1 TITLE PAGE

CLINICAL STUDY PROTOCOL

A Single-Arm, Open-Label, Phase II Trial Evaluating the Efficacy, Safety and Pharmacokinetics of Antroquinonol in Patients with Stage IV (including Pleural Effusion) Non-Squamous Non-Small Cell Lung Cancer (NSCLC) who have Failed Two Lines of Anti-Cancer Therapy

Protocol No.: GHNSCLC-2-001	EUDRACT/IND No.: 105226
Test Product:	Antroquinonol 100 mg capsules
Indication:	Non-small cell lung cancer (NSCLC)
Sponsor:	Golden Biotechnology Corporation
Development Phase:	II
Sponsor Signatory:	Dr. Howard Cheng
Sponsor Medical Expert:	Dr. Shou-Bao Wu
Principal Investigator:	David S. Ettinger, MD
Date of the Protocol:	06 December 2017
Version of the Protocol:	Version 6, Final

2 SIGNATURE PAGES

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: A Single-Arm, Open-Label, Phase II Trial Evaluating the Efficacy, Safety and Pharmacokinetics of Antroquinonol in Patients with Stage IV (including Pleural Effusion) Non-Squamous Non-Small Cell Lung Cancer (NSCLC) who have Failed Two Lines of Anti-Cancer Therapy

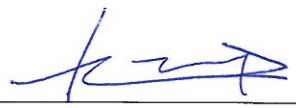
PROTOCOL NUMBER: GHNSCLC-2-001

Golden Biotechnology Corporation

I have read the attached protocol entitled "A single-arm, open-label, Phase II trial evaluating the efficacy, safety and pharmacokinetics of Antroquinonol in patients with stage IV (including pleural effusion) non-squamous non-small cell lung cancer (NSCLC) who have failed two lines of anti-cancer therapy", dated 06 December 2017 and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable Food and Drug Administration (FDA) regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56 and 312. Also, the human-rights and privacy of the patients will be protected based on the Declaration of Helsinki.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Golden Biotechnology Corporation.



Dr. Howard Cheng, V.P. Clinical Research
Golden Biotech Corporation

6th Dec 2017
Date (day/month/year)

INVESTIGATOR SIGNATURE PAGE

PROTOCOL TITLE: A Single-Arm, Open-Label, Phase II Trial Evaluating the Efficacy, Safety and Pharmacokinetics of Antroquinonol in Patients with Stage IV (including Pleural Effusion) Non-Squamous Non-Small Cell Lung Cancer (NSCLC) who have Failed Two Lines of Anti-Cancer Therapy

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Signature of Investigator	Date (day/month/year)
Investigator Name (print or type)	
Investigator's Title	

3 GENERAL INFORMATION

A Single-Arm, Open-Label, Phase II Trial Evaluating the Efficacy, Safety and Pharmacokinetics of Antroquinonol in Patients with Stage IV (including Pleural Effusion) Non-Squamous Non-Small Cell Lung Cancer (NSCLC) who have Failed Two Lines of Anti-Cancer Therapy

Protocol No.:	GHNSCLC-2-001
Date of the Protocol:	06 December 2017
Sponsor:	Golden Biotechnology Corporation 15F, No. 27-6, Sec. 2, Jhong-Jheng E. Rd., Danshuei, Taipei County 251, Taiwan
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Principal Investigator:	David S. Ettinger, MD Johns Hopkins Sidney Kimmel Comprehensive Cancer Center 401 N. Broadway Baltimore, MD 21231 Tel No.: 410-955-8964
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4 STUDY SYNOPSIS

Name of Sponsor/Company: Golden Biotechnology Corporation	**Individual Study Table Referring to Part of the Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Product: Hocena® 100 mg capsule		
Name of Active Ingredient: Antroquinonol		

Title of Study:

A single-arm, open-label, Phase II study evaluating the efficacy, safety and pharmacokinetics of antroquinonol in patients with stage IV (including pleural effusion) non-squamous non-small cell lung cancer (NSCLC) who have failed two lines of anti-cancer therapy

Principle Investigator: David S. Ettinger, MD; Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, 401 N. Broadway, Baltimore, MD 21231, United States of America (USA).

Study Centers:

It is planned that at least 10 centers will be initiated for this study in the USA (nine centers) and Taiwan (one center).

Publications: None.

Planned Study Period:	**Development Phase:**
Third quarter, 2013 to fourth quarter, 2016	Phase II

Objectives:

Primary Objective:

To evaluate the activity of antroquinonol in unselected, KRAS-positive, and KRAS-negative patients with stage IV (including pleural effusion) non-squamous NSCLC who have failed two lines of anti-cancer therapy.

Secondary Objective:

To assess the safety and tolerability and pharmacokinetics (PK) of antroquinonol in patients with stage IV (including pleural effusion) non-squamous NSCLC who have failed two lines of anti-cancer therapy.

Exploratory Objective:

To explore potential relationships between of antroquinonol exposure and safety and efficacy endpoints.

Methodology:

This is a single-arm, open-label, Phase II study in KRAS-positive and KRAS-negative patients with stage IV (including pleural effusion) non-squamous NSCLC who have failed two lines of anti-cancer therapy. This is defined as patients with radiologically confirmed disease progression following greater than or equal to two, but less than or equal to four, prior lines of systemic anti-cancer therapy (see Inclusion Criteria). A maximum of 60 evaluable patients with NSCLC will receive antroquinonol, of which 30 patients will be KRAS-positive and 30 patients KRAS-negative. An evaluable patient will have received at least one dose of antroquinonol and have a valid baseline tumor assessment (see Statistical Methods). Enrollment will continue until the target number of evaluable patients has been enrolled.

Written informed consent must be obtained from all patients before initiating Screening. The Screening period will be up to 42 days in duration (Days -42 to -1). Following completion of all Screening assessments and confirmation of eligibility criteria, patients will receive antroquinonol 200 mg three times a day (t.i.d. at 8-hour intervals) on Day 0 for 12 weeks (one treatment cycle) or until documented evidence of disease progression, unacceptable toxicity, non-compliance or withdrawal of consent by the patient, or the investigator decides to discontinue treatment, whichever comes first. Study drug should be taken at 8-hour intervals. The time of study drug administration should be recorded in the patient diary.

After the first 12-week treatment cycle, patients who are progression-free will be eligible to receive further (12-week) treatment cycles with antroquinonol (Extension Phase), until documented evidence of disease progression, unacceptable toxicity, non-compliance or withdrawal of consent by the patient, or the investigator decides to discontinue treatment, whichever comes first.

