To begin consolidation chemotherapy, all previous toxicities including neuropathy must have resolved to < grade 2, CTCAE, v4.03.

6.5.2.1 Consolidation Therapy Dose Modifications for Hematologic Toxicity

Table 6.5.2.1.1 Consolidation Dose Modification for Hematologic Toxicity

Toxicity NCI CTCAE Grade (CTCAE, v4.03)	Paclitaxel Dose At Start of Subsequent Cycles of Therapy[a,c]	Carboplatin Dose at Start of Subsequent Cycles of Therapy[a,c]
Neutropenia		
1 (1500-1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000-1499/mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3
3 (500-999/mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 1,500 mm^3
4 (< 500/mm^3)	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3
Neutropenic fever	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 1,500 mm^3
Thrombocytopenia		
1 (≥ 75,000/mm^3)	Maintain dose level	Maintain dose level
2 (50,000 - 74,999/ mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3
3 (25,000- 49,999/ mm^3)	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b]. Maintain dose level if fully recovered in 1 week. If not, decrease by 1 dose level when ≥ 75,000 mm^3
4 (< 25,000/mm^3)	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3	Hold therapy[b] and decrease by 1 dose level when ≥ 75,000 mm^3

[a]Dose levels are relative to the worst toxicities in the previous cycle. For consolidation therapy, dose reductions of paclitaxel and carboplatin below the –1 dose level will not be allowed.
[b]Repeat lab work weekly and resume chemotherapy based on this table.
[c]Dose delays greater than 2 weeks will warrant discontinuation of chemotherapy for the consolidation cycles.

6.5.2.2 Consolidation Therapy Dose Modifications for Non-Hematologic Toxicity

Table 6.5.2.2.1 Consolidation Dose Modification for non-Hematologic Toxicity

Worst Toxicity NCI CTCAE Grade (CTCAE, v4.03)[a]	Paclitaxel Dose At Start of Subsequent Cycles of Therapy[b]	Carboplatin Dose At Start of Subsequent Cycles of Therapy[b]
Paronychia		
Grade 2	Maintain dose level	Maintain dose level
Neuropathy		
≤ Grade 1	Maintain dose level	Maintain dose level
Grade 2	Hold therapy until Grade ≤ 1; restart at full dose	Maintain dose level
Grade 3	Discontinue therapy	Maintain dose level
Paclitaxel Infusion Reaction[c]		
Grade 1, 2, 3	Premedicate 24 hours before and/or desensitization	Maintain dose level
Grade 4	Discontinue paclitaxel	Maintain dose level
Other non-hematologic toxicities		
Grade 3	Hold treatment until ≤ Grade 2	Hold treatment until ≤ Grade 2

[a]For ≤ Grade 2 CTCAE, v4.03 non-hematologic toxicity not described above, excluding neuropathy, maintain dose level of all study drugs. For neuropathy, follow the guidelines above.
[b]Dose levels are relative to the worst toxicities in the previous cycle. For consolidation therapy, paclitaxel and carboplatin doses will not be adjusted.
[c]Most patients with hypersensitivity reactions to paclitaxel can be successfully treated by administration of steroid, H1 and H2 blocker prophylaxis, increased infusion times and/or desensitization. If the patient experiences repeated severe episodes (grade 3) or refuses further therapy with paclitaxel then paclitaxel should be discontinued. Carboplatin, should be continued. Substitution with docetaxel, nabpaclitaxel etc. is not permitted.

When a chemotherapy dose reduction is required during the consolidation course of therapy, re-escalation of the chemotherapy dose will not be allowed for subsequent doses during that specific course.

6.5.3 Carboplatin Dose Modifications for Renal Toxicity

The dose of carboplatin is only recalculated for major changes; for example, a > 10% change in the serum creatinine, based on weekly calculated creatinine clearance, will warrant a recalculation of the carboplatin dose. It is not necessary to recalculate the carboplatin dose based on the patient's weekly body weight.

6.5.4 Paclitaxel Dose Modifications for Neuropathy

If paclitaxel doses must be withheld for >2 consecutive weeks, the drug will be held permanently for the duration of consolidation therapy.

If protocol treatment is discontinued for any reason, follow up and data collection will continue as specified in the protocol. The reason(s) for discontinuation of protocol treatment should be documented in the patient's medical record and appropriate case report form.

6.5.5 Carboplatin for Neuropathy

During consolidation therapy carboplatin dosing will be maintained. Of the routinely used chemotherapeutics, carboplatin is generally considered to possess low neurotoxicity. Grade 3 peripheral neuropathy is not usually associated with carboplatin, but rather the more toxic chemotherapeutic paclitaxel.

6.5.6 Management of QTc prolongation

Patients will have ECGs performed to monitor QTc interval using Fridericia's correction.

For this study, QTc prolongation is defined as: A single QTc interval of ≥ 480 msec. The QTc prolongation threshold for holding BIO 300 has been defined as a QTc interval of ≥ 500 msec or an increase of > 60 msec from baseline.

The baseline will be the average of the screening day and the pre-BIO 300 Oral Suspension dose QTc interval values.

6.5.6.1 Abnormal QTc interval of ≥ 500 msec or baseline change of > 60 msec

If the QTc interval is ≥ 500 msec or an increase of > 60 msec from baseline is observed, BIO 300 will be held and concomitant medications should be re-inspected. Any medication that could contribute to QTc prolongation should be identified and removed as clinically indicated.

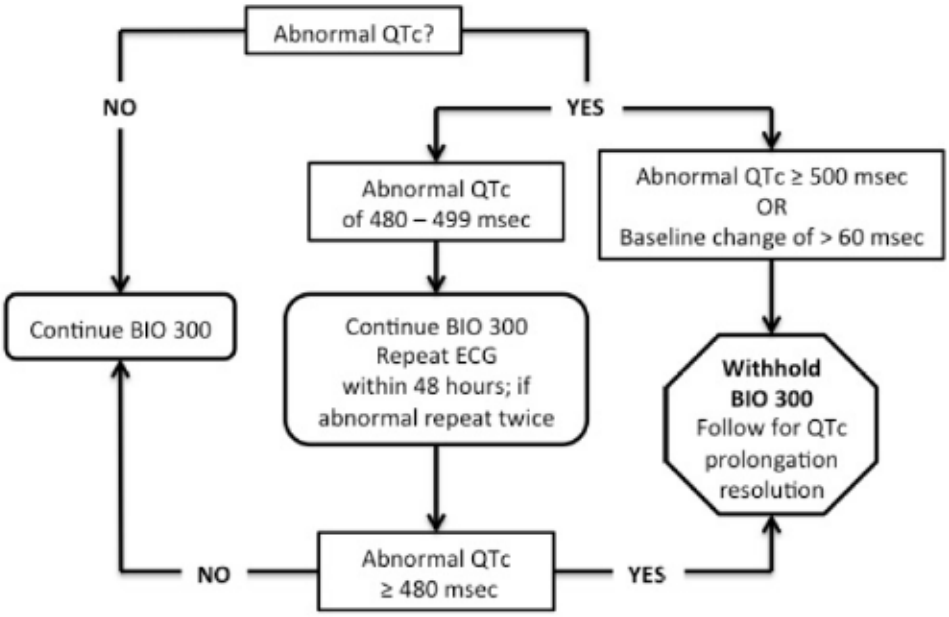
Serum potassium and magnesium levels should be checked. Aggressive replacement either through IV or PO should be attempted to maintain a level of potassium ≥ 4.0 mmol/dL and/or magnesium ≥ 2.0 mg/dL. ECGs and electrolytes should be followed 3 times a week until QTc interval falls below 480 msec.

After the QTc interval recovers to < 480 msec or returns to within 60 msec of baseline and following review of the data and consultation with the medical monitor, a decision how to proceed with BIO 300 dosing will be determined. If BIO 300 is restarted after the QTc prolongation has resolved, ECGs should be performed weekly. If BIO 300 must be withheld for > 3 weeks to allow for QTc prolongation to recover to < 480 msec or baseline, the patient will not be restarted on the study medication.

6.5.6.2 Abnormal QTc interval of 480-499 msec

If the QTc interval is 480 - 499 msec, BIO 300 should be continued along with electrolyte replacement as indicated but a repeat ECG must be obtained within 48 hours. If the ECG remains abnormal it will be repeated twice, 5 minutes apart. If the QTc interval is < 480 msec the patient will continue treatment and resume the ECG schedule as outlined in the Schedule of Assessments (see Table 7.1.1). If the QTc interval is ≥ 480 msec, BIO 300 will be held and the process for monitoring an abnormal QTc interval described in section 6.5.6.1 will be followed.

Figure 6.5.6.1 Management of QTc prolongation or abnormities



6.5.7 Dose Modification due to Gastrointestinal (GI) Toxicity

Nausea, vomiting, or both may be controlled with antiemetic therapy. Routine premedication for chemotherapy in accordance to standards is recommended. Symptomatic patients should pro-actively be treated with standard antinausea/antiemetic therapy as necessary to prevent dose modification or interruption. However, 5HT-3 antagonists may prolong QTc interval risk with use of Ondansetron. Increased monitoring is suggested.

7.0 SCHEDULE OF ASSESSMENTS

7.1 Time to Event

The Time to Event table (Table 7.1.1 for non surgical subjects and Table 7.1.2 for candidate surgical subjects) is a reference of what study assessments need to be completed at each specified visit. A week is defined as 5 consecutive business days e.g., Wednesday, Thursday, Friday, Monday, Tuesday. See Table 7.1.3 for visit window descriptions.

Table 7.1.1 Time to Event for non surgical subjects

VISIT #	1	2	3	4-5[a]	6-10	11-35[9]	S[c]	36	37	38	39	40	41	42
Procedure	Screening	Week 1, d1	Week 1, d2	Week 1, d3-4[a]	Week 2	Wks 3-6	Day 59	Day 66	Day 87	Post RT Completion				
										3 mo	6 mo	9 mo	11 mo	13 mo
Informed Consent	x													
Review I/E Criteria	x	x												
Medical History	x													
Physical Exam[1]	x	x[b]			x[b]	x[b]	x	x	x	x	x	x		x
ECOG Score	x	x[b]			x[b]	x[b]	x	x	x	x	x	x		x
Vital Signs	x	x[b]			x[b]	x[b]	x	x	x	x	x	x		x
Weight	x	x[b]			x[b]	x[b]	x	x	x	x	x	x		x
Height	x													
ECG	x[2]	x[3]			x[4b]	x[4c]								
CBC	x	x			x[b]	x[b]		x	x	x				
Serum Chemistry[5]	x	x			x[b]	x[b]		x	x	x				
Urinalysis[6]	x													
Pregnancy Test[7]	x	x												
Extent of Disease	x					x[d]	x		x	x	x	x	x	x
PK sampling		x	x	x[f]	x	x[b]								
PD sampling		x		x[f]	x	x[b]			x	x	x			
BIO 300 Admin.		x	x	x	x	x								
Concurrent Chemotherapy			x[b]		x[b]	x[b]								
Radiation Therapy				x	x	x								
Consolidation Chemotherapy								x	x					
Adverse Events[10]		x	x	x	x	x	x	x	x	x	x	x		x
Concomitant Medications	x	x[b]			x[b]	x[b]	x	x	x					
QoL Measures	x									x	x			x
Pulmonary Function Test	x						x				x			x
Diag. CT Scan	x						x			x	x		x	
4D-CT Scan	x					x[d]			x			x		x
Swallowing Diary	x	x[b]			x[b]	x[b]				x	x			
Diet Counseling[8]	x	x[b]			x[b]	x[b]								

[a]Optional visit 5b as needed, [b]weekly, [c]bi-weekly (every other week), [d]visit 20 only; visit window allowance of +/- 7 days, [e]Optional surgical evaluation, if subject is medically fit for surgery use table 7.1.2, [f]BIO300 +chemo PK scheduling allowed week 1 or 2, See Table 7.1.3 for details

Table 7.1.2 Time to Event for surgical subjects

VISIT #	1	2	3	4-5[a]	6-10	11-35[9]	S	36	37	38	39	40	41
Procedure	Screening	Week 1, d1	Week 1, d2	Week 1, d3-4[a]	Week 2	Wks 3-6	Day 59	6-12 wk post-surgery	10-16 wk post-surgery	Post Consolidation			
										3 mo	6 mo	9 mo	12 mo
Informed Consent	x												
Review I/E Criteria	x	x											
Medical History	x												
Physical Exam[1]	x	x[b]			x[b]	x[b]	x	x	x	x	x	x	x
ECOG Score	x	x[b]			x[b]	x[b]	x	x	x	x	x	x	x
Vital Signs	x	x[b]			x[b]	x[b]	x	x	x	x	x	x	x
Weight	x	x[b]			x[b]	x[b]	x	x	x	x	x	x	x
Height	x												
ECG	x[2]	x[3]			x[4b]	x[4c]							
CBC	x	x			x[b]	x[b]		x	x	x			
Serum Chemistry[5]	x	x			x[b]	x[b]		x	x	x			
Urinalysis[6]	x												
Pregnancy Test[7]	x	x											
Extent of Disease	x					x[d]	x			x	x	x	x
PK sampling		x	x	x[f]	x	x[b]							
PD sampling		x		x[f]	x	x[b]			x	x	x		
BIO 300 Admin.		x	x	x	x	x							
Concurrent Chemotherapy			x[b]		x[b]	x[b]							
Radiation Therapy				x	x	x							
Consolidation Chemotherapy								x	x				
Adverse Events[10]		x	x	x	x	x	x	x	x	x	x	x	
Concomitant Medications	x	x[b]			x[b]	x[b]	x	x	x				
QoL Measures	x									x	x		x
Pulmonary Function Test	x						x				x		x
Diag. CT Scan	x						x			x	x	x	x
4D-CT Scan	x												
Swallowing Diary	x	x[b]			x[b]	x[b]				x	x		
Diet Counseling[8]	x	x[b]			x[b]	x[b]							

[a]Optional visit 5b as needed, [b]weekly, [c]bi-weekly (every other week), [d]visit 20 only; visit window allowance of +/- 7 days, [f]BIO300 +chemo PK scheduling allowed week 1 or 2, See Table 7.1.3 for details

Description of schedule of assessments

1. A complete physical exam will be completed at screening. Other visits require a brief exam, focus on areas of tumor involvement or referable to adverse events.
2. ECGs will be performed in triplicate. Each reading will be separated by 5 minutes.
3. ECG is utilized to assess acute changes that may impact cardiac toxicity. ECGs to be obtained just prior to administration of BIO 300, and 1 hour post administration of BIO 300.
4. ECG data will be collected prior to BIO 300 or chemotherapy administration, whichever comes first.
5. To include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, magnesium, calcium, phosphorous and uric acid. Analysis of pancreatic enzymes also to be included in panel (amylase and lipase).
6. Urinalysis to include pH, specific gravity, dipstick determinations of glucose, ketones, protein, hemoglobin, bilirubin.
7. Pregnancy test may be urine or serum determination of β-HCG. Visit 2 test is only required if the screening pregnancy test was performed more than 72 hours prior to visit 2.
8. At the screening visit patients will be counseled and given instructions on a diet low in soy isoflavones. Diet counseling will occur weekly during the time period where BIO 300 is administered using the information provided in Appendix 8, Soy Rich Foods.
9. The total number of subject visits completed through concurrent chemoradiotherapy are flexible and dependent on radiotherapy and chemotherapy scheduling. Each subject will have a minimum of 32 visits through the conclusion of concurrent chemoradiotherapy (approximately 6-7 weeks of chemotherapy and daily RT fractions of 1.8-2.0 Gy, total dose of 60-70 Gy).
10. All adverse events will be collected from the time the subject signs informed consent until 30 days after the last administration of BIO 300. After this time, adverse event assessment will occur at each visit but only those events that are considered serious and possibly, probably or definitely related to BIO 300 will be documented and reported to the sponsor within 24 hours of awareness (see section 8.0 Safety Reporting for details).