Patients will attend study visits on Days 0, 14, 28, 42, 56 and 84 during the first 12-week treatment cycle, every 4 weeks during the second, third, and fourth treatment cycles (Extension Phase), and every 12 weeks during

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subsequent treatment cycles (Extension Phase).

The study-specific procedures include: physical examination, vital signs, 12-lead electrocardiogram (ECG), performance status, clinical laboratory tests, adverse events (AEs), concomitant medication and patient compliance.

Patients discontinuing the study will attend an End of Study Visit, 4 weeks after the last administration of study drug.

Intensive PK sampling will be performed on Days 0 and 28 in all patients enrolled in Stage 1. Sparse PK sampling will be performed on Days 28, 42, and 56 in all patients enrolled in Stage 2.

All patients who discontinue from study drug, but consent to be followed up for survival status, will be followed up by telephone contact every 3 months, for a maximum of 6 months from the date of last administration of study drug or death, whichever occurs first.

Tumor assessments will be performed at Screening, Day 42 and Day 84 using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1. Tumor assessments will be performed every 12 weeks during the Extension Phase.

The primary efficacy endpoint is progression-free survival (PFS) rate at 12 weeks, which is defined as the proportion of patients alive and progression-free at Week 12. Patients will be progression-free if they have no evidence of progressive disease (defined according to RECIST guidelines, version 1.1) from the start of treatment to Week 12.

The study uses a two-stage design seeking to detect a true PFS rate of more than 35% in the overall (unselected) population and 40% within the KRAS tumor mutation positive and negative strata. Thirty evaluable patients (15 in each stratum) will be treated initially (Stage 1), with expansion to a maximum of 60 evaluable patients (Stage 2). The rules for continuing the overall study and individual stratum are given in the Statistical Methods below.

An Independent Data Monitoring Committee will act in an advisory capacity to monitor patient safety and efficacy data from the study. The members will be selected on the basis of relevant experience and understanding of clinical research and the issues specific to the therapeutic area, as well as previous data monitoring committee experience.

Number of Patients:

The study uses a two-stage design. Thirty evaluable patients (15 in each stratum) will be treated initially (Stage 1), with expansion to a maximum of 60 evaluable patients (Stage 2). Enrollment will continue until the target number of evaluable patients has been enrolled.

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria

Patients eligible for enrollment in the study must meet all of the following criteria:

- Cytologically or histologically confirmed non-squamous NSCLC Stage IV (including pleural effusion).
- Radiologically confirmed disease progression following greater than or equal to two, but less than or equal to four, prior lines of systemic anti-cancer therapy, one of which should be a platinum-based regimen, OR the patient has refused treatment with approved treatment modalities, OR the investigator feels that the patient is not a candidate for other systemic therapy. Patients with epidermal growth factor receptor (EGFR)-positive mutations should have been offered treatment with an EGFR-TK inhibitor prior to enrolment in this study. Adjuvant therapy with or without maintenance therapy would count as one line of systemic therapy. A line of therapy requires at least two 3-4 week complete cycles unless it was stopped due to toxicity, in which case it would count as one line of therapy
- At least one radiologically measurable target lesion per RECIST version 1.1
- Fresh or archival biopsy tissue available to determine KRAS tumor mutation status
- At least 18 years of age at the time of signing informed consent
- Life expectancy of at least 3 months

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- Written informed consent that is consistent with International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice guidelines
- Patient or legally acceptable representative has granted written informed consent before any study-specific procedures (including special Screening tests) are performed
- Eastern Cooperative Oncology Group (ECOG) performance score of 0, 1 or 2
- Hemoglobin ≥ 9.0 g/dL; platelets ≥ 100 x 10^9/L; absolute neutrophil count ≥ 1.5 x 10^9/L without the use of hematopoietic growth factors
- Bilirubin and creatinine less than 2 × upper limit of normal (ULN) for the institution
- Albumin ≥ 2.5 g/dL
- Aspartate aminotransferase and alanine aminotransferase less than 5 × ULN for the institution
- Prothrombin time less than 1.5 × ULN for the institution
- Potassium, magnesium and phosphorus within the normal range for the institution (supplementation is permissible)
- Willing to use two medically accepted and effective methods of contraception from the list below during the study (both men and women as appropriate) and for 3 months after the last dose of study drug:
  - Established use of oral, injected or implanted hormonal methods of contraception.
  - Placement of an intrauterine device or intrauterine system.
  - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
  - Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
  - True abstinence: When this is in line with the preferred and usual lifestyle of the patient.
- Recovery to ≤ Grade 1 or baseline of any toxicities due to prior treatments, excluding alopecia

Exclusion criteria

Patients meeting any of the following criteria must not be enrolled in the study:

- Chemo-, hormone- or immunotherapy, within 4 weeks or within less than four half-lives of the date of first administration of study drug and/or persistence of toxicities of prior anti-cancer therapies which are deemed to be clinically relevant
- Radiotherapy within the past 2 weeks prior to the date of first administration of study drug
- Previous treatment with an histone deacetylase inhibitor or an EGFR inhibitor within at least 4 weeks of the date of first administration of study drug
- Treatment with any drug(s) known to be a strong inhibitor or inducer of cytochrome P450 (CYP)2C19, CYP3A4, CYP2C8, and CYP2E1, within 14 days of the date of first administration of study drug
- Brain metastases which are symptomatic; patients with treated brain metastases are eligible with stable brain disease for at least 4 weeks without the requirement for steroids or anti-epileptic therapy
- Inability to swallow oral medications or a recent acute gastrointestinal disorder with diarrhea e.g., Crohn's disease, malabsorption, or Common Terminology Criteria for Adverse Event (CTCAE) Grade > 2 diarrhea of any etiology at baseline
- Other malignancies diagnosed within the past five years (other than curatively treated cervical cancer i*n situ*, non-melanoma skin cancer, superficial bladder tumors Ta [non-invasive tumor] and TIS [carcinoma *in situ*], or non-metastatic prostate cancer stage 1 to 2, which has been previously treated with surgery or radiation therapy, and serum prostate-specific antigen is within normal limits [test performed within the past 12 months prior to the date of first administration of study drug])
- Patients with any serious active infection (i.e., requiring an intravenous antibiotic, antifungal, or antiviral agent)
- Patients with known human immunodeficiency virus, active hepatitis B or active hepatitis C

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- Patients who have any other life-threatening illness or organ system dysfunction, which in the opinion of the investigator, would either compromise patient safety or interfere with the evaluation of the safety of the study drug
- Known or suspected substance abuse or alcohol abuse
- Women of child-bearing potential or men who are able to father a child unwilling to use two medically accepted and effective methods of contraception during the study (as specified in the inclusion criteria)
- Pregnancy or breast feeding
- Patient unable to comply with the protocol
- History of clinically significant or uncontrolled cardiac disease, including congestive heart failure, angina, myocardial infarction, arrhythmia, including New York Heart Association functional classification of three

Test Product, Dose and Mode of Administration:

Antroquinonol 100 mg. Beginning on Day 0, patients will receive one 12-week cycle of antroquinonol 200 mg t.i.d. or until disease progression, unacceptable toxicity, non-compliance or withdrawal of consent by the patient, or the investigator decides to discontinue treatment, whichever comes first.

Study drug should be taken at 8-hour intervals with a glass of water, approximately 15 minutes after a meal or light snack, and not within ±1 hour of drinking an ethanol-containing beverage, e.g. an alcoholic drink. The date and time of each study drug administration should be recorded in the patient diary.

After the first 12-week treatment cycle, patients who are progression-free will be eligible to receive further (12-week) treatment cycles with antroquinonol (Extension Phase), until documented evidence of disease progression, unacceptable toxicity, non-compliance or withdrawal of consent by the patient, or the investigator decides to discontinue treatment, whichever comes first. Investigators should wait at least 7 days after the last administration of study drug before initiating alternative treatment.

Reference Therapy, Dose and Duration of Administration:

Not applicable.

Duration of Treatment:

Patients can be treated with antroquinonol, until documented evidence of disease progression, unacceptable toxicity, non-compliance or withdrawal of consent by the patient, or the investigator decides to discontinue treatment, whichever comes first.

Variables:

The primary and secondary efficacy analyses will be based on independent centralized assessment of medical images.

Efficacy:

Primary endpoint

The primary endpoint is as follows:

- Progression-free survival rate at 12 weeks, defined as the proportion of patients alive and progression-free at Week 12. Patients will be progression-free if they have no evidence of progressive disease (defined according to RECIST guidelines, version 1.1) from the start of treatment to Week 12.

  Tumor response will be assessed at 6-week intervals during the first treatment cycle using the RECIST criteria, version 1.1. Each patient will be assigned one of the following categories: 1) complete response (CR), 2) partial response (PR), 3) stable disease (SD), or 4) progressive disease (PD). Patients who died from any cause or discontinued the study for any reason without a post-screening or Week 12 tumor assessment will be considered as failing to respond to treatment.

Secondary efficacy endpoints

Secondary efficacy endpoints are as follows:

- Objective response rate (ORR), defined as the proportion of patients whose best overall response is either CR or PR according to RECIST version 1.1. The best overall response is the best response recorded during

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the first 12-week treatment cycle.

- Disease control rate (DCR), defined as the proportion of patients with a documented CR, PR and SD during the first 12-week treatment cycle according to RECIST version 1.1.
- Duration of overall tumor response (DR), defined as the interval between the date of the first observation of tumor response (CR or PR) and the date of disease progression or death.
- Progression-free survival defined as the time from the date of first administration of study drug to objective tumor progression by RECIST version 1.1 or death due to any cause, whichever occurs first.
- Overall survival (OS) defined as the time from the date of first administration of study drug to death from any cause.
- Time to progression (TTP) defined as the time from the date of first administration of study drug to objective tumor progression by RECIST version 1.1.

Patient Reported Outcome endpoint

The Patient Reported Outcome (PRO) endpoint is as follows:

- European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C30 (QLQ-C30) and EORTC QLQ – Lung Cancer Module (QLQ-LC13)

Pharmacokinetics:

PK endpoints will be derived for intensively sampled PK profiles by non-compartmental methods and include:

- C_{max}: peak concentration
- C_{trough}: trough plasma concentration
- T_{max}: peak time
- AUC_{τ}: area under the plasma concentration-time curve over the 8-hour dosing interval
- $T_{½}$: terminal half-life
- Vz/F: apparent volume of distribution during elimination
- CL/F: apparent oral clearance
- $T_{½, eff}$: effective half-life

If possible, PK data from all patients will be analyzed using population-based PK (PopPK) methods and *post hoc* estimates of antroquinonol exposure (i.e., C_{max}, C_{trough} and $AUC_{\tau)}$ computed for exploration of potential exposure-response relationships.

Safety:

The safety endpoints are the incidence of reported AEs and abnormal laboratory tests. Adverse events will be assessed using the National Cancer Institute (NCI) CTCAE version 4.03.

Tumor biomarkers:

Subgroup analyses will assess the predictive value of tumor biomarkers.

Statistical Methods:

Sample size and power:

The statistical design is based on literature published by Green and Dahlberg (1992), von Mehren et. al. (2012), and Hoang et. al. (2013). It is assumed that within each of the KRAS tumor mutation positive and negative strata, a PFS rate at 12 weeks of 40% and 35% overall (unselected) population will be of interest. Further testing will not be pursued if the PFS rate at 12 weeks is less than 15%.

Initially, 15 evaluable patients are to be accrued within each stratum. If two or more patients are alive and progression-free at Week 12 within a stratum, then an additional 15 evaluable patients will be accrued to that stratum for a total of 30 evaluable patients.

If nine or more patients are alive and progression-free at Week 12 within the 30 evaluable patients in the stratum then antroquinonol will be considered worthy of further study in that cohort. This design will allow a significance level of 2.8% and a power of 90.5% within each stratum.

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In addition to within-stratum hypothesis testing, this study is also designed to investigate the PFS rate at 12 weeks in the overall (unselected) population. If less than three patients are alive and progression-free at Week 12 in the first 20 evaluable patients and, the criterion for continuing the individual stratum are not met, then the accrual for all strata will be discontinued. Otherwise, a maximum of 40 additional evaluable patients will be entered (depending on whether any individual stratum is closed). Fifteen or more patients alive and progression-free at Week 12 out of the maximum 60 evaluable patients would warrant further study.

The overall design has a significance level of 2.8% (probability of falsely declaring the regimen with a 15% PFS rate at 12 weeks to warrant further study) and power 95.6% (probability of declaring the regimen with a 35% PFS rate at 12 weeks in the overall population to warrant further study).

Efficacy:

Except for the primary efficacy analysis, there will be no formal statistical testing. All data will be summarized and listed as appropriately. All efficacy endpoints will be evaluated in both the overall (unselected) population and within-stratum.

The primary analysis will be performed on the evaluable population. The evaluable population will consist of all enrolled patients who receive at least one dose of antroquinonol and have a valid baseline tumor assessment. A valid baseline assessment is defined as a readable scan performed within 14 (± 7) days of the date of first administration of study drug. For the efficacy analysis, enrollment will continue until the target number of evaluable patients has been enrolled.