Table 7.1.3 Visit Window Table

Visit or Procedure	Visit Window	Notes
Screening Visit	Within 28d prior to registration.	Pulmonary Function Test, Medical History, Physical Exam and CTs may be completed within 10 wks prior to registration
Concurrent Chemotherapy	Day 1 of chemotherapy may be scheduled at the discretion of the investigator provided the subject has completed a minimum of 1 days of BIO 300 dosing.	Should visits be delayed due to a holiday, standard of care should be followed.
Radiation Therapy	Day 1 of radiation therapy may be scheduled at the discretion of the investigator provided the subject has completed a minimum of 2 day of BIO 300 dosing.	Should visits be delayed due to a holiday, standard of care should be followed.
BIO 300 + Chemo PK	BIO 300 + Chemo pharmacokinetics may be scheduled week 1 or week 2 at the discretion of the investigator provided the subject has completed at least 4 days and no more than 9 days of BIO 300 dosing.	
PK sampling	For the pre-BIO 300 administration time point and the 0.5 and 1 hour time points, blood will be collected within ± 5 minutes of the defined draw time post BIO 300 dosing. For the 2, 3, 4 and 8 hour time points, blood will be collected within ± 10 minutes for the defined draw time post BIO 300 dosing. The 24hr draw should occur as close to 24 hours after the dose of BIO 300 and prior to the morning dose of BIO 300.	See Appendix 9, summary of blood draws for safety, PK, and PD assessment.
CBC	May be drawn up to 4d prior to visits where chemotherapy is administered	
Serum Chemistry	May be drawn up to 4d prior to visits where chemotherapy is administered	
Visit S, Surgical Evaluation	+/- 7d	
Visit 36-37, Consolidation Chemotherapy	+/- 7d	+/- 14d for CT
Visit 38-39, 3 and 6 month follow up	+/- 14d	
Visit 40-42, 9-13 month follow up	+/- 21d	For surgical subjects visit 41, 12 month follow up (end of study)

7.2 Administration of BIO 300 Oral Suspension

Following the screening visit, subjects will be requested to maintain a low isoflavone diet for the duration of the study. Subjects will be provided a list of dietary requirements for the study and encouraged to maintain their diet within an acceptable range. In preparation for the Visit 2 (Day 1) PK/PD studies, all subjects will arrive at the clinic after an overnight (8 hour) fast. The first blood sample for these studies will be taken prior to the initial dose of BIO 300. (see section 7.3 for details on blood sampling for PK/PD). The subject will be asked to remain fasting for 2 hours after this initial dose to allow for additional blood sampling at which time the subject will be given a standard meal. Drinking of clear fluids (preferably water only, 8 ounces) will be encouraged following administration of BIO 300 Oral Suspension. The test article will be consumed at the beginning of the day immediately after the initial (time 0) blood sampling on the days that require a blood draw. Following the pharmacokinetic portion of the trial, and throughout the entire study, subjects will be encouraged to take the daily dose of BIO 300 Oral Suspension as close to 1 hour prior to radiation therapy as is logistically feasible. On days in which subjects do not receive radiation therapy, study subjects will be encouraged to take the daily dose of BIO 300 Oral Suspension as close to the same time as they take it on days where they receive radiation. For example, if their radiation sessions are scheduled for 11:00 AM, they should take their daily dose of BIO 300 Oral Suspension at 10:00 AM each day.

7.3 Subject Blood Sampling for Safety, Pharmacokinetics and Pharmacodynamics

Blood will be collected on all subjects to monitor safety, pharmacokinetics, and pharmacodynamics of BIO 300 alone or in combination with chemotherapy. BIO 300, paclitaxel, and carboplatin pharmacokinetics analysis will be completed on 6 subjects in each of the dosing cohorts. PK will not be completed on cohort 4 (optimal biological dose).

At each visit where blood sampling occurs, blood will be collected prior to any treatment administration including the daily BIO 300 dosing.

A summary of blood draws for safety, PK, and PD assessment can be found in Appendix 9. Below is an overview of the details of the blood collection summarized by visit.

Visit 1 (Screening)

At the screening visit, blood will be collected for a CBC and blood chemistries to evaluate the subject's bone marrow and hepatic reserve and renal function. If a pregnancy test is required for the subject, either a serum or urine test will be done at this time. These test results will assist in determining the subject's ability to be included in the trial (see section 4.2.1 Inclusion Criteria).

Visit 2 (Day 1)

For subjects in the PK group, after an 8-hour fast and prior to the initial dose of BIO 300, these subjects will have their blood collected for CBC, blood chemistries and BIO 300 pharmacodynamic (PK) and pharmacodynamic (PD) baseline values. The CBC and blood chemistries may be drawn up to 4 days prior to visits where chemotherapy is administered. For those subjects who had a pregnancy test at Visit 1 but occurred over 72 hours prior to this visit, a repeat test is required.

All subjects will remain fasting until their blood sampling is completed at 2 hours post BIO 300 dose, at that time the subjects will be allowed to eat and will be given a standard meal.

For the subjects in the PK group, blood will be drawn for pharmacokinetic and pharmacodynamic sampling of BIO 300 at the following times: pre-dose, 0.5, 1, 2, 3, 4, and at 8 hours. For the 0.5 and 1 hour time points, blood will be collected within ± 5 minutes of the defined draw time post BIO 300 dosing. For the 2, 3, 4, and 8 hour time points, blood will be collected within ± 10 minutes for the defined draw time post BIO 300 dosing. Nonclinical studies demonstrated that the half-life of total genistein in serum is approximately 7 hours. The final blood collection for PK analysis as close to 24 hours post dosing is constrained by the dosing regimen, but still allows for PK sampling for 3-4 half-lives. This sampling regimen should provide sufficient data to study the elimination phase of the study drug.

For each BIO 300 time point (PK or PK and PD), a 3cc tube of blood will be collected in a 3 cc red top blood collection tube. The blood will be allowed to clot 20-30 minutes and then centrifuged at room temperature for 10-15 minutes. For the pre-dose and 2-hour post dose blood draw (BIO 300 PK and PD), the serum from the single blood collection tube will be separated into two aliquots (0.3mL for BIO 300 PD analysis and the remainder for BIO 300 PK analysis) and frozen at -80°C. The tube for BIO 300 PK analysis will be shipped to the sponsor-designated bioanalytical lab for determination of BIO 300 PK parameters.

The second tube from the pre-dose and 2 hr blood draw described above (0.3 mL serum) will be used for BIO 300 pharmacodynamic marker analysis; the tube will be shipped to the sponsor-designated lab for analysis. Blood serum will be analyzed for PD biomarker expression levels. PD Biomarkers may include IL6, IL-1α, IL-1β, IL-8, IL-10, TNFα, TGFβ1, TGFβ2, TGFβ3, G-CSF, C-reactive protein and prostaglandin E2.

For any subjects not undergoing PK testing, after an 8-hour fast and prior to the initial dose of BIO 300, these subjects will have their blood collected for CBC, blood chemistries and BIO 300 pharmacodynamic (PD) baseline value. For those subjects who had a pregnancy test at Visit 1 but occurred over 72 hours prior to this visit, a repeat test is required.

For these subjects, a second blood sample will be taken for at 2-hour post BIO 300 dose for pharmacodynamics marker analysis. Blood will be collected within ± 10 minutes of the defined draw time post BIO 300 dosing.

All subjects will remain fasting until their blood sampling is completed at 2 hours post BIO 300 dose at that time the subjects will be allowed to eat and will be given a standard meal.

Visit 3 (Day 2)

Prior to the days BIO 300 dose, those in the PK group will have their blood collected at the 24 hr. post BIO 300 dosing for PK analysis. The same amount of blood will be drawn and the same process will be followed as described above in Visit 2. Because there will be no

BIO 300 PD assessment, the entire portion of serum will be frozen in a single tube. Those not in the PK group will not have blood drawn this day.

BIO 300 + Chemo PK

After an 8-hour fast and prior to the daily BIO 300 dosing, blood will be collected as described in Visit 2 above with the addition of PK sampling for paclitaxel and carboplatin for those subjects in the PK group.

Blood sampling for paclitaxel time points will be: pre-dose, 2, 3, 4, 8, and 24 hours. Carboplatin time points will be: pre-dose, 2, 4, 8, and 24 hours. For the 0.5 and 1 hour time points, blood will be collected within ± 5 minutes of the defined draw time post BIO 300 dosing. For the 2, 3, 4, and 8 hour time points, blood will be collected within ± 10 minutes for the defined draw time post BIO 300 dosing. The 24 hour time point, blood should be collected as close to 24 hours post-BIO 300 dose as possible. For each time point, a 3 cc tube of blood will be collected in a K2 EDTA tube. This single blood collection yields sufficient plasma for both paclitaxel and carboplatin assessment. The blood plasma will be collected, centrifuged at approximately 4°C and transferred equally into two sterile tubes and frozen at -80°C. The tube will be shipped to the sponsor-designated lab for determination of paclitaxel and carboplatin PK parameters. These times are relative to the morning dose of BIO 300 Oral Suspension. No carboplatin PK parameters will be measured at the 3 hr. time point, only parameters for paclitaxel.

The following day, as close to 24 hours post BIO 300 dosing and prior to that days dose of BIO 300, those in the PK group will have their blood collected for PK analysis. Those not in the PK group will not have blood drawn this day. For paclitaxel and carboplatin PK assessment, a 3 cc tube of blood will be collected in a K2 EDTA tube. The plasma will be collected, centrifuged at approximately 4°C and divided into two sterile tubes and frozen at -80°C. For BIO 300 PK assessment, a 3cc tube of blood will be collected in a red top blood collection tube. The blood will be allowed to clot 20-30 minutes and then centrifuged at room temperature for 10-15 minutes. The serum will be collected and transferred to a sterile tube and frozen in a -80°C freezer.

Weeks 2-6

In addition to the blood sampling for CBC and blood chemistries, trough levels for BIO 300, paclitaxel, carboplatin, and the BIO 300 pharmacodynamic markers will be determined weekly during concurrent chemoradiotherapy, prior to that week's chemotherapy treatment course and prior to that days BIO 300 dose. For BIO 300 trough levels and PD assessment, one 3 cc tube of blood will be collected in a red top blood collection tube. The blood will be allowed to clot 20-30 minutes and then centrifuged at room temperature for 10-15 minutes. The serum from the single blood collection tube will be separated into two aliquots (0.3mL for BIO 300 PD analysis and the remainder for BIO 300 PK analysis). The tubes will be frozen at -80°C and shipped to the sponsor-designated labs for analysis. One tube will be shipped to the sponsor-designated bioanalytical lab for analysis and determination of BIO 300 trough levels, and the second tube will be shipped to the sponsor-designated lab for BIO 300 pharmacodynamic marker analysis.

In addition, at that same time point, a 3 cc tube of blood will be collected in a K2 EDTA tube. The blood will be collected, centrifuged at approximately 4°C and divided into two sterile tubes and frozen at -80°C. The tube will be shipped to the sponsor-designated lab for determination of paclitaxel and carboplatin trough levels.

Visit S
All subjects will have a CBC and blood chemistries drawn for safety monitoring. No other blood sampling required.

Visits 36
All subjects will have a CBC and blood chemistries drawn for safety monitoring. No other blood sampling required.

Visit 37
All subjects will have a CBC and blood chemistries drawn for safety monitoring. In addition, blood serum will be collected for BIO 300 pharmacodynamic marker analysis. A 3cc tube of blood will be collected in a red top blood collection tube. The blood will be allowed to clot 20-30 minutes and then centrifuged at room temperature for 10-15 minutes. The serum will be separated and placed into a sterile tube and frozen at -80°C. The tube will be shipped to the sponsor-designated lab for analysis.

Visit 38
All subjects will have a CBC and blood chemistries drawn for safety monitoring. In addition, blood serum will be collected for BIO 300 pharmacodynamic marker analysis. A 3cc tube of blood will be collected in a red top blood collection tube. The blood will be allowed to clot 20-30 minutes and then centrifuged at room temperature for 10-15 minutes. The serum will be separated and placed into a sterile tube and frozen at -80°C. The tube will be shipped to the sponsor-designated lab for analysis.

Visit 39
Blood serum will be collected for BIO 300 pharmacodynamic marker analysis. A 3cc tube of blood will be collected in a red top blood collection tube. The blood will be allowed to clot 20-30 minutes and then centrifuged at room temperature for 10-15 minutes. The serum will be separated and placed into a sterile tube and frozen at -80°C. The tube will be shipped to the sponsor-designated lab for analysis.

For all other visits, no protocol blood collection is required.

(See section 7.0 Schedule of Assessments for additional information.)

7.4 Subject Blood Volume Requirements

A summary of the blood volume required at each visit for each study subject is shown in the tables below. Table 7.4.1 summarizes the required blood volumes for those subjects enrolled to complete both PK and PD analysis. Table 7.4.2 summarizes the required blood volumes for those subjects only enrolled to complete PD analysis. The CBC and blood chemistries may be drawn up to 4 days prior to visits where chemotherapy is administered. *Week 2 blood draws required only when BIO 300 + Chemo PK occurs on week 1.

Table 7.4.1 Blood volume, subjects enrolled for PK and PD analysis

	Blood volume (mL) required													
	Visit													
	1	2	3							36	37	38	39	
	Screening	Day 1	Day 2	BIO 300 + Chemo PK	Wk 2*	Wk 3	Wk 4	Wk 5	Wk 6	Day 66	Day 87	3 months	6 months	TOTAL
CBC	4	4		4	4	4	4	4	4	4	4	4		44
Serum Chemistry	7	7		7	7	7	7	7	7	7	7	7		77
BIO 300 PK/PD **(Red top Serum)**		21 (3cc x 7 draws)	3	24 (3cc x 8 draws)	3	3	3	3	3		3	3	3	72
Paclitaxel/Carboplatin PK **(K_2-EDTA Plasma)**				18 (3cc x 6 draws)	3	3	3	3	3					33
Subtotals	11	32	3	53	17	17	17	17	17	11	14	14	3	
STUDY TOTAL														226

Table 7.4.2 Blood volume, subjects enrolled for PD analysis

	Blood volume (mL) required													
	Visit													
	1	2	3							36	37	38	39	
	Screening	Day 1	Day 2	BIO 300 + Chemo PK	Wk 2*	Wk 3	Wk 4	Wk 5	Wk 6	Day 66	Day 87	3 months	6 months	TOTAL
CBC	4	4		4	4	4	4	4	4	4	4	4		44
Serum Chemistry	7	7		7	7	7	7	7	7	7	7	7		77
BIO 300 PD **(Red top Serum)**		6 (3cc x 2 draws)		6 (3cc x 2 draws)	3	3	3	3	3		3	3	3	36
Subtotals	11	17		17	14	14	14	14	14	11	14	14	3	
STUDY TOTAL														157

7.5 Specimen Collection Summary

Table 7.5.1 Specimen Collection Summary

Specimens for BIO 300 – specific analyses			
Specimens taken from patient	Collected when:	Submitted as:	Shipped:
SERUM	Follow time to event schedule	Frozen serum samples	Serum sent frozen on dry ice via overnight courier (Mon-Wed)
PLASMA (K_2-EDTA)	Follow time to event schedule	Frozen plasma samples	Plasma sent frozen on dry ice via overnight courier (Mon-Wed)
SERUM – protein and cytokine analysis	Follow time to event schedule	Frozen serum samples	serum sent frozen on dry ice via overnight courier (Mon-Wed)

7.6 Health-Related Quality of Life (HRQOL) Analysis

7.6.1 FACT-TOI

FACT-TOI is a validated instrument (questionnaire) that sums the functional well-being (FWB), physical well-being (PWB), and the lung cancer subscale (LCS) of the Functional Assessment of Cancer Therapy – Lung (FACT-L) QOL instrument. The FACT-TOI instrument will be used at 4 specific time points to minimize patient burden: baseline (pretreatment), at the 3 and 6 month follow-up visits and end of study visit (12 or 13 months). This instrument has been extensively used for measuring QOL in patients with lung cancer [20, 21]. In a review of the literature reported that the FACT-L scale has been used in more than 5,000 patients and has been found to be sensitive to changes in performance status, treatment response [22, 23]. All items are rated on a 5 item (point) Likert Scale, from 0 (not at all) to 4 (very much).