The full analysis set (FAS) and per-protocol set (PPS) will be used for supportive efficacy analyses. The FAS will consist of patients in the evaluable population who have at least one post-baseline tumor assessment. The PPS will consist of patients in the FAS who do not have any major protocol violations.

The primary analysis will follow the two stage procedure, as specified in the sample size section. All secondary efficacy endpoints will be reported with category counts, percentage and 95% confidence interval (CI). All time-to-event endpoints, PFS, OS and TTP will be evaluated using Kaplan-Meier estimates and curves will be generated based on these estimates.

Safety:

All patients who are treated with at least one dose of study drug will be evaluated for safety. Safety data will be summarized for the overall (unselected) population and within-stratum. There will be no formal statistical analysis of safety data. Demographic and Screening data will be listed and summarized, as appropriate. All AEs will be coded using the Medical Dictionary for Regulatory Activities, graded using the NCI CTCAE version 4.03 and listed by patient. Treatment-emergent AEs will be summarized by treatment, severity and causal relationship to study drug. Any serious AEs will be listed separately. System organ class and preferred terms within each body system will be used for frequency summaries. Clinical laboratory data, vital signs and ECG data will be listed by patient and summarized, as appropriate.

Patient Reported Outcome:

The PRO population will consist of all patients who have completed the QLQ on Day 0 and on at least one occasion after the first administration of study drug. All data will be summarized and listed, as appropriate. Patient Reported Outcome data will be summarized for the overall (unselected) population and within-stratum.

Pharmacokinetics:

Non-compartmental PK analysis will be performed for the PK population. The PK population will consist of patients in the first stage who have an evaluable PK profile, defined as a profile from which at least one of the PK parameters stated as endpoints can be estimated, and no protocol deviations that would affect the PK of antroquinonol. Descriptive statistics will be presented for all PK parameters. The PopPK methods will be used to estimate exposure metrics for patients with at least two plasma concentrations and sufficient and reliable dosing histories.

Tumor biomarkers:

The predictive value of tumor biomarkers will be assessed in appropriate subgroup analyses. Full details of this analysis will be provided in the Statistical Analysis Plan.

Date of the Protocol: 06 December 2017

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6 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
Akt	Protein kinase B
ALT	Alanine aminotransferase
AMES	Bacteria reversed mutation assay
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the plasma concentration-time curve from 0 to 24 hours
AUC_{τ}	Area under the plasma concentration-time curve over the 8-hour dosing interval
BMI	Body mass index
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Apparent oral clearance
C_{max}	Peak concentration
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough plasma concentration
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose limiting toxicity
DR	Duration of overall tumor response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of Study
FAS	Full analysis set
FDA	Food and Drug Administration
FFPE	Formalin fixed paraffin embedded
FTase	Farnesyltransferase
GCP	Good Clinical Practice
HCl	Hydrogen chloride

Abbreviation	Definition
HDAC	Histone deacetylase
HIV	Human immunodeficiency virus
HR	Heart rate
HNSTD	Highest non-severely toxic dose
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MRI	Magnetic resonance imaging
MSAP	Modeling and simulation analysis plan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetic
PopPK	Population-based pharmacokinetic
PPS	Per-protocol set
PR	Partial response
PRO	Patient Reported Outcome
QLQ	Quality of Life Questionnaires
QoL	Quality of Life
QTc	Corrected QT
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCLC	Small cell lung cancer
SD	Stable disease
TEAE	Treatment-emergent adverse event

Abbreviation	Definition
$T_{½}$	Terminal half-life
$T_{½, eff}$	Effective half-life
T_{max}	Peak time
t.i.d.	Three-times-a-day
TTP	Time to progression
ULN	Upper limit of normal
US	United States
Vz/F	Apparent volume of distribution during elimination

7 INTRODUCTION

7.1 Background

Lung cancer is the most frequently diagnosed major cancer in the world and leading cause of cancer mortality worldwide. In the United States of America (USA), it is estimated that 219,440 new cases of lung cancer (116,090 men and 103,350 women) will be diagnosed and 159,390 deaths will be related to this malignancy in 2009.[1] In Taiwan, 8,748 new cases of lung cancer were diagnosed in 2006, accounting for 11.94% of cancer diagnoses, and 7,479 patients died of this disease, contributing to 19.68% cancer deaths. The mortality was 44.42 and 20.65 per 100,000 men and women, respectively.[2]

Lung cancers are categorized on the basis of important prognostic and therapeutic implications as either non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC). Non-small cell lung cancer contributed to about 80% of new cases diagnosed each year.[3] NSCLC typically proliferates slower with lower doubling time than SCLC and can be characterized as three primary histologic types: adenocarcinoma, squamous cell, and large cell carcinoma. Adenocarcinoma has become the dominant histologic type of NSCLC and is the most common type in women and non-smokers.[3] It typically arises in the periphery with glandular differentiation or mucin production, forms tubular or papillary structures, and metastasizes widely and early, compared to squamous carcinoma.[3]

About 70% of NSCLC patients are diagnosed with advanced, poor-prognosis stage III or IV disease (approximately 50% for stage IV).[4] The majority of these advanced tumors are considered inoperable due to disseminated (multiple sites) metastatic disease or metastatic sites that are not amendable to local therapy. For these patients, platinum-based chemotherapy is the standard treatment recommended by American Society of Clinical Oncology and National Comprehensive Cancer Network (NCCN).[5,6] Available treatment options, including systemic therapy using non-specific cytotoxic chemotherapy or targeted therapies, for advanced NSCLC have progressed significantly in the past two decades; however, survival for indicated patients remains modest.[7] In addition, treatment for stage IV lung cancer remains a disappointment. Future directions toward new therapy are therefore necessary.

7.2 Investigational Product

Antroquinonol, trade name Hocena®, a novel cyclohexenone compound, is a purified compound from extract of *Antrodia camphorata*. *Antrodia camphorata* is an endemic species in Taiwan, and has been traditionally used for food and drug intoxication, and the treatment of diarrhea, abdominal pain, hypertension, itching of the skin, and liver cancer.[8] Other research has shown *Antrodia camphorata* to have detoxification,[9,10] anti-inflammatory, [11,12] immunomodulatory,[13] liver protection,[14] and anti-cancer effects.[15-21] The mycelium of *Antrodia camphorata* has been marketed as a food supplement by Golden Biotechnology Corporation since 2005 and this product was further tested and found to be safe and efficacious in nonclinical settings. It was approved as a functional food for improving liver health by the Department of Health in Taiwan in 2008.

The marketed food supplement product contains 1.1 mg antroquinonol per capsule and the recommended dosage is three capsules per intake twice daily (six capsules per day). The cumulative exposure in humans is over 7.8 million capsules, translating to 8.6 kg of antroquinonol for duration of approximately 4 years.

7.3 Preclinical Data

Antroquinonol caused cell death with an IC_{50} of 2.22 to 6.42 μM for different cancer cell lines. Antroquinonol significantly enhanced the ratio of unprocessed to processed Ras in lung cancer cells in a dose-dependent manner ($P < 0.01$) and this enhancement was competed by farnesyl pyrophosphate. Antroquinonol inhibited farnesyltransferase (FTase) activity and molecular docking analysis predicted that the isoprene unit and the 4'-hydroxy group of antroquinonol may play important roles in the interaction between antroquinonol and FTase. In addition, antroquinonol increased the expression level of beclin-1 (three-fold), LC3-II/I ($P < 0.01$) and PC3 puncta formation in lung cancer cells. Antroquinonol may therefore inhibit Ras activation through inhibition of FTase, leading to autophagic cell death.

Previous studies revealed that antroquinonol triggers anti-tumor activity through several signaling molecules, including AMPK, PI3K, and mTOR. Recent research suggests that antroquinonol indirectly inhibits Ras processing through inhibition of FTase activity. The Ras-PI3K-Akt-mTOR pathway, which is associated with proliferation, motility, metabolism, and differentiation, is inhibited in response to antroquinonol. Thus, antroquinonol may promote its anti-cancer effects by regulating cross talk in a complex signaling network that results in apoptosis and autophagy.

An i*n vivo* study in non-obese diabetes/severe combined immunodeficiency mice with A549 subcutaneous xenografts consistently showed tumor growth suppression results after 2 weeks of oral 30 and 60 mg/kg antroquinonol treatment. Safety pharmacology studies including central nervous system effect in Sprague-Dawley rat, binding activity with hERG ion channel in *in vitro* setting, cardiovascular effect in beagle dogs and respiratory system effect study in Sprague-Dawley rat were all completed and the results showed no particular safety concerns of antroquinonol. Pharmacokinetic (PK) studies including absolute bioavailability determination, organ distributions, metabolism related to cytochrome P450 (CYP), main metabolites in rat urine and cross-species metabolite comparisons were all completed, with results indicating fast absorption, substantial organ distribution especially in the lung, heart, and kidney, and CYP involved metabolism profiles of antroquinonol.

Two 7-day toxicity studies[22,23] were performed in both Sprague-Dawley rats and beagle dogs and the maximum tolerated doses (MTD) determined were between 100 mg/kg/day for rats and 100 mg/kg/day for dogs. Two 28-days toxicity studies were conducted to determine no observed adverse effect level (NOAEL) for Sprague-Dawley rats and beagle dogs. The rat NOAEL was 30 mg/kg/day and the high dose of 100 mg/kg/day was not severely toxic.

A NOAEL in the dog was not identified (i.e., loose feces, liquid feces, and vomiting were observed at all doses); the 30 mg/kg/day dose level was tolerated and is the highest non-severely toxic dose (HNSTD).

Toxicokinetic evaluations were performed on a 7-day dog study (100, 250, 500 mg/kg/day single dose, 500 mg/kg/day 3 days dose) and the two 28-day studies mentioned above (Rat: 10, 30, 100 mg/kg/day single and 28 days dose; Dog: 10, 30, 100 mg/kg/day single and 28 days dose). Fast absorption of antroquinonol was repeatedly seen in rats and dogs with peak time (T_{max}) ranging from 0.25 to 6 hours. A trend of dose proportionality in the rat and dog was more or less shown after 1 day of treatment. After 28 days of treatment, rat and dog studies showed inconsistent phenomena in dose proportionality view, one was greater and the other was less than linear in the dose-exposure relationship.

No genotoxicity and no reproductive toxicity (up to 80 mg/kg/day) of antroquinonol was observed via Ames test, mammalian cell gene mutation test, micronucleus test, erythrocyte micronucleus test and *in vivo* study in Sprague-Dawley rats.

As known to the sponsor, no fatal or severe/serious adverse drug reaction has been reported for the marketed product (food supplement) of *Antrodia camphorata*.

7.4 Clinical Study Data – Phase 1 Study

A first-in-human phase I study was performed to determine the MTD and to evaluate PK, safety / tolerability and efficacy profiles of antroquinonol in NSCLC patients who are refractory to conventional treatment modalities. This open-label, non-randomized, dose-escalation study, which completed in February 2013, enrolled a total of 13 patients; seven males and six females, all of whom were Asian. A total of five patients were enrolled an accelerated titration phase (one patient each in the 50, 100, 200, 300, and 450 mg dose groups) and eight patients were enrolled in a standard titration phase (three patients in the 450 mg dose group and five patients in the 600 mg dose group).

No Dose Limiting Toxicities (DLTs) were reported in any patient for any of the doses (50, 100, 200, 300, 450, and 600 mg) in the Intent-to-Treat Population in the accelerated titration phase or standard titration phase.

Pharmacokinetic results indicated that the rate and extent of absorption of antroquinonol increased in a dose proportional manner over the dosing range of 50 to 600 mg after multiple administrations of antroquinonol. However, the rate and extent of antroquinonol absorption increased in a non-dose proportional and a dose proportional manner, respectively, over the dosing range of 50 to 600 mg under single dose conditions. No clear trend was observed when comparing the PK parameters under single dose conditions to those under multiple dose conditions.

Due to the limited number of patients per dose group (one patient each received 50, 100, 200, and 300 mg, four patients received 450 mg, and five patients received 600 mg), these results should be interpreted with caution.

Efficacy results indicated that the tumor overall response at the end of treatment showed stable disease for all three patients included in the Per-Protocol population: one patient in the 200 mg dose group and two patients in the 600 mg dose group (100%).

Safety results indicated that antroquinonol at 50, 100, 200, 300, 450, and 600 mg dose levels, given daily for 4 weeks, was generally safe and well tolerated. Antroquinonol at 50, 100, 200, 300, 450, and 600 mg dose levels exhibited a low toxicity profile. Overall, four patients reported four serious adverse events (SAEs) with two patients each in the 450 and 600 mg dose groups. Of these, one patient from each dose group died due to progressive disease and discontinued from the study (one patient in the 600 mg dose group discontinued due to the adverse event [AE] of pleural effusion). None of the deaths, SAEs, and AEs leading to discontinuations was related to the study drug. No Grade 4 treatment-emergent adverse events (TEAEs) were reported as determined by the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03.[24]

Treatment-emergent AEs of toxicity Grade 3 were reported in two patients (one patient in the 200 mg dose group experienced vertigo and one patient in the 450 mg dose group experienced decreased appetite and encephalitis); all events were unrelated to the study drug.