7.6.2 UCSD-SOB

The UCSD-SOB questionnaire is designed to assess dyspnea longitudinally in patients [24]. The UCSD is a 24-item dyspnea questionnaire that asks respondents to rate themselves from 0 ("Not at all") to 5 ("Maximally or unable to do because of breathlessness") in two areas: 1) how short of breath they are while performing various activities (21 items); and 2) how much shortness of breath, fear of hurting themselves by overexerting, and fear of shortness of breath limit them in their daily lives (3 items). Scores range from 0–120, with higher scores indicating greater dyspnea.

7.6.3 Swallowing Diary

We will use a patient-swallowing diary, which takes 2-3 minutes to fill out. The swallowing diary was modified from a Medical Research Council (MRC) swallowing diary card for lung cancer [25, 26]. This swallowing diary will be filled out by patients. The patients will be asked to fill out the diary at baseline, on a weekly basis during concurrent chemoradiation and then at the follow-up visits.

8.0 SAFETY REPORTING

8.1 Definitions

8.1.1 Adverse Events

Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

8.1.2 Serious Adverse Events

SAEs that fit any one of the criteria in the SAE definition below must be reported to the Sponsor within 24 hours of awareness of the event.

Definition of an SAE: Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE drug experience, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

8.1.3 Unexpected Adverse Events

Any adverse experience that (a) is not identified in nature or severity, or frequency in the current investigator brochure; (b) that is not identified in nature, severity, or frequency in the risk information described in the general investigational plan or elsewhere in the current application as amended; (c) or that has not been previously observed.

8.2 Documenting Adverse Events

All AEs, including clincially significant laboratory abnormalities will be collected in the sites source document and reported on the AE case report form (CRF) from the time the subject is enrolled in the study until 30 days after last administration of study drug. If the AE is a serious event that is possibly, probably or definitely related to study drug, the event should be reported to the Sponsor even if occurring more than 30 days after the last dose of study drug. Documentation of the serious event will be reported on the Serious Adverse Event CRF and submitted to the sponsor within 24 hours of awareness.

8.2.1 Adverse Event Data Elements

- Assessment period
- Adverse event term CTCAE version 4.03
- Severity Grade (0-5) CTCAE version 4.03
- Attribution to study agent (relatedness)

- Date AE occurred
- Date AE resolved
- Whether or not the event was reported as an SAE
- Whether or not the participant dropped due to the event
- Action taken with study agent
- Outcome of the event
- Comments

8.2.2 Severity of AEs

Identify the adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE provides descriptive terminology and a scale for each adverse event listed. A link to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 can be found in Appendix 5.

Table 8.2.2.1 Grading and Description of Adverse Events

Grade	Description
0	No AE or within normal limits
1	Mild AE; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
2	Moderate AE; minimal, local or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE, which is defined above in section 7.1.2.

8.2.3 Assessment of Relationship of AE to Treatment

The possibility that the adverse event is related to the study agent will be classified as one of the following: unrelated, unlikely, possible, probable, definite. The investigator will be responsible for determining the relatedness of the AE to the study agent.

8.2.4 Follow-up of AEs

Follow-up on events, AEs and SAEs, will be documented and submitted to the Sponsor as new information is collected until resolution or until their last study visit.

8.3 Reporting AEs to IRB

Investigators are required to report promptly to the IRB all *unanticipated problems* involving risks to human subjects or others, including adverse events that should be considered unanticipated problems. The following AEs should be considered as *unanticipated problems* that must be reported to the IRB:

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure.
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population.

- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects.
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations.
- A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence.
- Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects.

8.4 Expedited reporting of adverse events

Investigators are required to report promptly to the sponsor any adverse event that may reasonably be regarded as caused by, or probably caused by, the study drug. If the adverse event meets the serious adverse event criteria, the investigator shall report the event to the sponsor within 24 hours of awareness.

The sponsors will notify the FDA and all participating investigators in a written IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected and any finding from tests in laboratory animals that suggests a significant risk for human subjects. The sponsor will submit an IND safety report to the FDA and all participating investigators no later than 15 calendar days after the sponsor determines that the suspected adverse reaction or other information qualifies for reporting. Unexpected fatal or life-threatening suspected adverse reactions will be reported to the FDA no later than 7 calendar days after the sponsor's initial receipt of the information. If the FDA requests any additional data or information, the sponsor will submit it to FDA as soon as possible, but no later than 15 calendar days after receiving the request.

8.5 Dose Limiting Toxicities (DLTs)

Blood sampling for the laboratory parameters will be performed during the study according to the time to event schedule in this protocol. Laboratory parameters include CBC/differential, chemistry profile (CMP), phosphorus, pancreatic lipase & amylase. ECG and vital signs will also be performed according to the Time to Event table (Table 7.1.1). Toxicities will be graded according to the Version 4.03 (v4.03) of the NCI *Common Terminology Criteria for Adverse Events (CTCAE)*. Adverse event reporting and serious adverse event reporting will follow the guidelines defined by FDA Statutes. Discontinuation of a subject and early stopping of one of the trial cohorts will be based on the following unacceptable adverse events (AEs) and must be attributable to the investigational drug BIO 300 Oral suspension (i.e. possibly, probably or definitely related to the study drug) to constitute a Dose-Limiting Toxicity (DLT). Only adverse events which occur before or during concurrent chemoradiation will be counted as DLTs.

- Toxicities must be attributable to the study regimen (i.e. possibly, probably or definitely related to the investigational study drug) to constitute a Dose-Limiting Toxicity (DLT).
- Dose limiting toxicities are to be defined as follows:
  1) Radiation esophagitis Grade 3 that lasts > 7 consecutive days or Grade 4.
  2) Grade 4 neutropenia for more than 7 days or neutropenia fever (defined as ANC < 500 and a temperature of 38.5° C or above).
  3) Grade 3 thrombocytopenia with clinically significant bleeding
  4) Grade 4 thrombocytopenia > 7 days.
  5) Grade 4 nausea/vomiting despite appropriate antiemetic therapy.
  6) Grade 3 AST/ALT elevations > 7 days
  7) Delays in radiotherapy or chemotherapy due to toxicity of more than 3 weeks. Delays in the current standard of care treatment are likely to have a negative effect on patient outcome and thus are to be designated as a DLT.
  8) All other non-hematologic toxicities of Grade 3 or higher, with the following exceptions:
     a) anorexia
     b) fatigue
     c) infection without neutropenia
     d) Grade 3 AST/ALT elevations ≤ 7 days
     e) Infusion reactions. Patients with Grade 3 or worse infusion reactions will be removed from the study and replaced and will not be considered evaluable for DLT.
     f) Grade 3 or 4 electrolyte abnormalities that are corrected to Grade 2 or less in less than 48 hours.

Any DLT should be reported to the sponsor within 48 hours of discovery for review by the medical monitor. The medical monitor will determine whether the event is a DLT. If a DLT occurs, the sponsor will communicate the DLT to the sites within 48 hours of the determination.

A minimum of 6 subjects will be treated per dose level. Dose escalation may occur when a cohort has completed concurrent chemoradiotherapy with less than 33% DLTs. If one or fewer DLTs occur, the dose will be escalated to the next cohort of 6 subjects. If 2 DLTs occur (2/6 subjects), an additional 2 subjects will be treated with the same dose. If no additional DLTs occur (2/8 subjects), dose escalation may proceed. If 1 additional DLT occurs (3/8 subjects), an additional 2 subjects will be treated at the same dose for a total of 10 subjects. If no additional DLTs occur (3/10 subjects), dose escalation may proceed.

The study sponsor will temporarily cease enrollment in any given cohort if 4 subjects (out of a total of 10), experience DLTs attributable to BIO 300 Oral Suspension as the MTD will have been exceeded. The sponsor's medical monitor will assess the safety data collected to date to determine if enrollment should permanently cease at that dose. If the decision is made to cease enrollment, the sponsor and the principal investigator will determine if the dose should cease or be modified for those subjects in that cohort who

have not experienced DLTs. The study sponsor, together with the PI, may consider amending the protocol through a modification of the dosing regimen.

9.0 DATA MANAGEMENT

Data collection will start at study baseline and then continue during the study following the time to event table in the protocol. Data will be recorded on a case report form for each subject. This database will be 21 CFR Part 11 compliant. Subject data will be kept confidential. At Visit 2, each subject will be assigned a Subject ID#. The first number in the Subject ID# is the site number. Site numbers will start with 100 and increase by increments of 100 (i.e., 100, 200, 300), as needed. The second number will be that of the subject in the order they are screened starting with 01; additional numbers being assigned sequentially (101, 102, 103, etc.). In addition, only the subject initials (first, middle & last) will be used on study documents. All medical records are required to be de-identified prior to submission to the sponsor. Study records will be stored in a locked and secure storage area at the study and sponsor facilities. The investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to all source data/documents including electronic medical records.

There will be no imputation for missing QOL observations. The cause of missing data is assumed to be missing completely at random.

Data required for the Interim Analysis will be monitored and cleaned prior to database freeze and no new data will be added to the database until the Project Manager or Statistician gives approval.

The trial database will be audited, cleaned and locked after completion of the trial according to the study specific Data Management Plan (DMP). A copy of this locked database will be burned onto a CD-ROM and made available for statistical analysis. Data will be analyzed for adverse events, primary outcomes, and secondary outcomes.

9.1 Data Capture Methods

The data that will be used to complete the CRFs will be derived from the subjects source documents (EMR and/or paper documents). The research site's study personnel will complete the CRFs and retain them for monitoring by the sponsor. Once monitoring has been completed and the CRFs have been reviewed and signed by the investigator, they will be submitted to the sponsor. Data entry, verification and cleaning will be done according to the sponsor's study specific Data Management Plan.

All pharmacokinetic calculations will be performed using validated software as arranged by the Sponsor. Individual time-concentration data will be used in all pharmacokinetic analyses. The area under the serum (or plasma) concentration-time curve, will be estimated using the linear trapezoidal rule. T_{max}, half-life and ratios will be listed to two significant figures. All other parameters will be listed to three significant figures.

9.2 Data quality assurance

Quality control and quality assurance will be provided as specified in the sponsor's SOP's to ensure appropriate clinical care and data integrity.

9.3 Sample size rationale

We have chosen a sample size of 6 patients per cohort, with the option to enroll up to an additional 12 at a single dose level (optimal biological dose). This is a sufficient number of patients to identify DLTs.

9.4 Interim data anaylsis

At the completion of dose escalation, interim data analysis will be completed to assess BIO 300 safety and to review secondary outcome measures. Data trends will be used to choose a single BIO 300 dose (500, 1000 or 1500mg/d) as the optimal biological dose. Up to an additional 12 subjects will be enrolled at the optimal biological dose to further evaluate BIO 300's safety and efficacy. The maximum tolerated dose will be used for cohort 4 if there are no apparent differences in efficacy.

9.5 Statistical analysis of data

An independent statistician using standard statistical techniques will determine statistically significant differences in the trial measurement data at the nominal 0.05 level of significance. Data will be summarized by descriptive statistics (mean/medians and standard errors/confidence intervals for continuous response variables and distribution tables or histograms for discrete response variables). In addition, relationships between these response variables will be explored using non-parametric approaches (e.g., Spearman rank correlation), parametric correlation analysis methods (e.g., correlation coefficient), or appropriate statistical tests (e.g., the Chi-square trend test for categorical data). Furthermore, appropriate regression techniques for these response variables (e.g., analysis of variance/covariance (ANOVA/ANCOVA)), linear regression, proportional hazards regression, logistic regression, GEE and mixed effects models) will be employed to further examine their relationship with one another. Confidence intervals will be calculated for the differences. The computed change from baseline will be calculated for all measured variables and expressed as the mean change from baseline + standard deviation (SD) of the change from baseline. A two-sample t-test will be used to test the tumor size reduction and a log-rank test will be used to compare time to event outcomes.

Statistical analyses of the FACT-TOI data will be performed with the use of SPSS software, version 16.0; each patient will be used as his/her own control. Analysis of variance (ANOVA) will be used to compare mean UCSD-SOB change scores longitudinally (from baseline to follow-up visits). The ANOVAs can be followed with p-value-adjusted, pair-wise (parametric and then non-parametric) comparisons of the mean UCSD-SOB change scores. Multivariate linear regression analyses, adjusted for baseline scores, will be used to examine the patient reported outcomes (PRO). The swallowing diary will be scored and analyzed as previously described [26].

Using known pharmacokinetic parameters of paclitaxel and carboplatin, the area under the serum (or plasma) concentration-time curve (AUC in mg*min/mL) will be used by the sponsor to assess the effect of BIO 300 Oral Suspension on the pharmacokinetic profile of the individual chemotherapeutics. A similar method will be used to assess the effect of paclitaxel and carboplatin on the pharmacokinetics of BIO 300 Oral Suspension. Following a single dose of BIO 300 Oral suspension (the first week of the study) the AUC will be determined. The following week chemotherapy will be added to the treatment regimen and

AUC values will be determined for each of the drugs (paclitaxel, carboplatin, and BIO 300 Oral Suspension). The AUC values at this timepoint will be compared to that obtained after a BIO 300 dose only and to the predetermined planned AUC values of paclitaxel and carboplatin. This methodology will determine potential BIO 300-mediated effects on drug exposure of the chemotherapeutics and any chemotherapeutic-mediated effects on BIO 300 drug exposure. Provided that the incidence of DLTs has not exceeded the threshold for trial discontinuation and dose escalation the trial will be allowed to continue.

In addition to the data and methods described above, additional trial data to be analyzed frequency of DLTs, pharmacodynamics, pulmonary function test, and ECOG performance. Potential pharmacodynamics markers include the cytokines IL-6, IL-1β, IL-1α, IL-8, IL-10, TNFα, TGFβ1, TGFβ2, and TGFβ3. Serum proteins of interest include granulocyte colony stimulating factor (G-CSF), C-reactive protein, and prostaglandin E2. Finally, pulmonary function (by spirometry) will be measured in the study. Forced Vital Capacity (FVC) and Forced Expiratory Volume in the first second (FEV1) will be scored longitudinally for individual subjects in the study as described above.