All 13 (100%) patients treated reported TEAEs that were considered treatment-related. The most commonly occurring TEAEs, reported in > two patients, overall, were in the system organ classes of gastrointestinal disorders (12 patients, 92.3% [seven patients in Grade 1, 53.8%, and five patients in Grade 2, 38.5%]), and by preferred term were diarrhea (10 patients, 76.9% [nine patients in Grade 1, 69.2%, and one patient in Grade 2, 7.7%]), vomiting (nine patients, 69.2% [six patients in Grade 1, 46.2%, and three patients in Grade 2, 23.1%]), and nausea (seven patients, 53.8% [six patients in Grade 1, 46.2%, and one patient in Grade 2, 7.7%]).

No patient had any laboratory abnormality recorded as a TEAE except for one case of hematuria of Grade 1 in the 450 mg dose group. Per the sonogram report of the kidney, stones sized 0.47 cm and 0.50 cm in the left kidney without hydronephrosis were noted. The event was considered to be unrelated to the study drug. There were slight increases or decreases in the hematology and biochemistry parameters but none were considered abnormal results.

For urinalysis, at Cycle 1 baseline, four patients had abnormal urinalysis results: one patient each in the 200 and 600 mg dose groups and two patients in the 450 mg dose group. At follow-up, five patients had abnormal urine values: two patients in the 450 mg group that had abnormal values at baseline and three new patients at lower dose levels (one patient each in the 50, 100, and 300 mg dose groups).

None of the patients were reported to have clinically significant changes in any of the vital sign, electrocardiogram (ECG), and physical examination parameters at the Follow-Up Visit.

The Eastern Cooperative Oncology Group (ECOG) score was 1 for all patients at all time points, except for two patients in the 450 mg group who had an ECOG score of 4 (completely disabled, cannot carry on any self-care) at the Follow-Up Visit and a score of 2 (ambulatory and capable of all self-care but unable to carry out any work activities) at the Cycle 3, Day 28 visit.

7.5 Rationale for the Study

Existing treatments for advanced NSCLC have not brought very satisfactory survival results and poor-prognosis remains for patients with advanced NSCLC. Preclinical pharmacology and toxicology studies, described above, have indicated that antroquinonol is a drug with potential lung cancer cytotoxic activity and relatively low toxicity profile. The cumulative exposure in humans of antroquinonol contained in *Antrodia camphorata*, the currently marketed health food supplement product, is over 7.8 million capsules, translating to 8.6 kg of antroquinonol for duration of approximately 4 years. Although supplied at a different dose unit and daily dose strength, no fatal, serious/severe drug adverse reactions have ever been reported to the sponsor due the marketed product.

In the phase I study in NSCLC patients refractory to conventional treatment modalities, antroquinonol at 50, 100, 200, 300, 450, and 600 mg dose levels, given daily for 4 weeks, was generally safe and well tolerated as no particular safety concerns or DLTs were identified in the study. In addition, efficacy results indicated that the tumor overall response at the end of treatment showed stable disease for all three patients included in the per-protocol population: one patient in the 200 mg dose group and two patients in the 600 mg dose group (100%). Therefore its progression to further clinical development is warranted in a larger number of patients with NSCLC.

The rationale for the study design is described in more detail in Section 9.2.

8 STUDY OBJECTIVES

8.1 Primary Objective

To evaluate the activity of antroquinonol in unselected, KRAS-positive, and KRAS-negative patients with stage IV (including pleural effusion) non-squamous NSCLC who have failed two lines of anti-cancer therapy.

8.2 Secondary Objective

To assess the safety and tolerability and PK of antroquinonol in patients with stage IV (including pleural effusion) non-squamous NSCLC who have failed two lines of anti-cancer therapy.

8.3 Exploratory Objective

To explore potential relationships between antroquinonol exposure and safety and efficacy endpoints.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

9.1.1 Description

This is a single-arm, open-label, Phase II study in KRAS-positive and KRAS-negative patients with stage IV (including pleural effusion) non-squamous NSCLC who have failed two lines of anti-cancer therapy. This is defined as patients with radiologically confirmed disease progression following greater than or equal to two, but less than or equal to four, prior lines of systemic anti-cancer therapy (see Section 9.3.1 for a detailed description of the eligibility criteria). A maximum of 60 evaluable patients with NSCLC will receive antroquinonol, of which 30 patients will be KRAS-positive and 30 patients KRAS-negative. An evaluable patient will have received at least one dose of antroquinonol and have a valid baseline tumor assessment (see Section 14.2 for further details). Enrollment will continue until the target number of evaluable patients has been enrolled.

Written informed consent must be obtained from all patients before initiating Screening. The Screening period will be up to 42 days in duration (Days -42 to -1). Following completion of all Screening assessments and confirmation of eligibility criteria, patients will receive antroquinonol 200 mg three-times-a-day (t.i.d. at 8-hour intervals) on Day 0 for 12 weeks (one treatment cycle) or until documented evidence of disease progression, unacceptable toxicity, non-compliance or withdrawal of consent by the patient, or the investigator decides to discontinue treatment, whichever comes first. Study drug should be taken at 8-hour intervals. The time of study drug administration should be recorded in the patient diary.

After the first 12-week treatment cycle, patients who are progression-free will be eligible to receive further (12-week) treatment cycles with antroquinonol (Extension Phase), until documented evidence of disease progression, unacceptable toxicity, non-compliance or withdrawal of consent by the patient, or the investigator decides to discontinue treatment, whichever comes first. Investigators should wait at least 7 days after the last administration of study drug before initiating alternative treatment.

Patients will attend study visits on Days 0, 14, 28, 42, 56 and 84 during the first 12-week treatment cycle, every 4 weeks during the second, third, and fourth treatment cycles (Extension Phase); and every 12 weeks during subsequent treatment cycles (Extension Phase). The study-specific procedures include: physical examination, vital signs, 12-lead ECG, performance status, clinical laboratory tests, AEs, concomitant medication and patient compliance. The schedule of assessments is presented in Table 9.1.

Patients discontinuing study drug will attend an End of Study (EOS) Visit, 4 weeks after the last administration of study drug. In the event that a patient is scheduled to start a new treatment earlier than 3 weeks after the last dose of study drug, the EOS Visit should occur before the start of the new treatment and the reason documented.

Intensive PK sampling will be performed on Days 0 and 28 in all patients enrolled in Stage 1. Sparse PK sampling will be performed on Days 28, 42, and 56 in all patients enrolled in Stage 2.