10.0 ADMINISTRATIVE PROCEDURES

10.1 Subject informed consent

All potential study participants will be given a copy of the IRB-approved Informed Consent to review. The investigator will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign the Informed Consent document. A copy of the signed Informed Consent will be given to the study participant and the original Informed Consent document will be kept on file. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

The informed consent document must be reviewed and approved by the IRB, any changes to the informed consent must be submitted to the IRB for approval prior to initiation.

10.2 IRB Approval

Prior to initiating the study and receiving agent, the research site must obtain written approval to conduct the study from the appropriate IRB and submit the approval documents to the sponsor.

10.3 Subject confidentiality

In order to maintain subject confidentiality, a subject number and initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor.

10.4 Ethical conduct of the study

Prior to initiating this study, the Principal Investigator at each research site will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations and listing the investigators that will be participating in the protocol.

This study will be performed as outlined under IND 119322 in compliance with this protocol and all applicable regulations and guidelines (e.g. Good Clinical Practice

Guidelines, the Declaration of Helsinki, 21 CFR50–Protection of Human Subjects, and 21 CFR56–Institutional Review Boards).

10.5 Protocol amendments

Should changes become necessary, protocol amendments will be submitted and approved by the IRB prior to implementation.

10.6 Monitoring

10.6.1 On-site Monitoring

The sponsor will monitor the progress of all clinical investigations being conducted under its IND based on the study specific Monitoring Plan. Monitoring visits are intended to ensure the protocol and applicable regulatory requirements are being followed, the investigator is adequately overseeing the conduct of the study, subjects' rights and safety are protected and to confirm data integrity and quality. After the research site has been qualified, receives IRB approval and has been trained and intiated the monitor will perform routine interim visits. Interim visits will occur on an ongoing basis, as described below. At a minimum, periodic monitoring will occur on an annual basis for any investigational site with at least 1 subject enrolled.

Frequency of On-Site Monitoring Visits

Phase of Study	Estimated Monitoring Visit Frequency
Initial Enrollment	After enrollment of the first 1 or 2 subjects at each site.
Treatment & Follow-up	Every 6-8 weeks depending on the number of subjects enrolled and visits to be monitored
Prior to dose escalation to next cohort	After successful completion (less than 33% DLTs) in the concurrent chemoradiation period
End of followup	After last subject last visit in each site
Close-out	After all data queries have been closed

In addition to the monitoring frequency listed above, interim visits may need to be more frequent if there is

1) A change in study personnel (to allow for training and additional sponsor oversight)
2) A protocol amendment/safety issue that significantly affects study procedures or design
3) A documented or suspected lack of study compliance or investigator oversight
4) An issue with recruitment or enrollment

If the study sponsor discovers that a participating investigator is not complying with the signed agreement (Form FDA-1572), the general investigational plan, or other requirements the study sponsor shall promptly either secure compliance or discontinue the investigator's participation in the investigation.

10.6.2 Safety Data Monitoring and Reporting

The sponsor will review and evaluate the evidence relating to the safety and effectiveness of the drug as it is obtained from the participating investigator. For reviewing and reporting

of safety data, the sponsor will follow FDA regulations, ICH GCP E6, applicable sponsor SOPs and the study specific Clinical Safety Plan.

The notification process to the study sponsor of all safety data begins with the completion and submission of the appropriate CRFs or in the case of a initial serious event reporting, by phone. Investigators are required to report promptly to the sponsor any adverse events that may reasonably be regarded as caused by, or probably caused by, the drug. If the Adverse Event (AE) meets the Serious Adverse Event (SAE) criteria, the investigator is required to report the event to the sponsor within 24 hours of awareness.

To Report a SAE call the Humanetics Adverse Event Reporting line:
[redacted] or by contacting the medical monitor

Medical Monitor
Michael Kurman, MD
[redacted]
[redacted]
[redacted]

Prompt review of the SAE by the medical monitor will be completed to determine if the event meets any of the criteria for reporting to the FDA, Investigators, and/or Institutional Review Boards (IRB). Should an SAE be determined to meet the criteria for a 7 or 15 day reportable event, the FDA will be notified accordingly.

The medical monitor will assist in writing the IND safety report with the study sponsor. The sponsor will submit all necessary reports to FDA regarding information relevant to the safety of the drug.

No Data Safety Monitoring Board (DSMB) is required for this study however, safety data will be reviewed by the sponsor on an ongoing basis and quarterly for trending of adverse events and clinically relevant safety data over time to identify potential safety signals and then determine if any action is needed to ensure the safety of subjects.

The sponsor will notify the PIs at each site regarding any dose limiting toxicity (DLT) and/or SAE related to BIO 300. Should the sponsor determine that the investigational drug presents an unreasonable and significant risk to subjects the study shall be discontinued. In this case, the study sponsor will notify the FDA, all institutional review boards, and all investigators who have at any time participated in the investigation of the discontinuance and assure the disposition of all stocks of the drug outstanding, and furnish FDA with a full report of the sponsor's actions.

10.6.3 Protocol Deviations

Compliance with the study protocol and all study procedures will be assessed at each on-site monitoring visit. A protocol deviation for this study is defined as any departure from the protocol whether pre-approved by the sponsor or unplanned. Protocol deviations may be identified during monitoring visits or by the site either in anticipation of a devaiation or

upon discovery. The research site should complete a Protocol Deviation CRF and submit it to the sponsor after review and signature by the investigator.

On a quarterly basis, the sponsor will review protocol deviations by site and overall to determine if there are any trends identified that may affect patient safety, data integrity and the impact on analysis and to determine if any actions need to be taken prevent continued deviations.

10.7 Records retention

Clinical records for all participants, including all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.), as well as IRB records and other regulatory documentation will be retained by the Protocol Lead Investigator in a secure storage facility in compliance with HIPAA, OHRP, FDA regulations and guidance, unless the standard at the site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two (2) years after the approval of an NDA. The sponsor will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration.

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12.0 APPENDICES

Appendix 1: Contact list

Site 100: Henry Ford Hospital

Role	Name/Address	Tel/Fax/Email
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Principal Investigator Clinical Trial Leader and Medical Oncologist	Ding Wang, MD Clinical Trials Leader and Senior Staff Physician Henry Ford Hospital 2799 West Grand Boulevard Detroit, MI, 48202-2689 http://www.henryford.com	[redacted]
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Appendix 2: Drugs that may prolong QTc

To determine if a drug may prolong the QTC interval, access the following link for a current listing of drugs with a known or possible risk of prolonging the QTc interval or inducing Torsades de Pointes (TdP), or contact the study sponsor. The use of these drugs should be carefully evaluated for this study.

https://crediblemeds.org/

Appendix 3: New York Heart Association Functional Classification

Class	Cardiac Symptom	Limitations	Need for Additional Rest	Physical Ability to Work
I	None	None	None	Full time
II	Only Moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually Moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

Appendix 4: RECIST Criteria

Response Assessment (RECIST Criteria)

Measurement of Response

The rate of progressive disease will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [redacted] See http://ctep.info.nih.gov/guidelines/recist.html for further details.

Response Criteria: Evaluation of target lesions
*Complete Response (CR): Disappearance of all target lesions
*Partial Response (PR): At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
*Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new Lesions
*Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Appendix 5: CTCAE version 4.03

Common Terminology Criteria for Adverse Events (CTCAE)

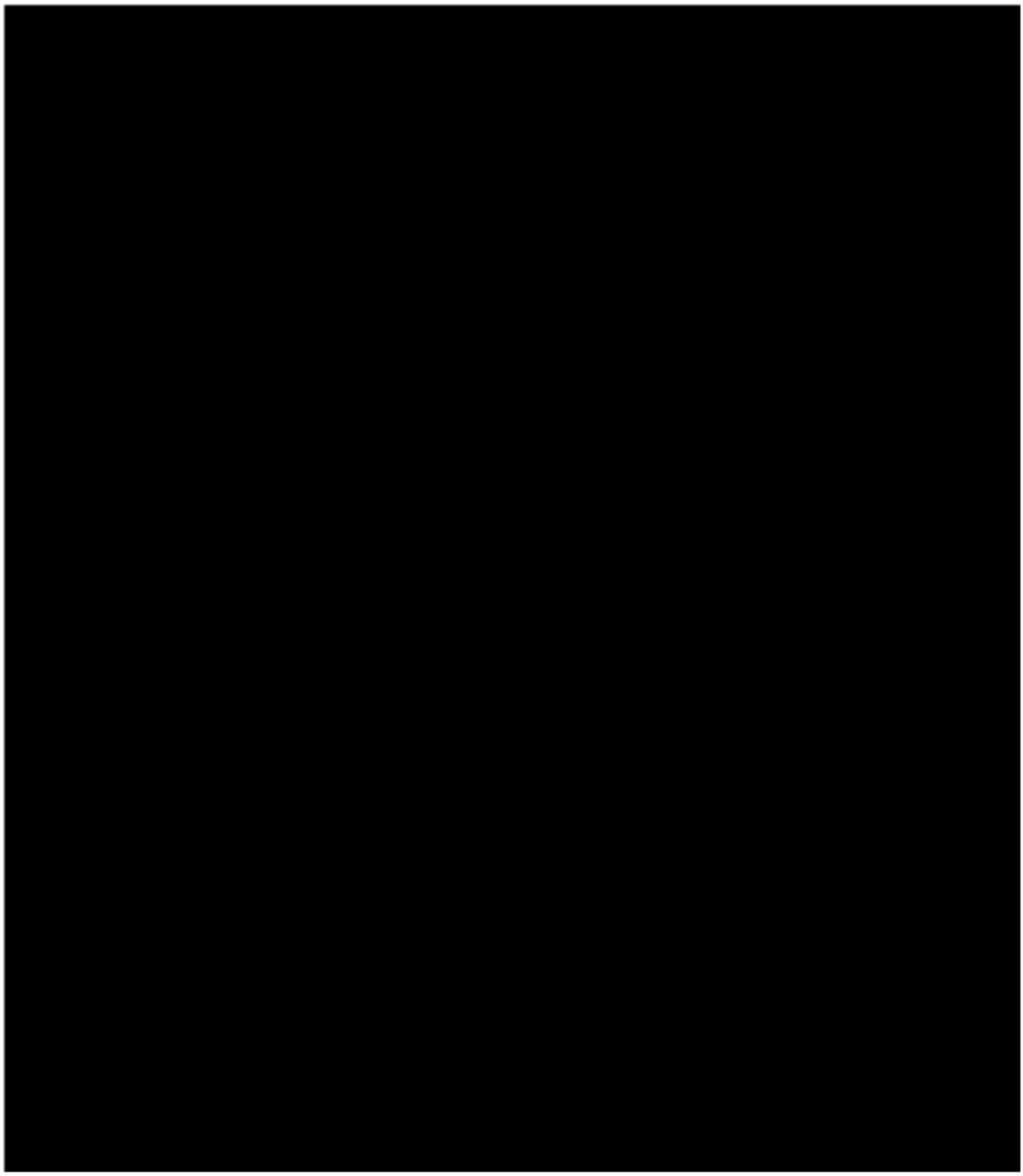
The most recent version of the CTCAE (v4.03) can be found and downloaded at the following link.

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Appendix 6: ECOG Performance status

To monitor and follow the patient's general well-being and activities of normal life the ECOG/Zubrod performance status will be determined throughout the course of the clinical study. The performance status score will be recorded at baseline, weekly during the 8-week study, at the follow up visits for consolidation therapy, at the first follow-up (3 months), and at 6 and 12 months.

ECOG Performance Status	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead



Appendix 8: Soy Rich Foods

The following is a list of soy rich foods that study participants should be counseled to avoid while participating in the study:

Edamame
Meat Alternatives containing soy protein or tofu, e.g.no meat hot dogs
Miso
Natto
Nutritional drinks and bars with added soy protein
Soymilk
Soy cheese
Soy ice cream
Soy yogurt
Soy Nuts
Tempeh
Textured Soy Protein
Tofu
Whole Soybeans

Use to the following links for additional information on soy rich foods:

http://www.ucsfhealth.org/education/a_guide_to_foods_rich_in_soy/

http://www.ars.usda.gov/SP2UserFiles/Place/80400525/Data/isoflav/Isoflav_R2.pdf

Appendix 9: Summary of blood draws for safety, PK, and PD assessment

		BIO 300 PK									BIO 300 + Chemo PK									Wk 2-6[f]				V36	V37	V38	V39
	Screening	Predose	Time post BIO 300 (hours) 0	0.5	1	2	3	4	8	24	Predose	Time post BIO 300 (hours) 0	0.5	1	1.5	2	2.5	3	4	8	24	Trough	Time post BIO 300 (hours) 0	0.5	1	1.5	2				
CBC	X	X									X										X						X	X	X	
Blood Chemistry	X	X									X										X						X	X	X	
Pregnancy (if applicable)	X[a]	X[a]																												
BIO 300 Dosing			X							X		X								X		X								
BIO 300 PK		X		X	X	X		X	X	X	X[b]	X[c]		X	X	X	X	X	X	X[e]	X[c]									
BIO 300 PD							X									X												X	X	X
Paclitaxel Infusion																											X	X		
Paclitaxel PK											X[c]				X[d]	X	X	X	X[e]		X[c]									
Carboplatin PK																														
Carboplatin Infusion																											X	X		
Draw #	1	1		2	3	4	5	6	7	8	1		2	3	4	5	6	7	8		1						1	1	1	1

[a] Pregnancy test can be either from urine or serum; [b] Blood draw should be 24 hours from previous days BIO 300 dose and prior to Visit 3 dose; [c] Blood draw should be prior to that days BIO 300 dose; [d] End of carboplatin infusion; [e] Blood draw should be 24 hours from previous days BIO 300 dose and prior to that visit's dose; [f] Trough level completed week 2 only if BIO 300 + Chemo PK completed on week 1.

Appendix 10: Criteria for Pathologic Response of Target Lesions and Extent of Surgical Resection

Criteria for Pathologic Response of Target Lesions

- Pathologic Complete Response (PCR): Complete resection (R0 resection) achieved and no evidence of viable tumor in the entire resection specimen;
- Mediastinal Pathologic Complete Response (MCR) (to be assessed only if there were mediastinal LNs (N2 disease) present at diagnosis): Complete resection achieved with no evidence of residual viable tumor in the mediastinal lymph nodes, regardless of the primary tumor status;
- Progressive Disease (PD): New sites of disease identified pathologically (e.g., malignant pleural studding, multiple pulmonary metastases, etc.);
- Stable Disease (SD): Not meeting the criteria of any of the three categories above.

Extent of Surgical Resection

- R0: Complete resection of all disease with negative margins and the highest lymph node resected negative for residual tumor;
- R1: Complete resection of all gross disease with pathologically positive margins and/or pathologic evidence of tumor cells in the highest lymph node resected in the mediastinum and/or extracapsular nodal spread;
- R2: Gross residual disease left behind after surgical resection.

Appendix 11: Radiation Pneumonitis quantification via CT changes

Quantifying CT Changes	
Score	**Description**
0	No change
1	Slight homogeneous increase in radiographic density (eg, ground glass appearance)
2	Patchy or multifocal consolidation that does not conform to irradiated area (presumably as too patchy)
3	Severe confluent consolidation that conforms to shape of irradiated area but does not uniformly involve it

Statistical Analysis Plan
(SAP)

PROTOCOL NUMBER:	CL0101-01
SAP VERSION:	Draft 6
SAP DATE:	9-Oct-2017
PROTOCOL DATE:	Original: 7 Apr 2015 Version 3.0: 18 Aug 2015 Version 3.0: 16 Feb 2016 Version 4.0: 2 May 2016 Version 5.0: 15 Aug 2016 Version 6.0: 20 Dec 2016 Version 7.0: 15 Aug 2017
SPONSOR:	Humanetics
PREPARED BY:	Humanetics
AUTHOR(S):	Melissa Ingram, Ph.D.
APPROVED:	
Name Title, Company	Date
Name Title, Company	Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under Curve
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
Cmax	Maximum Serum or Plasma Concentration
CR	Complete Response
CRFs	Case Report Forms
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DLCO	Diffusing capacity of the lungs for carbon monoxide
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Easter Cooperative Oncology Group
FACT-TOI	Functional Assessment of Cancer Therapy-Trial Outcome Index (lung cancer)
FAS	Full Analysis Set
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
Gy	Gray unit of absorbed ionizing-radiation dose
M-F	Monday-Friday
MTD	Maximum Tolerated Dose
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PD	Pharmacodynamics
PET	Positron Emission Tomography
PFS	Progression Free Survival
PFT	Pulmonary Function Test
PK	Pharmacokinetics
PLT	Platelet
PR	Partial Response
QOL	Quality of Life
QT	Time from ECG Q wave to the end of the T wave
QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiation Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOBQ	The University of California, San Diego Shortness of Breath Questionnaire
SOC	System Organ Class
STD	Standard Deviation
T1/2	Serum or Plasma half-life
Tmax	Time at Peak Serum or Plasma Concentration

1 INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of study data from Protocol CL0101-01. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

2 STUDY OBJECTIVES, TREATMENTS AND ENDPOINTS

2.1 STUDY OBJECTIVES

2.1.1 Primary Objectives

The primary objective is to describe any dose limiting toxicities of the combination of BIO 300 with chemoradiotherapy in subjects with non-small cell lung cancer (NSCLC) and to determine the recommended dose (the optimal dose) of this combination.

2.1.2 Secondary Objectives

Secondary objectives of this study are:

- To describe the overall adverse event profile of the combination of BIO 300 and chemoradiotherapy in the target patient population
- To determine the pharmacokinetics of BIO 300 and the chemotherapy components of the regimen (paclitaxel and carboplatin) when given in combination
- To determine the pharmacodynamic effects of BIO 300 in combination with chemoradiotherapy by the determination of certain serum protein and cytokine levels
- To report local progression rate as defined per RECIST (1.1) criteria or for surgical patients pathological response.
- Pulmonary function test (PFT) and quality of life (QOL) measures (FACT-TOI, USCD-SOB, and swallowing diary)
- To study the effect of BIO 300 on the incidence of pulmonary fibrosis following chemoradiotherapy in the target population as assessed by 4D CT scanning
- To determine overall survival (OS) and progression free survival (PFS) in the study population

2.2 TREATMENT GROUPS

A minimum of 6 subjects will be accrued sequentially at each dose of BIO 300. BIO 300 will be administered daily for the entire course of concurrent chemoradiotherapy, a minimum of 6 weeks; chemotherapy will be administered weekly for 6 weeks and radiotherapy will be administered daily (M-F) for a period of 6 weeks. The initial dose of BIO 300 will be 500 mg/d; subsequent doses will be 1000 mg/d and 1500 mg/d. Paclitaxel and carboplatin will be administered intravenously weekly, paclitaxel in a dose of 45 mg/m^2 and carboplatin in a dose sufficient to achieve an AUC of 2 mg*min/mL. Radiotherapy will be administered 5 days a week (M-F) for 6 weeks in a daily fraction of 2.0 Gy to a total dose of 60 Gy.

Following accrual of 6 subjects at a particular BIO 300 dose level, dose escalation may occur when a cohort has completed concurrent chemoradiotherapy with fewer than 33% DLTs attributed to BIO 300 Oral Suspension. Interim data analysis will be completed once the highest cohort concludes chemoradiation therapy, in an effort to determine the optimal biological dose. Following

analysis, there will be an option to enroll up to an additional 12 subjects at the optimal biological dose.

2.3 STUDY ENDPOINTS

2.3.1 Primary Endpoints

The primary endpoint of optimal BIO 300 dose is determined by DLT and MTD. Please refer to Section 3.1 for details in the determination of the optimal dose.

2.3.2 Secondary Endpoints

Adverse events and serious adverse events coded according to Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03.

Pneumonitis/fibrosis incidence according to documented AEs and quantification via CT.

- Pharmacokinetic endpoints for BIO 300, paclitaxel and carboplatin are:
  - Maximum concentration (C_{max})
  - Time at max concentration (T_{max})
  - Area under the concentration-time curve (AUC)
  - Half-life ($T_{1/2}$)
  - Clearance (Cl)
- Pharmacodynamic endpoints are:
  - Cytokines IL-6, IL-1β, IL-1α, IL-8, IL-10, TNFα, TGFβ1, TGFβ2, and TGFβ3
  - Granulocyte colony stimulating factor (G-CSF)
  - C-reactive protein, and
  - Prostaglandin E2
- Disease progression/Tumor response:
  - Objective tumor response Tumor diameter
  - Objective tumor response according to RECIST 1.1 Criteria
  - Progression Free Survival
- Quality of Life Measures:
  - SOBQ
  - FACT-TOI
  - Swallowing diary
- Pulmonary Function:
  - FVC/FEV1
  - DLCO

3 STUDY DESIGN

3.1 OVERALL STUDY DESIGN

This study is an open label, dose escalation trial with sequential cohorts of subjects receiving BIO 300 Oral Suspension and chemoradiation therapy. Three doses of BIO 300 Oral Suspension (500 mg/d, 1000 mg/d, and 1500 mg/d) will be administered during the course of concurrent chemoradiation therapy. Each cohort will begin with a study of the pharmacokinetics of BIO 300 Oral Suspension followed by a pharmacokinetic study of BIO 300 Oral Suspension in combination with paclitaxel and carboplatin. This is to describe any potential drug-drug interactions of BIO 300

Oral Suspension with the chemotherapeutics. The subjects will complete six (6) weeks of concurrent chemoradiation therapy while continuing daily BIO 300 Oral Suspension dosing. Following chemoradiation therapy patients will complete consolidation therapy as described. During consolidation therapy patients will not be dosed with the study drug.

A minimum of 6 subjects will be accrued sequentially at each dose of BIO 300. BIO 300 will be administered daily for the entire course of concurrent chemoradiotherapy, a minimum of 6 weeks; chemotherapy will be administered weekly for 6 weeks and radiotherapy will be administered daily (M-F) for a period of 6 weeks. The initial dose of BIO 300 will be 500 mg/d; subsequent doses will be 1000 mg/d and 1500 mg/d. Paclitaxel and carboplatin will be administered intravenously weekly, paclitaxel in a dose of 45 mg/m^2 and carboplatin in a dose sufficient to achieve an AUC of 2 mg*min/mL. Radiotherapy will be administered 5 days a week (M-F) for 6 weeks in a daily fraction of 2.0 Gy to a total dose of 60 Gy.

The initial dose of BIO 300 will be administered on Day 1, Visit 2, in which safety data (adverse events, ECGs, results of safety laboratory determinations), pharmacokinetic (PK) and pharmacodynamic (PD) data will be collected. PK data will be collected from a minimum of six (6) study participants from each study cohort. Blood samples for PD data collection will be collected prior to and post BIO 300 dosing (2 hr) from all subjects in each study cohort.

Day 1 of *chemotherapy* may be scheduled at the discretion of the investigator provided the subject has completed a minimum of 1 day of BIO 300 dosing. BIO 300 will be administered in combination with the chemotherapy components of the protocol therapy (paclitaxel and carboplatin). During the first or second chemotherapy infusion, as before, additional safety, PK and PD data will be collected. Blood samples for PD data collection will be collected prior to and post BIO 300 dosing (2 hr) from all subjects in each study cohort.

Day 1 of *radiation therapy* (RT) may be scheduled at the discretion of the investigator provided the subject has completed a minimum of 2 days of BIO 300 dosing. BIO 300 will continue to be administered daily; paclitaxel and carboplatin will be administered weekly and radiotherapy will be administered daily as described above until a total dose of 60 Gy has been administered. During the period of combined BIO 300 and chemoradiotherapy (6 weeks), additional safety, PK and PD data will be collected weekly. Trough levels for BIO 300, paclitaxel, and carboplatin will be collected weekly. Blood samples for PD data collection will be collected weekly during the combined BIO 300 and chemoradiotherapy period at the same time as the trough levels, just prior to that week's chemotherapy treatment and that days' BIO 300 dose. Total duration of BIO 300 treatment will be a minimum of 6 weeks. Blood samples for PD data will also be collected at the end of the consolidation phase, and at the 3 and 6 months follow up visits.

Following accrual of 6 subjects at a particular BIO 300 dose level, dose escalation may occur when a cohort has completed concurrent chemoradiotherapy with fewer than 33% DLTs attributed to BIO 300 Oral Suspension. Interim data analysis will be completed once the highest cohort concludes chemoradiation therapy, in an effort to determine the optimal biological dose. Following analysis, there will be an option to enroll up to an additional 12 subjects at the optimal biological dose.

3.2 DOSE LIMITING TOXICITIES

Dose limiting toxicities are defined by any of the following BIO 300 related events which occur before or during concurrent chemoradiation and is collected in the AE CRFs:

1) Radiation esophagitis Grade 3 that lasts > 7 consecutive days or Grade 4.
2) Grade 4 neutropenia for more than 7 days or neutropenia fever (defined as ANC < 500 and a temperature of 38.5° C or above).
3) Grade 3 thrombocytopenia with clinically significant bleeding
4) Grade 4 thrombocytopenia > 7 days.
5) Grade 4 nausea/vomiting despite appropriate antiemetic therapy.
6) Grade 3 AST/ALT elevations > 7 days
7) Delays in radiotherapy or chemotherapy due to toxicity of more than 3 weeks. Delays in the current standard of care treatment are likely to have a negative effect on patient outcome and thus are to be designated as a DLT.
8) All other non-hematologic toxicities of Grade 3 or higher, with the following exceptions:
    a. anorexia
    b. fatigue
    c. infection without neutropenia
    d. Grade 3 AST/ALT elevations ≤ 7 days
    e. Infusion reactions. Patients with Grade 3 or worse infusion reactions will be removed from the study and replaced and will not be considered evaluable for DLT.
    f. Grade 3 or 4 electrolyte abnormalities that are corrected to Grade 2 or less in less than 48 hours.

3.3 EARLY TERMINATION

3.3.1 Potential Reasons for Subject Attrition

For any subject leaving the study early, the final study measurements will be performed at the time of departure (or as shortly thereafter as possible).

1) Drug-Related Reasons
    a. Subject experiences an adverse reaction and does not wish to remain in the trial.
    b. Subject experiences a serious adverse reaction or a specific adverse reaction that requires discontinuation according to the protocol as determined by the investigator.
    c. Clinical trial is terminated prematurely because of unacceptable safety concerns (risks) of the supplement being tested.
2) Clinical-Trial-Related Reasons
    a. Subject indicates the requirements are too onerous, or too long, or loses interest; or refuses to participate.
    b. Clinical trial is terminated at a preset date and some subjects are not completed.
3) Subject-Related Reasons Determined by the Investigator
    a. Subject fails to maintain adequate compliance with one or more aspects of the protocol or subject fails to cooperate adequately during clinical visits.
    b. Subject found not to meet or no longer meets the original entry requirements.
    c. Subject has used a non-approved medicine or treatment during the trial.
    d. Subject who at the Investigator's discretion feels that continuing in the study would not be in their best interest.
    e. Subject becomes pregnant (observation and follow-up procedures must be initiated).
    f. Subject withdraws informed consent.

4) Other Reasons
    a. Subject refuses to state reasons for dropping out.
    b. Subject develops an intercurrent illness and is unable or unwilling to continue in a clinical trial; however, Investigator did not wish to discontinue the subject.
    c. Subject's personal situation changes: e.g. more work responsibility/travel or home changes (moves, marries, family) and subject has less time/motivation to participate.
    d. Other issues requiring withdrawal of the subject from the trial.
5) Lost to Follow-up
6) Death

3.3.2 Criteria for Discontinuation of Subjects from the Trial

Protocol treatment may be discontinued for any of the following reasons:

1) At the discretion of the Investigator, atypical progression of disease;
2) If 40% or more of subjects (4 out of a total of 10) in a cohort experience a DLT attributable to BIO 300 Oral Suspension, the MTD will have been exceeded and enrollment into that cohort and any higher-dose cohort currently open to enrollment will cease (see section 8.5, Dose Limiting Toxicities (DLTs).
3) A delay in protocol treatment of greater than 3 weeks during the concurrent phase and more than 4 weeks in the consolidation chemotherapy phase.
4) Any one of the Dose Limiting Toxicities listed in section 8.5, Dose Limiting Toxicities (DLTs).
5) If protocol treatment is discontinued due to delay or dose limiting toxicity (DLT), at the discontinuation visit, CBC with differential and serum chemistries will be completed for safety reporting. At the discretion of the Investigator, additional follow-up blood work may be requested.
6) If protocol treatment is discontinued for any other reason, at the discretion of the Investigator, CBC with differential and serum chemistries may be requested for safety reporting purposes.