All patients who withdraw from the study drug, but consent to be followed up for survival status, will be followed up by telephone contact every 3 months, for a maximum of 6 months from the date of last administration of study drug or death, whichever occurs first.

Tumor assessments will be performed at Screening, Days 42 and 84 using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, version 1.1 (see Appendix 1). Tumor assessments will be performed every 12 weeks during the Extension Phase.

The primary efficacy endpoint is progression-free survival (PFS) rate at 12 weeks, which is defined as the proportion of patients alive and progression-free at Week 12. Patients will be progression-free if they have no evidence of progressive disease (defined according to RECIST guidelines, version 1.1) from the start of treatment to Week 12.

The study uses a two-stage design seeking to detect a true PFS rate of more than 35% in the overall (unselected) population and 40% within the KRAS tumor mutation positive and negative strata. Thirty evaluable patients (15 in each stratum) will be treated initially (Stage 1), with expansion to a maximum of 60 evaluable patients (Stage 2). The rules for continuing the overall study and individual stratum are provided in Section 14.2.

An Independent Data Monitoring Committee will act in an advisory capacity to monitor patient safety and efficacy data from the study. The members will be selected on the basis of relevant experience and understanding of clinical research and the issues specific to the therapeutic area, as well as previous data monitoring committee experience.

9.1.2 Schedule of Assessments

The schedule of assessments is presented in Table 9.1.

Table 9.1 Schedule of Study-Specific Procedures

Study Procedure	**Screening (-42 days)**	**Visit (Day)**						**End of Study (EOS) Visit[2]**	**Extension Phase[3]**
		1 (0)	**2 (14)**	**3 (28)**	**4 (42)**	**5 (56)**	**6 (84)**		
Study visit window (days)	N/A	0	± 3	± 3	± 3	± 3	± 3	± 7	± 7
Informed consent[1]	X								
Demographics	X								
Medical & surgical history	X								
Concomitant medication	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion criteria	X								
Tumor biomarkers[4]	X								
Physical examination[5]	X	X	X	X	X	X	X	X	X
Pregnancy test[6]	X								
Vital signs[7]	X	X	X	X	X	X	X	X	X
ECOG performance score	X	X		X	X	X	X	X	X
12-Lead ECG	X	X		X	X	X	X	X	X
Clinical laboratory tests[8]	X	X	X	X	X	X	X	X	X
Tumor assessments[9]	X				X		X	X	X
Dispense study drug[10]		X		X		X	X		X
Drug accountability				X	X	X	X	X	X
PK sampling[11]		X		X	X	X			
AE assessment[12]		X	X	X	X	X	X	X	X
Patient compliance		X	X	X	X	X	X	X	X

Study Procedure	Screening (-42 days)	Visit (Day)						End of Study (EOS) Visit[2]	Extension Phase[3]
		1 (0)	2 (14)	3 (28)	4 (42)	5 (56)	6 (84)		
EORTC QLQ[13]		X			X		X	X	X
Overall survival[14]								X	

ECOG: Eastern Cooperative Oncology Group; ECG: Electrocardiogram; PK: Pharmacokinetics; AE: Adverse Event; EORTC: European Organization for Research and Treatment of Cancer; QLQ: Quality of Life Questionnaire.

[1] Informed consent must be obtained before the patient undergoes any study-specific procedures.

[2] Patients discontinuing study will attend an EOS Visit, 4 weeks after the last administration of study drug. In the event that a patient is scheduled to start a new treatment earlier than 3 weeks after the last dose of study drug, the EOS Visit should occur before the start of the new treatment and the reason documented. Tumor assessment does not need to be performed at the EOS Visit if this was conducted at the Day 84 Visit. For patients participating in the Extension Phase, the tumor assessment does not need to be performed at the EOS Visit if it has been assessed within 8 weeks of the EOS Visit.

[3] After the first 12-week treatment cycle, patients who are progression-free will be eligible to receive further (12-week) treatment cycles with antroquinonol (Extension Phase), until documented evidence of disease progression, unacceptable toxicity, non-compliance or withdrawal of consent by the patient, or the investigator decides to discontinue treatment, whichever comes first. Investigators should wait at least 7 days after the administration of study drug before initiating alternative treatment is administered. Patients discontinuing the study will attend an EOS Visit 4 weeks after last administration of study drug. Patients will attend visits every 4 weeks (± 7 days) during the second, third, and fourth treatment cycles in the Extension Phase. After completion of the fourth treatment cycle, patients will attend visits every 12 weeks (± 7 days).

[4] Tumor tissue blocks or slides will be obtained from archival material or from fresh biopsy during the Screening period to determine the tumor KRAS mutation status before the patient is enrolled. A patient may be enrolled based on KRAS test results from the local laboratory. Pleural fluid cytology may be used to determine KRAS mutation status if the cytology was pathologically reviewed and reported to contain malignant cells consistent with NSCLC. Tumor tissue will also be used to study arrays of genomic and proteomic markers of interest.

[5] Weight, height and body mass index (BMI) will be measured at Screening Visit only.

[6] A urine pregnancy test will be performed during the Screening Visit for women of child-bearing potential. This test can be repeated during the study if required by local regulations.

[7] Vital signs (respiratory rate, heart rate, blood pressure, and body temperature) will be performed at each visit. They will be obtained in the sitting position after the patient has rested for 5 minutes. The date and time of the assessment should be recorded.

[8] Hematology, chemistry, and urinalysis. All tests performed at the Central Laboratory Facility.

[9] Radiological and clinical tumor assessments will be performed at Screening, Day 42 and Day 84 using the RECIST criteria version 1.1. Evaluation during Screening must be performed within 14 (± 7) days of the date of first administration of study drug. Tumor assessments will be performed every 12 weeks during the Extension Phase.

[10] All Screening procedures and laboratory results must be available and reviewed before the patient receives the first dose of study drug. Study drug should be taken at 8-hour intervals. The time of study drug administration should be recorded in the patient diary.

[11] Intensive PK sampling will be performed on Days 0 and 28 in all patients enrolled in Stage 1. Samples will be taken 30 minutes prior to and 0.5, 1, 2, 3, 4, 6, and 8 hours after the first dose on Day 0, and immediately before and 0.5, 1, 2, 3, 4, 6, and 8 hours after the first dose on Day 28. Sparse PK sampling will be performed on Days 28, 42, and 56 in all patients enrolled in Stage 2. At least two samples will be collected on each occasion, one of which will be a trough concentration (30 minutes prior to

dosing and approximately 8 hours after the last dose on the prior day). At least one sample per patient will be timed to coincide with the peak concentration (approximately 3 hours after dosing). The remainder may be taken at any time during the dosing interval.