3.4 SCHEDULE OF STUDY ASSESSMENTS

Table 3-1: Time to Event for non surgical subjects

VISIT #	1	2	3	4-5[a]	6-10	11-35[b]	S[c]	36	37	38	39	40	41	42
Procedure	Screening	Week 1, d1	Week 1, d2	Week 1, d3-4[a]	Week 2	Wks 3-6	Day 59	Day 66	Day 87	Post RT Completion				
										3 mo	6 mo	9 mo	11 mo	13 mo
Informed Consent	x													
Review I/E Criteria	x	x												

Medical History	x													
Physical Exam[1]	x	x[b]			x[b]	x[b]	x	x	x	x	x	x		x
ECOG Score	x	x[b]			x[b]	x[b]	x	x	x	x	x	x		x
Vital Signs	x	x[b]			x[b]	x[b]	x	x	x	x	x	x		x
Weight	x	x[b]			x[b]	x[b]	x	x	x	x	x	x		x
Height	x													
ECG	x[2]	x[3]			x[4b]	x[4c]								
CBC	x	x			x[b]	x[b]		x	x	x				
Serum Chemistry[5]	x	x			x[b]	x[b]		x	x	x				
Urinalysis[6]	x													
Pregnancy Test[7]	x	x												
Extent of Disease	x					x[d]	x		x	x	x	x	x	x
PK sampling		x	x	x[f]	x	x[b]								
PD sampling		x		x[f]	x	x[b]			x	x	x			
BIO 300 Admin.		x	x	x	x	x								
Concurrent Chemotherapy			x[b]		x[b]	x[b]								
Radiation Therapy				x	x	x								
Consolidation Chemotherapy								x	x					
Adverse Events[10]		x	x	x	x	x	x	x	x	x	x	x		x
Concomitant Medications	x	x[b]			x[b]	x[b]	x	x	x					
QoL Measures	x									x	x			x
Pulmonary Function Test	x						x				x			x
Diag. CT Scan	x						x			x	x		x	
4D-CT Scan	x					x[d]			x			x		x
Swallowing Diary	x	x[b]			x[b]	x[b]				x	x			

Diet Counseling[g]	x	x[b]		x[b]	x[b]							

[a]Optional visit 5b as needed, [b]weekly, [c]bi-weekly (every other week), [d]visit 20 only; visit window allowance of +/- 7 days, [e]Optional surgical evaluation, if subject is medically fit for surgery use table 7.1.2, [f]BIO300 +chemo PK scheduling allowed week 1 or 2, See Table 7.1.3 for details

Table 3-2: Time to Event for surgical subjects

VISIT #	**1**	**2**	**3**	**4-5[a]**	**6-10**	**11-35[g]**	**S**	**36**	**37**	**38**	**39**	**40**	**41**
Procedure	Screening	Week 1, d1	Week 1, d2	Week 1, d3-4[a]	Week 2	Wks 3-6	Day 59	6-12 wk post-surgery	10-16 wk post-surgery	Post Consolidation			
										3 mo	6 mo	9 mo	12 mo
Informed Consent	x												
Review I/E Criteria	x	x											
Medical History	x												
Physical Exam[1]	x	x[b]			x[b]	x[b]	x	x	x	x	x	x	x
ECOG Score	x	x[b]			x[b]	x[b]	x	x	x	x	x	x	x
Vital Signs	x	x[b]			x[b]	x[b]	x	x	x	x	x	x	x
Weight	x	x[b]			x[b]	x[b]	x	x	x	x	x	x	x
Height	x												
ECG	x[2]	x[3]			x[4b]	x[4c]							
CBC	x	x			x[b]	x[b]		x	x	x			
Serum Chemistry[5]	x	x			x[b]	x[b]		x	x	x			
Urinalysis[6]	x												
Pregnancy Test[7]	x	x											
Extent of Disease	x					x[d]	x			x	x	x	x
PK sampling		x	x	x[f]	x	x[b]							
PD sampling		x		x[f]	x	x[b]			x	x	x		
BIO 300 Admin.		x	x	x	x	x							
Concurrent Chemotherapy			x[b]		x[b]	x[b]							
Radiation Therapy				x	x	x							

Consolidation Chemotherapy								x	x				
Adverse Events[10]		x	x	x	x	x	x	x	x	x	x	x	
Concomitant Medications	x	x[b]			x[b]	x[b]	x	x	x				
QoL Measures	x									x	x		x
Pulmonary Function Test	x						x				x		x
Diag. CT Scan	x						x			x	x	x	x
4D-CT Scan	x												
Swallowing Diary	x	x[b]			x[b]	x[b]				x	x		
Diet Counseling[g]	x	x[b]			x[b]	x[b]							

[a]Optional visit 5b as needed, [b]weekly, [c]bi-weekly (every other week), [d]visit 20 only; visit window allowance of +/- 7 days, [f]BIO300 +chemo PK scheduling allowed week 1 or 2, See Table 7.1.3 for details

Description of schedule of assessments

1. A complete physical exam will be completed at screening. Other visits require a brief exam, focus on areas of tumor involvement or referable to adverse events.
2. ECGs will be performed in triplicate. Each reading will be separated by 5 minutes.
3. ECG is utilized to assess acute changes that may impact cardiac toxicity. ECGs to be obtained just prior to administration of BIO 300, and 1 hour post administration of BIO 300.
4. ECG data will be collected prior to BIO 300 or chemotherapy administration, whichever comes first.
5. To include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, total bilirubin, albumin, total protein, magnesium, calcium, phosphorous and uric acid. Analysis of pancreatic enzymes also to be included in panel (amylase and lipase).
6. Urinalysis to include pH, specific gravity, dipstick determinations of glucose, ketones, protein, hemoglobin, bilirubin.
7. Pregnancy test may be urine or serum determination of β-HCG. Visit 2 test is only required if the screening pregnancy test was performed more than 72 hours prior to visit 2.
8. At the screening visit patients will be counseled and given instructions on a diet low in soy isoflavones. Diet counseling will occur weekly during the time period where BIO 300 is administered.
9. The total number of subject visits completed through concurrent chemoradiotherapy are flexible and dependent on radiotherapy and chemotherapy scheduling. Each subject will

have a minimum of 32 visits through the conclusion of concurrent chemoradiotherapy (6 weeks of chemotherapy and daily RT fractions of 2.0 Gy, total dose of 60 Gy).

10. All adverse events will be collected from the time the subject signs informed consent until 30 days after the last administration of BIO 300. After this time, adverse event assessment will occur at each visit but only those events that are considered serious and possibly, probably or definitely related to BIO 300 will be documented and reported to the sponsor within 24 hours of awareness.

Table 7.1.3 Visit Window Table

Visit or Procedure	Visit Window	Notes
Screening Visit	Within 28d prior to registration.	Pulmonary Function Test, Medical History, Physical Exam and CTs may be completed within 10 wks prior to registration
Concurrent Chemotherapy	Day 1 of chemotherapy may be scheduled at the discretion of the investigator provided the subject has completed a minimum of 1 days of BIO 300 dosing.	Should visits be delayed due to a holiday, standard of care should be followed.
Radiation Therapy	Day 1 of radiation therapy may be scheduled at the discretion of the investigator provided the subject has completed a minimum of 2 day of BIO 300 dosing.	Should visits be delayed due to a holiday, standard of care should be followed.
BIO 300 + Chemo PK	BIO 300 + Chemo pharmacokinetics may be scheduled week 1 or week 2 at the discretion of the investigator provided the subject has completed at least 4 days and no more than 9 days of BIO 300 dosing.	
PK sampling	For the pre-BIO 300 administration time point and the 0.5 and 1 hour time points, blood will be collected within ± 5 minutes of the defined draw time post BIO 300 dosing. For the 2, 3, 4 and 8 hour time points, blood will be collected within ± 10 minutes for the defined draw time post BIO 300 dosing. The 24hr draw should occur as close to 24 hours after the dose of BIO 300 and prior to the morning dose of BIO 300.	
CBC	May be drawn up to 4d prior to visits where chemotherapy is administered	
Serum Chemistry	May be drawn up to 4d prior to visits where chemotherapy is administered	
Visit S, Surgical Evaluation	+/- 7d	
Visit 36-37, Consolidation Chemotherapy	+/- 7d	+/- 14d for CT
Visit 38-39, 3 and 6 month follow up	+/- 14d	
Visit 40-42, 9-13 month follow up	+/- 21d	For surgical subjects visit 41, 12 month follow up (end of study)

4 SAMPLE SIZE CONSIDERATIONS

No formal sample size calculation will be performed as this study is meant to be hypothesis generating.

5 ANALYSIS POPULATIONS

5.1 FULL ANALYSIS SET

The Full Analysis Set (FAS) will include all subjects who receive at least one dose of BIO 300. This analysis set will be used to summarize all safety endpoints.

5.2 EFFICACY ANALYSIS SET

The Efficacy Analysis Set (EAS) will include all subjects who receive at least one dose of BIO 300 and have at least one extent of disease assessment following the conclusion of concurrent therapy.

5.3 PHARMACOKINETIC (PK) POPULATION

The PK Population will include all subjects who receive at least 1 dose of BIO 300 and have sufficient, valid PK samples to estimate key parameters for at least 1 of the days of sampling. PK summaries will be based on the PK population.

5.4 PHARMACODYNAMICS (PD) POPULATION

The PD Population will include all subjects who receive at least 1 dose of BIO 300 and have sufficient, valid PD samples to estimate key parameters for at least 1 of the days of sampling. PD summaries will be based on the PD population.

6 CONSIDERATIONS FOR DATA ANALYSIS

6.1 PROGRAMMING ENVIRONMENT

Data will be exported from the study specific validated clinical trial database and imported into the R software environment for statistical computing and graphics generation [1].

6.2 STRATA AND COVARIATES

There are no strata or covariates for this study.

6.3 SUBGROUPS

Subgroups will not be analyzed in this study. Future studies will include subgroup analyses, subgroups may include:

- Gender
- Cancer stage at enrollment
- Histology (e.g. subtype of NSCLC)
- Tumor location

6.4 MULTIPLE COMPARISONS AND MULTIPLICTY

There are no planned adjustments for multiplicity.

6.5 SIGNIFICANCE LEVEL

An independent statistician using standard statistical techniques will determine statistically significant differences in the trial measurement data at the nominal 0.05 level of significance.

6.6 STATISTICAL NOTAION AND METHODOLOGY

Unless stated otherwise, the term "descriptive statistics" refers to the number of subjects (n), mean, median, standard deviation (STD), minimum (min), and maximum (max) and standard errors/confidence intervals for continuous response variables and distribution tables or histograms for discrete response variables. Min and max values will be rounded to the precision of the original value, means and medians will be rounded to 1 decimal place greater than the precision of the original value, and STDs will be rounded to 2 decimal places greater than the precision of the original value. Percentages will be rounded to the nearest whole number (zeros are not displayed) with values of "< 1%" and "> 99%" shown as necessary for values falling near the boundaries.

In addition, relationships between these response variables will be explored using non-parametric approaches (e.g., Spearman rank correlation), parametric correlation analysis methods (e.g., correlation coefficient), or appropriate statistical tests (e.g., the Chi-square trend test for categorical data). Furthermore, appropriate regression techniques for these response variables (e.g., analysis of covariance (ANCOVA)), linear regression, proportional hazards regression, logistic regression, generalized estimating equation (GEE) and mixed effects models) will be employed to further examine their relationship with one another. Confidence intervals will be calculated for the differences. The computed change from baseline will be calculated for all measured variables and expressed as the mean change from baseline + standard deviation (STD) of the change from baseline. A two-sample t-test will be used to test the tumor size reduction and a log-rank test will be used to compare time to event outcomes. Analysis of covariance will be used to compare dosage groups on "change from baseline" measures (with baseline measurement considered as an adjustment covariate).

Unless otherwise note, all data collected during the study will be included in data listings and will be sorted by treatment group, subject number and then by visit for each subject number.

7 DATA HANDLING METHODS

7.1 MISSING DATA

Given the small sample size, descriptive statistics and other analyses will be completed without replacing or imputing missing values, with the exception of the FACT-TOI which will be prorated as described below.

7.1.1 FACT-TOI Handling of Missing Items

FACT scoring will be completed as described in the Administration and Scoring Guidelines in the manual or on-line at www.facit.org. Briefly, if there are missing items, subscale scores will be

When there are missing data, prorating by subscale in this way is acceptable as long as **more than** 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc.). The total score is then calculated as the sum of the un-weighted subscale scores. The FACT scale is considered to be an acceptable indicator of patient quality of life as long as **overall item response rate** is greater than 80% (e.g., at least 22 of 27 FACT-G items completed). This is not to be confused with individual subscale item response rate, which allows a subscale score to be prorated for missing items if greater than 50% of items are answered. In addition, a total score should only be calculated if ALL of the component subscales have valid scores.

7.2 VISIT WINDOWS

Values will be presented for all scheduled study visits according to the nominal value obtained from the CRF. If an unscheduled visit falls in a visit window with an existing nominal visit assessment, the nominal assessment will be used for summary presentation. If no nominal visit assessment exists for a visit window with unscheduled visit(s), then the latest unscheduled visit within the visit window will be used. If multiple nominal assessments are collected within the same visit, the latest value and corresponding date will be used for summary presentation.

7.3 DATA DERIVATIONS AND DEFINITIONS

Baseline will be considered as the last non-missing assessment prior to the first administration of BIO 300.

Changes from baseline will be calculated as differences between assessment values and their corresponding baseline values.

Percent changes from baseline will be calculated as differences between assessment values and their corresponding baseline values divided by the corresponding baseline values.

Age will be calculated from the date of birth to screening visit date.

If multiple dates occur for the screening visit, the convention as described at the end of Section 7.2 will be used.

The following will define prior medication use versus concomitant medication use:

- Prior use ended before the first administration of BIO 300
- Concomitant use is on or after the first administration of BIO 300 and prior to 30 days post the last administration of BIO 300

8 STUDY POPULATION

Unless otherwise stated, all study population analyses will be performed on the Full Analysis Set (FAS).

8.1 ANALYSIS POPULATION

The analysis population listing will include, for each population detailed in Section 5, whether or not the subject was included in the population and the reason for being excluded from the population. Number of subjects in each analysis population will be summarized both overall and by treatment group.

8.2 SUBJECT DISPOSTITION

Subject disposition will be presented for all subjects. The composition of the analysis populations and those who enrolled, completed or discontinued from the study will be summarized by treatment group and overall with descriptive statistics. Reasons for discontinuation will be present with frequencies and percentages for all categories. A comprehensive data listing will also be included.

8.3 INCLUSION/EXCLUSION CRITERIA

Inclusion and exclusion criteria failures will be included in a data listing.

8.4 PROTOCOL DEVIATIONS

Protocol deviations will be summarized by treatment group and category and included in a data listing.

Major protocol deviations include, but are not limited to the following:

- Non-fulfillment of all inclusion criteria or fulfillment of at least one exclusion criteria;
- Improper Informed Consent process;
- Non-delegated study personnel dispensing investigational product;
- Other relevant violations, to be judged on an individual basis.

Minor protocol deviations include, but are not limited to:

- Measurements obtained outside the visit window to a limited degree;
- Missed visit assessments;
- Lack of source documentation;
- Other deviations will be judged on an individual basis.

8.5 DEMOGRAPHIC CHARACTERISTICS

Demographic and baseline characteristic data will be summarized with descriptive statistics for age, gender, race, ethnicity, height, weight, initial tumor stage, tumor histology, tumor location, and marital status. A comprehensive listing will also be included.

8.6 CONCOMITANT MEDICATIONS

A data listing will be included that shows all medications by verbatim name.

8.7 MEDICAL HISTORY

A comprehensive data listing of medical history will be included.

9 EFFICACY ANALYSIS

9.1 OBJECTIVE RESPONSES

Objective responses of the target lesion based on measurements from a conventional CT scan, PET/CT, 4D-CT or other will be determined in all subjects at baseline according to the RECIST 1.1 criteria (see Appendix 4 of the protocol). The proportion of patients experiencing progressive

disease, stable disease (SD), partial responses (PR) or complete responses (CR) will be summarized in tabular format.

Per RECIST 1.1, overall response rate (ORR) will be calculated using best overall response with confirmation of CR and PR. The corresponding 95% exact confidence interval will be calculated based on the binomial distribution.

Best overall response (progressive disease, stable disease, PR, CR, or not applicable/not evaluable) will be tabulated. If SD is believed to be best response, measurements must have met the SD criteria at least once after study entry at a minimum interval of 42 days. If the minimum time is not met when SD is the best time point response, the patient's best response depends on the subsequent assessments (according to RECIST 1.1).

Tumor diameter measurements and change from baseline will be summarized with descriptive statistics by visit with respect to treatment group. A plot of tumor diameter over time will also be included.

9.2 DURATION OF RESPONSE (DOR)

Duration of response (DOR) is defined as the time from the first tumor response of CR or PR to documented tumor progression or death, whichever is the earliest.

DOR will be summarized for the responders only. Responder is defined as those subjects who had tumor response of CR or PR.

A Kaplan-Meier analysis of DOR will be performed together with its 95% confidence interval.

The DOR will be censored in the following scenarios:

1) Subjects who go off treatment for reasons other than progression and begin treatment with other anti-neoplastic therapies will also be censored at the date of last tumor assessment before starting other anti-neoplastic therapies.
2) If subject had progressive disease or death occurred after missing two tumor assessments, the patient will be censored at the date of the previous tumor assessment with CR, PR or SD.
3) If subject does not have post baseline tumor assessment or with no PD or death within two assessments after enrollment, the DOR will be censored at the date of the first dose of study drug.
4) If a subject withdraws from the study prematurely for reasons other than disease progression or death, DOR will be censored at the subject's last date known alive and not PD.

DOR will be presented in a by-subject listing.

9.3 PROGRESSION FREE SURVIVAL

Progression free survival (PFS) will be calculated from the first administration of BIO 300 until death or until the criteria for disease progression are met (according to RECIST 1.1 or in the opinion of the treating physician). A Kaplan-Meier analysis of PFS will be performed and median survival time and its 95% confidence interval will be computed by treatment cohort and overall. A Kaplan-Meier curve will be presented.

If the subject has not progressed or dies at the time of the final data cutoff, PFS will be censored using the same rules described in 9.2.

PFS (in days) is calculated as:

(Date of death of documented progression) – (Date of first administration of BIO 300) + 1, if event

(Date of last tumor assessment with CR, PR, or SD) – (Date of first administration of BIO 300) + 1, if censor

A comprehensive data listing will also be included.

9.4 PULMONARY FUNCTION TEST

The measurements of PFT including forced vital capacity (FVC), forced expiratory volume (FEV_1), FEV_1/FVC, diffusion capacity (DLCO) and change from baseline will be summarized with descriptive statistics by time point with respect to treatment group.

A data listing of all results will also be included.

9.5 SWALLOWING DIARY

The patient self-assessed daily swallowing score (the swallowing questionnaire) from 0 to 5, 1 no problems swallowing; 2 mild soreness only; 3 some difficulty swallowing solids; 4 cannot swallow solids; and 5 cannot swallow liquids. The measurements will be analyzed using area under the curve (AUC) methodology, which incorporates both the grade and duration of the measured end point. The average score from the swallowing diary will be plotted by treatment group.

A comprehensive data listing will also be included.

9.6 SOBQ

The SOBQ will be scored by summing responses across the 24 items to form a total score, ranging from 0 to 120. The measurements and change from baseline will be summarized with descriptive statistics and time point with respect to treatment group.

9.7 FACT-TOI

The FACT-TOI will be scored according to FACT-L Scoring Guidelines Version 4. The measurements and change from baseline will be summarized with descriptive statistics and time point with respect to treatment group.

10 SAFETY

The full analysis set will be used for all the analyses of safety data. Safety data will include AEs, safety laboratory (CBC/hematology, serum chemistry and urinalysis), pregnancy test (if applicable), physical exam, ECG, ECOG and vital signs. The proportion of subjects experiencing adverse events, serious adverse events, and dose limiting toxicities will be summarized for each dosing cohort. A data listing of subjects experiencing treatment delays will also be included.

10.1 EXPOSURE TO STUDY DRUG

BIO 300 will be orally administered daily through concurrent chemoradiotherapy for up to 8 weeks. Total dose administered (mg), duration of exposure (weeks) and study treatment dosing

compliance will be summarized with descriptive statistics by treatment group. A comprehensive data listing for BIO 300 administration will also be provided.

10.2 DLT AND MTD

The primary objective of the study is to describe any dose limiting toxicities and to determine the recommended dose (the optimal dose) of this combination.

The definition of DLT is specified in Section 3.2. Methodology for determining the MTD is specified in Section 3.1.

The dose selected as the MTD or the optimal dose of BIO 300 will be summarized. DLT will also be summarized for the dose levels.

10.3 ADVERSE EVENTS

The CTCAE Version 4.03 will be used to grade all AEs. All reported terms and descriptions for AEs will be coded using CTCAE Version 4.03 and summarized with frequencies and percentages by treatment group, system organ classification (SOC) and preferred term.

Additionally, AE summaries will be provided for the following:

- DLT
- AEs
- AEs leading to discontinuation from the study
- AEs by relationship to BIO 300
- AEs by severity using CTCAE grade
- AEs with 10% or higher incidence rates

For all AE summaries, events will be counted only once per subject by primary SOC and preferred term. When an AE occurs more than once for a subject, the maximum severity and causality will be used.

All AEs will be included in comprehensive data listings. Separate listings will be provided for AEs of DLTs, all AEs related to BIO 300, all Grade 3 or 4 AEs, AEs leading to discontinuation from study, and AEs collected more than 30days post final BIO 300 administration that were not included in AE summaries or analysis.

10.4 SERIOUS ADVERSE EVENTS AND DEATH

Separate data listings and summaries will be present for all SAEs and deaths.

10.5 LABORATORY EVALUATIONS

Laboratory assessments will be summarized with descriptive statics, by test and treatment group. Additionally, abnormal results of CTCAE grade 3 or higher will be summarized.

A data listing will display all laboratory test results and findings.

10.6 PREGNANCY TEST

A data listing of pregnancy test results will be provided.

10.7 PHYSICAL EXAMINATIONS

The results of physical examinations will be in a data listing.

10.8 ELECTROCARDIOGRAMS

ECG QTc measurements will be summarized with descriptive statistics and time point with respect to treatment group. All ECG data will be displayed in a data listing.

10.9 ECOG

The ECOG performance status is a physician assigned rating scale used to assess how a patient's disease is progressing in addition to how the disease affects the daily living abilities of the patient. The score values are 0 to 5, where 0 indicates "fully active, able to carry on all pre-disease performance without restriction" and 5 indicates the subject has died. It will be conducted at screening, weekly during concurrent chemoradiotherapy, and every visit thereafter except visit 41, 11 month post-RT completion for non-surgical subjects. Listings of ECOG performance status will be provided.

10.10 VITAL SIGNS

The results of vital signs (including temperature, respiratory rate, heart rate, systolic and diastolic blood pressure, height and weight) will be summarized with descriptive statistics by treatment group. A data listing of all vital signs data will be included.

11 PHARMACOKINETICS ANALYSES

A detailed PK analysis plan and results will be included in a separate PK analysis report.

12 PHARMACODYNAMIC ANALYSES

Potential pharmacodynamics markers include the circulating levels of cytokines IL-6, IL-1β, IL-1α, IL-8, IL-10, TNFα, TGFβ1, TGFβ2, and TGFβ3. Similarly, serum proteins of interest include granulocyte colony stimulating factor (G-CSF), C-reactive protein, and prostaglandin E2. The PD results and change from baseline will be summarized with descriptive statistics, by test and time point with respect to treatment group. A data listing will display all PD results.

13 INTERIM ANALYSIS

Two interim analyses are planned. The first will be completed at the conclusion of the NCI contract 19 September 2017. Second, at the completion of dose escalation, interim data analysis will be completed to assess BIO 300 safety and to review secondary outcome measures. Data trends will be used to choose a single BIO 300 dose (500, 1000 or 1500mg/d) as the optimal biological dose. Up to an additional 12 subjects will be enrolled at the optimal biological dose to further evaluate BIO 300's safety and efficacy. The maximum tolerated dose will be used for cohort 4 if there are no apparent differences in efficacy.

14 END-OF-STUDY ANALYSIS

A final analysis will be conducted after the last subject completes or discontinues the study and the resulting clinical database has been cleaned, quality checked and locked.

15 TABLE OF CONTENTS FOR DATA DISPLAYS

15.1 DEMOGRAPHISC SUMMARY FIGURES AND TABLES

Study Population Tables

Table	Title	Population
14.1.1	Summary of Analysis Populations	FAS
14.1.2	Summary of Demographic and Baseline Characteristics	FAS
14.1.3	Summary of Protocol Deviations	FAS
14.1.4	Summary of Total Dose of BIO 300 Administration	FAS

Study Population Figures

Figure	Title	Population
14.1.1	Disposition of Subjects	FAS

15.2 EFFICACY SUMMARY FIGURES AND TABLES

Efficacy Tables

Table	Title	Population
14.2.1	Summary of Overall Response Rate and Best Overall Response per RECIST 1.1	EAS
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14.2.3	Summary of Tumor Diameter	Evaluable
14.2.4	Summary of Duration of Response	EAS
14.2.5	Summary of Duration of Response	Evaluable
14.2.6	Summary of Progression Free Survival per RECIST 1.1	FAS
14.2.7	Summary of Progression Free Survival per RECIST 1.1	Evaluable
14.2.8	Summary of Absolute Value and change from baseline in Pulmonary Function Testing Measurements	EAS
14.2.9	Summary of Swallowing Dairy AUC	EAS
14.2.10	Summary of SOBQ Findings	EAS
14.2.11	Summary of FACT-TOI Findings	EAS

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Figures	Title	Population
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14.2.2	Kaplan-Meier Curve for Progression Free Survival	Evaluable
14.2.3	Kaplan-Meier Curve for Progression Free Survival	Evaluable

14.2.4	Kaplan-Meier Curve for Duration of Response	FAS
14.2.5	Kaplan-Meier Curve for Duration of Response	Evaluable
14.2.6	Plot of the Average Scores for Swallowing Diaries	EAS

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15.3.1 Adverse Events

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14.3.1.2	Summary of Frequency and Reasons for Dose Interruptions	FAS
14.3.1.3	Summary of Adverse Events	FAS
14.3.1.4	Summary of Adverse Events Leading to Discontinuation from the Study	FAS
14.3.1.5	Summary of Adverse Events by Relationship to BIO 300	FAS
14.3.1.6	Summary of Adverse Events by Severity Using CTCAE Grade	FAS
14.3.1.7	Summary of Adverse Events with 10% or Higher Incident Rate	FAS

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14.3.2.2	Summary of Serious Adverse Events by relationship to BIO 300	FAS
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Not applicable.

15.3.4 Laboratory Results

Table	Title	Population
14.3.4.1	Summary of Clinical Laboratory Results	FAS
14.3.4.2	Summary of Abnormal Clinical Laboratory Results	FAS
14.3.4.3	Summary of Urinalysis/Pregnancy Results	FAS

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Table	Title	Population
14.3.5.1	Summary of Electrocardiogram QTc Results	FAS
14.3.5.2	Summary of Vital Signs	FAS

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15.4.7.7 CTCAE Grade 3 or 4 Adverse Events
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15.4.8.2 Clinical Laboratory Results
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15.4.9 Listings of Other Safety Endpoints

15.4.9.1 Physical Examinations
15.4.9.2 Electrocardiogram Findings
15.4.9.3 Eastern Cooperative Oncology Group (ECOG) Performance Status
15.4.9.4 Vital Signs Test Results

16 REFERENCES

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2. Movsas, B., et al., *Randomized trial of amifostine in locally advanced non-small-cell lung cancer patients receiving chemotherapy and hyperfractionated radiation: radiation therapy oncology group trial 98-01*. J Clin Oncol, 2005. **23**(10): p. 2145-54.

Shell Tables and Figures

Table 14.1.1 Summary of Analysis Population

Analysis Set	All	500 mg	1000 mg	1500 mg
Full Analysis Set (FAS)	N	N	N	N
Efficacy Analysis Set (EAS)	N	N	N	N
PK Population	N	N	N	N
PD Population	N	N	N	N

Table 14.1.2 Summary of Demographic and Baseline Characteristics

Patient Characteristic	All (N)	500 mg (N)	1000 mg (N)	1500 mg (N)
M/F				
Median age (range)				
Race				
American Indian or Alaskan Native				
Asian				
Black or African American				
Native Hawaiian or Other Pacific Islander				
White or Caucasian				
Unknown or Not Reported				
Ethnicity				
Hispanic				
Non-Hispanic				
Unknown or Not Reported				
Initial Stage				
II				
III				
IV				
Histology				
Squamous				
Adenocarcinoma				
Large Cell				
Mixed				
Other				
Primary tumor location				
Left upper lobe				
Left lower lobe				
Left lingula				
Right upper lobe				
Right middle lobe				
Right lower lobe				
Unknown				
Marital status				
Married/other live-in partner				
Single/divorced/widowed/separated				
Unknown or Not Reported				

Table 14.1.3 Summary of Protocol Deviations

Deviation Category	Frequency (Major/Minor)		
	500 mg	1000 mg	1500 mg
Concurrent Medication & Treatment Deviation			
Eligibility			
Study Drug Administration			
Visit Assessment			
Visit Window			
Other			
Total			

Table 14.1.4 Summary of Total Dose of BIO 300 Administration

Drug Exposure	500 mg	1000 mg	1500 mg	All
Mean Total Dose (range)				
Mean Duration of exposure (range)				
Frequency missed doses (range)				

Figure 14.1.1 Disposition of Subjects

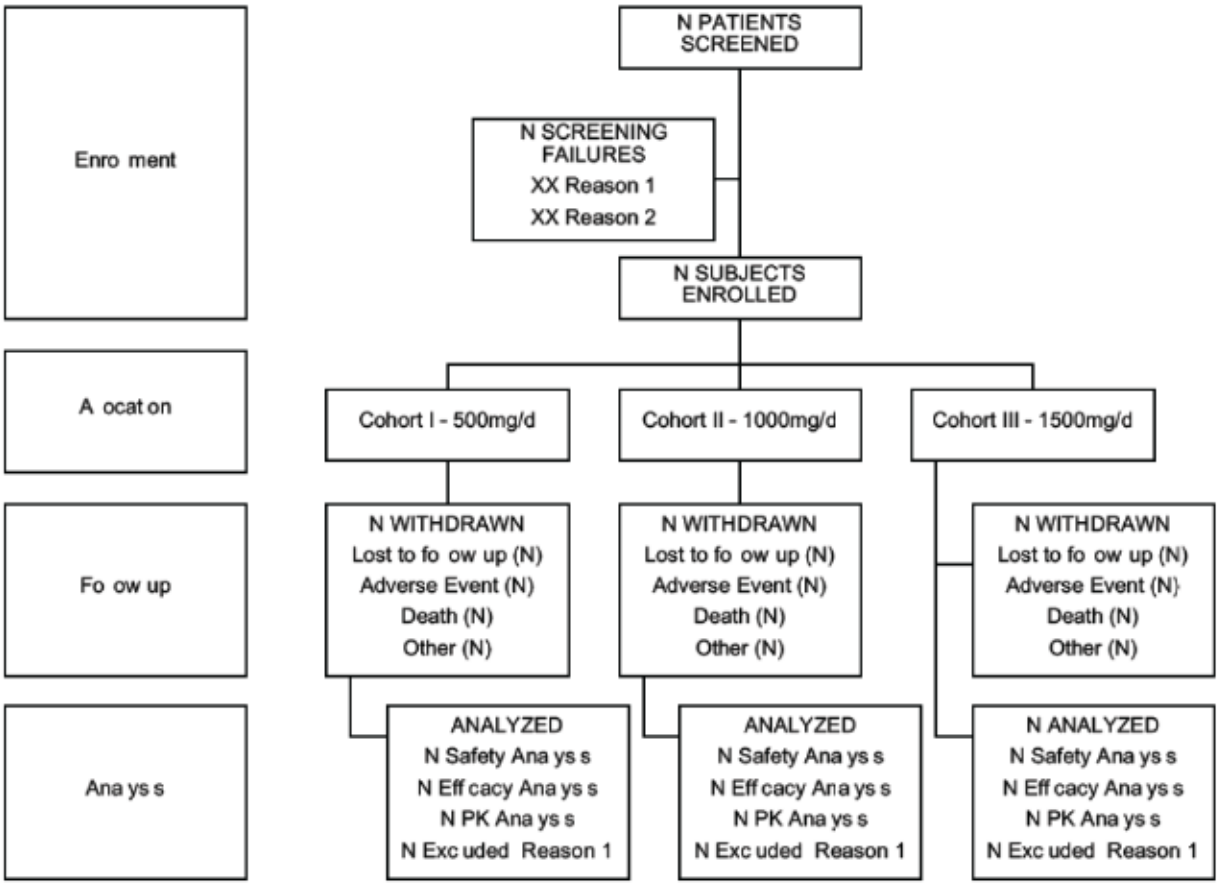

Table 14.2.1 Summary of Overall Response Rate and Best Overall Response per RECIST 1.1 (EAS)

Response	**500 mg**	**1000 mg**	**1500 mg**	**All**
Response Type, No. (%)				
Complete				
Partial				
Stable Disease				
Progressive disease				
Overall Response Rate				
Overall Response, No. (%)				
95% CI, %				

Table 14.2.2 Summary of Overall Response Rate and Best Overall Response per RECIST 1.1 (Evaluable)

Response	**500 mg**	**1000 mg**	**1500 mg**	**All**
Response Type, No. (%)				
Complete				
Partial				
Stable Disease				
Progressive disease				
Overall Response Rate				
Overall Response, No. (%)				
95% CI, %				

Table 14.2.3 Summary of Tumor Diameter

Tumor Diameter	**500 mg**	**1000 mg**	**1500 mg**	**All**
Baseline				
n				
Mean				
STD				
Median				
Range				
Visit				
n				
Mean				
STD				
Median				
Range				
Change from Baseline to Visit				
n				
Mean				
SE				
95% CI				

Table 14.2.4 Summary of Duration of Response (EAS)

Subject	Dose	Duration of Response (months)
#	500 mg	
#	500 mg	
Median DOR, months (95% CI)		
#	1000 mg	
#	1000 mg	
Median DOR, months (95% CI)		
#	1500 mg	

Table 14.2.5 Summary of Duration of Response (Evaluable)

Subject	Dose	Duration of Response (months)
#	500 mg	
#	500 mg	
Median DOR, months (95% CI)		
#	1000 mg	
#	1000 mg	
Median DOR, months (95% CI)		
#	1500 mg	
#	1500 mg	
Median DOR, months (95% CI)		

Table 14.2.6 Summary of Progression Free Survival (FAS)

	500 mg	1000 mg	1500 mg	All
Median Progression Free Survival (Months)				
95% CI				

Table 14.2.7 Summary of Progression Free Survival (Evaluable)

	500 mg	1000 mg	1500 mg	All
Median Progression Free Survival (Months)				
95% CI				

Table 14.2.8 Summary of Absolute Value and change from baseline in Pulmonary Function Measurements

Variables	500 mg	1000 mg	1500 mg	p-value
Baseline				
FEV1 (L)	X ± STD			
FVC (L)				
FEV1/FVC				
DLCO (mL/mmHg/min)				
Visit X, month X				
FEV1 (L)	X ± STD			
FVC (L)				
FEV1/FVC				
DLCO (mL/mmHg/min)				
PFT changes after X months				
FEV1 change (L)	X ± STD			
FVC change (L)				
FEV1/FVC change				
DLCO (mL/mmHg/min) change				

Table 14.2.9 Summary of Swallowing Diary Findings

	500 mg	1000 mg	1500 mg	p-value
Swallowing Diary AUC	X ± STD			

Table 14.2.10 Summary of SOBQ Findings

SOBQ	500 mg	1000 mg	1500 mg	All
Baseline				
n				
Mean				
STD				
Median				
Range				
Visit				
n				
Mean				
STD				
Median				
Range				
Change from Baseline to Visit				
n				
Mean				
SE				
95% CI				

Table 14.2.11 Summary of FACT-TOI Findings

FACT-TOI	500 mg	1000 mg	1500 mg	All
Baseline				
n				
Mean				
STD				
Median				
Range				
Visit				
n				
Mean				
STD				
Median				
Range				
Change from Baseline to Visit				
n				
Mean				
SE				
95% CI				

Figure 14.2.2 Tumor Diameter

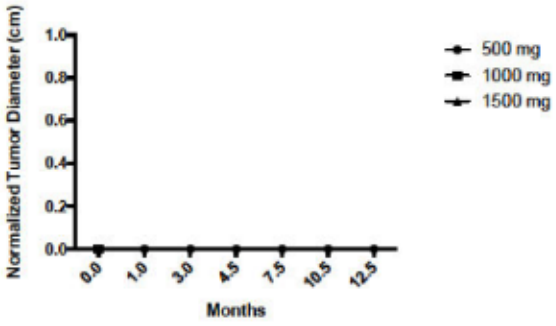

Figure 14.2.2 Kaplan-Meier Curve for Progression Free Survival (FAS)

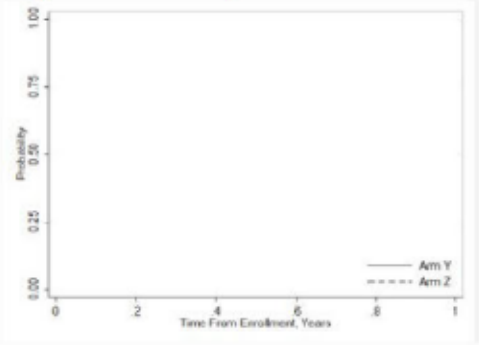

Figure 14.2.3 Kaplan-Meier Curve for Progression Free Survival (Evaluable)

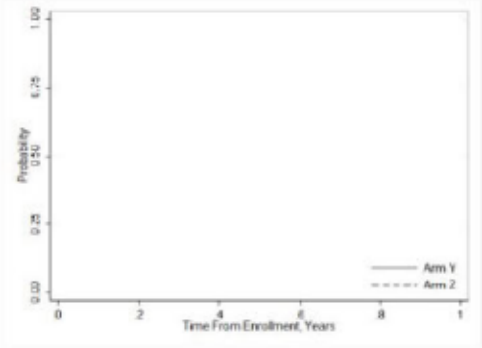

Figure 14.2.4 Kaplan-Meier Curve for Duration of Response (FAS)

Figure 14.2.5 Kaplan-Meier Curve for Duration of Response (Evaluable)

Figure 14.2.6 Plot of the Average Score from Swallowing Diaries

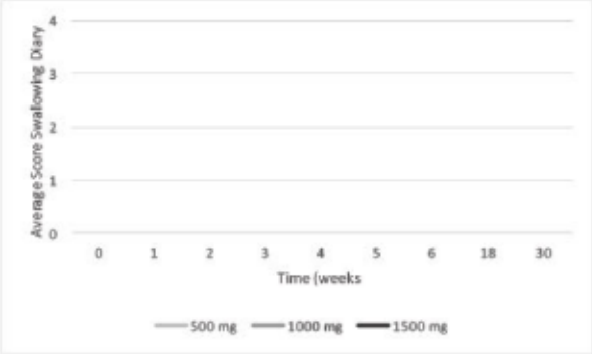

Table 14.3.1.1 Summary of Dose Limiting Toxicities

Subject ID	CTCAE v4 SOC	AE Term	Dose (mg)	Severity	PI Attribution	Medical Monitor Attribution	DLT Details

Table 14.3.1.2 Summary of Frequency and Reason for Dose Interruptions

Subject	Reason for Dose Interruption	Length of Delay (days)

Table 14.3.1.3 Summary of Adverse Events

CTCAE v4 SOC/AE	Number of Subjects Experiencing Event (%)			
	500 mg	100 mg	1500 mg	Total
Cardiac Disorders				
Acute Coronary Syndrome				
Cardiac Arrest				
Systolic Murmur				
Eye disorders				
Blepharitis				
Subconjunctival hemorrhage				
Gastrointestinal disorders				
Abdominal Pain				
Constipation				
Diarrhea				
Dyspepsia				
Dysphagia				
Flatulence				
Mucositis Oral				
Nausea				
General disorders and administration site conditions				
Edema Limbs				
Fatigue				
Infections and infestations				
Lung Infection				
Other, specify: Oral Candidiasis				
Skin Infection				
Urinary tract infection				
Upper respiratory infection				
Injury, poisoning, and procedural complications				
Bruising				
Other, specify: Skin abrasion				
Investigations				
Anemia				
Neutrophil count decreased				
Other, specify: Hematocrit decreased				
Platelet count decreased				
White blood cell decreased				
Metabolism and nutrition disorders				
Anorexia				
Hypomagnesemia				
Hyponatremia				
Hypokalemia				
Musculoskeletal and connective tissue disorders				
Back Pain				
Bone pain				
Myalgia				
Other, specify: Generalized muscle weakness				

CTCAE v4 SOC/AE	Number of Subjects Experiencing Event (%)			
	500 mg	100 mg	1500 mg	Total
Other, specify: Joint pain in hips				
Nervous system disorders				
Dizziness				
Paresthesia				
Peripheral Sensory Neuropathy				
Respiratory, thoracic and mediastinal disorders				
Cough				
Dyspnea				
Epistaxis				
Laryngeal inflammation				
Nasal Congestion				
Other, specify: Radiation pneumonitis				
Vascular disorders				
Hypotension				
Thromboembolic event				

Table 14.3.1.4 Summary of Adverse Events Leading to Discontinuation of Study

Preferred Term	500 mg (N = XX) n (%)	1000 mg (N = XX) n (%)	1500 mg (N = XX) n (%)	P-value
Number of Subjects reporting adverse events leading to discontinuation	xx (xx x)	xx (xx x)	xx (xx x)	xx
[System Organ Class Class #1]				
[Preferred Term #1]	xx (xx x)	xx (xx x)	xx (xx x)	xx
[Preferred Term #2]	xx (xx x)	xx (xx x)	xx (xx x)	xx
…				

Table 14.3.1.5 Summary of Adverse Events by Relationship to BIO 300

Preferred Term	Relationship	500 mg (N = XX) n (%)	1000 mg (N = XX) n (%)	1500 mg (N = XX) n (%)
Number of subjects reporting adverse events	Possible	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Probable	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Definitely	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)
[System Organ Class Class #1]				
[Preferred Term #1]	Possible	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Probable	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Definitely	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)
[Preferred Term #2]	Possible	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Probable	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Definitely	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Total	xx (xx.)	xx (xx.)	xx (xx.)

Table 14.3.1.6 Summary of Adverse Events by Severity Using CTCAE Grade

Preferred Term	Maximum Grade	500 mg (N = XX) n (%)	1000 mg (N = XX) n (%)	1500 mg (N = XX) n (%)	P-value
Number of subjects reporting treatment-emergent adverse events	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	--
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	--
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
[System Organ Class Class #1]					
[Preferred Term #1]	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	--
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	--
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
	Total	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
[Preferred Term #2]	Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	--
	Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	--
	Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx
	Total	xx (xx.)	xx (xx.)	xx (xx.)	xx

Table 14.3.1.7 Summary of Adverse Events with 10% or Higher Incident Rate

Subject ID	CTCAE v4 SOC	AE Term	Dose (mg)	Severity

Table 14.3.2.1 Summary of Serious Adverse Events

Preferred Term	500 mg (N = XX) n (%)	1000 mg (N = XX) n (%)	1500 mg (N = XX) n (%)	P-value
Number of subjects reporting serious adverse events	xx (xx.x)	xx (xx x)		xx
[System Organ Class Class #1]				
[Preferred Term #1]	xx (xx.x)	xx (xx x)		xx
[Preferred Term #2]	xx (xx.x)	xx (xx x)		xx
…				

Table 14.3.2.2 Summary of Serious Adverse Events by Relationship to BIO 300

Preferred Term	Relationship	500 mg (N = XX) n (%)	1000 mg (N = XX) n (%)	1500 mg (N = XX) n (%)
Number of subjects reporting Serious adverse events	Possible	xx (xx x)	xx (xx x)	xx (xx.x)
	Probable	xx (xx x)	xx (xx x)	xx (xx.x)
	Definitely	xx (xx x)	xx (xx x)	xx (xx.x)
	Total	xx (xx x)	xx (xx x)	xx (xx.x)
[System Organ Class Class #1]				
[Preferred Term #1]	Possible	xx (xx x)	xx (xx x)	xx (xx.x)
	Probable	xx (xx x)	xx (xx x)	xx (xx.x)
	Definitely	xx (xx x)	xx (xx x)	xx (xx.x)
	Total	xx (xx x)	xx (xx x)	xx (xx.x)
[Preferred Term #2]	Possible	xx (xx x)	xx (xx x)	xx (xx.x)
	Probable	xx (xx x)	xx (xx x)	xx (xx.x)
	Definitely	xx (xx x)	xx (xx x)	xx (xx.x)
	Total	xx (xx.)	xx (xx.)	xx (xx.)

Table 14.3.2.3 Summary of Deaths

Subject ID	Age	Date of Death	AE Term	Date of Final Study Drug/Dose (mg)	PI Attribution	Medical Monitor Attribution

Table 14.3.4.1 Summary of Clinical Laboratory Values

Lab Test	500 mg			1000 mg			1500 mg			P-value
	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	
HGB (g/dL)										
HCT (vol %)										
RBC (M/uL)										
WBC (K/uL)										
NE# (K/uL)										
LY# (K/uL)										
MO# (K/uL)										
EO# (K/uL)										
BA# (K/uL)										
PLT (K/uL)										
Protein, Total (g/dL)										
Albumin (g/dL)										
CA^{2+} (mg/dL)										
PO_4 (mg/dL)										
Cholesterol (mg/dL)										
TG (mg/dL)										
Glucose (mg/dL)										
UA (mg/dL)										
BUN (mg/dL)										
Creatinine (mg/dL)										
Bilirubin, total (mg/dL)										
Alkaline phosphatase (IU/L)										
Na^+ (mmol/L)										
K^+ (mmol/L)										
Cl^- (mmol/L)										
CO_2 (mmol/L)										
AST (IU/L)										
ALT (IU/L)										
Amylase (IU/L)										
Lipase (IU/L)										

Table 14.3.4.2 Summary of Abnormal (Grade 3 or worse) Clinical Laboratory Values

Subject ID	CTCAE v4 SOC	AE Term	Dose (mg)	Severity

Table 14.3.4.3 Summary of Urinalysis/Pregnancy Results

Test	500 mg			1000 mg			1500 mg			P-value
	Mean	Min	Max	Mean	Min	Max	Mean	Min	Max	
Specific Gravity										
pH										
Protein (mg/dL)										
Glucose (mg/dL)										
Kentones (mg/dL)										
Blood (mg/dL)										
HCG (mIU/mL)										

Table 14.3.5.1 Summary of Electrocardiogram QTc Results

	500 mg	1000 mg	1500 mg	p-value
Baseline				
n				
Mean				
STD				
Range				
1 hour post BIO 300				
n				
Mean				
STD				
Range				
BIO 300 steady state				
n				
Mean				
STD				
Range				
Change from Baseline to 1 hour post BIO 300				
n				
Mean				
SE				
95% CI				
Change from Baseline to BIO 300 steady state				
n				
Mean				
SE				
95% CI				

Table 14.3.5.2 Summary of Vital Signs

	500 mg			1000 mg			1500 mg		
Measurement	**Mean**	**Max**	**Min**	**Mean**	**Max**	**Min**	**Mean**	**Max**	**Min**
Temperature (F)									
Respiratory Rate									
Heart Rate									
Systolic BP									
Diastolic BP									
Height									
Weight (lbs)									