[12] Patients must be followed for AEs from the date of informed consent until resolution or stabilization, alternative treatment for NSCLC is started, 6 months after last dose of study drug, or loss to follow-up, whichever occurs first. In the event of serious or study drug-related toxicities, the patient will be followed until resolution or stabilization. Safety follow-up data may be collected by telephone contact every 3 months after the EOS Visit.

[13] Day 0 evaluation to be performed before the patient receives the first dose of study drug.

[14] All patients who withdraw from the study drug, but consent to be followed up for survival status, will be followed up by telephone contact every 3 months, for a maximum of 6 months from the date of last administration of study drug or death, whichever occurs first..

The schedule of blood samples that will be drawn for each patient is presented in Table 9.2.

Table 9.2 Schedule of Blood Sampling

Day	Sample No.	Time Schedule (hour)	Time* (hhmm)	Time Window	Activity
Stage 1					
0	N/A	-1	0700		Patient registration
0	N/A	-0.5	0730		Take blood for laboratory test
0	1	-0.5	0730		Take pre-dose sample
0	N/A	-0.25	0745		Take meal or light snack
0	N/A	0	0800		Take dose
0	2	0.5	0830	± 5 min	
0	3	1	0900	± 10 min	
0	4	2	1000	± 15 min	
0	5	3	1100	± 20 min	
0	6	4	1200	± 20 min	
0	7	6	1400	± 20 min	
0	8	8	1600	± 20 min	
28	N/A	-1	0700		Patient registration
28	N/A	-0.5	0730		Take blood for laboratory test
28	9	-0.5**	0730		Take pre-dose sample
28	N/A	-0.25	0745		Take meal or light snack
28	N/A	0	0800		Take dose
28	10	0.5	0830	± 5 min	
28	11	1	0900	± 10 min	
28	12	2	1000	± 15 min	
28	13	3	1100	± 20 min	
28	14	4	1200	± 20 min	
28	15	6	1400	± 20 min	
28	16	8	1600	± 20 min	
Stage 2					
28	1	-0.5**	N/A		Trough
28	2	3	N/A	± 1 hr	Peak
42	3	-0.5**	N/A		Trough
42	4	N/A	N/A		Random***
56	5	-0.5**	N/A		Trough
56	6	N/A	N/A		Random***

* Provided for guidance in scheduling the sampling timing for the visits; the time windows must be followed.

** Sample should be taken approximately 8 hours after the prior dose.

*** Sample may be taken at any time during the dosing interval.

9.1.3 Study Procedures

9.1.3.1 Screening (up to 42 days before Day 0)

- Explain the nature of the study and have patients to read and sign an Informed Consent Form (ICF)
- Assign patient identifier (Screening number) to patients
- Obtain demographic characteristics
- Record medical and surgical history including cancer history
- Record medication history including cancer treatment history
- Screen patients for inclusion/exclusion criteria.
- Obtain a tissue sample (tumor biopsy or archived tumor tissue) to determine KRAS tumor mutation status prior to study enrollment. A patient may be enrolled based on KRAS test results from the local laboratory. Pleural fluid cytology may be used to determine KRAS mutation status if the cytology was pathologically reviewed and reported to contain malignant cells consistent with NSCLC. Tumor tissue from patients will also be used to evaluate arrays of genomic and proteomic markers of interest.
- Perform physical examinations. Weight, height and body mass index (BMI) will be measured at Screening Visit only
- Perform urine pregnancy test for applicable patients only. A urine pregnancy test will be performed during the Screening Visit for women of child-bearing potential. This test can be repeated during the study if required by local regulations
- Obtain vital signs. Vital signs (respiratory rate, heart rate, blood pressure, and body temperature) will be obtained in the sitting position after the patient has rested for 5 minutes. The date and time of the assessment should be recorded.
- Perform ECOG performance status evaluation (see Appendix 2)
- Perform 12-Lead ECG examinations
- Perform clinical laboratory tests (hematology, biochemistry, and urinalysis)
- Tumor assessments (radiological and clinical tumor assessments). Evaluation at the Screening Visit must be performed within 14 (± 7) days of the date of first administration of study drug.

9.1.3.2 Visit 1 (Day 0)

- Record concomitant medications
- Perform physical examinations
- Obtain vital signs
- Perform ECOG performance status evaluation
- Perform 12-Lead ECG examinations

- Perform clinical laboratory tests (hematology, biochemistry, and urinalysis)
- Dispense study drug. All Screening procedures, laboratory results and repeat laboratory results must be available and reviewed before the patient receives the first dose of study drug
- Collect pre-dose blood sample within 30 minutes prior to dosing (Stage 1 only)
- Administer the first dose of study drug at site and collect PK blood samples 0.5, 1, 2, 3, 4, 6, and 8 hours after dosing (Stage 1 only)
- Document study drug dosing time
- Record AE and grade possible toxicity
- Calculate patient compliance
- Perform European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ) (see Appendix 3)

9.1.3.3 Visit 2 (Day 14 ± 3)

- Record concomitant medications
- Perform physical examinations
- Obtain vital signs
- Perform clinical laboratory tests (hematology, biochemistry, and urinalysis)
- Record AE and grade possible toxicity
- Calculate patient compliance

9.1.3.4 Visit 3 (Day 28 ± 3)

- Record concomitant medications
- Perform physical examinations
- Obtain vital signs
- Perform ECOG performance status evaluation
- Perform 12-Lead ECG examinations
- Perform clinical laboratory tests (hematology, biochemistry, and urinalysis)
- Dispense study drug
- Perform drug accountability
- Collect pre-dose blood sample 30 minutes prior to dosing (Stage 1 and 2; approximately 8 hours after the prior dose)
- Administer study drug at site and collect PK blood samples 0.5, 1, 2, 3, 4, 6, and 8 hours after dose (Stage 1 only). Stage 2 only: collect PK blood sample 3 hours after dose
- Document study drug dosing time

- Record AE and grade possible toxicity
- Calculate patient compliance

9.1.3.5 Visit 4 (Day 42 ± 3)

- Record concomitant medications
- Perform physical examinations
- Obtain vital signs
- Perform ECOG performance status evaluation
- Perform 12-Lead ECG examinations
- Perform clinical laboratory tests (hematology, biochemistry, and urinalysis)
- Tumor assessments (radiological and clinical tumor assessments)
- Perform drug accountability
- Collect pre-dose blood sample 30 minutes prior to dosing (Stage 2 only; approximately 8 hours after the prior dose)
- Administer study drug at site and collect random PK blood sample (Stage 2 only)
- Record AE and grade possible toxicity
- Calculate patient compliance
- Perform EORTC QLQ

9.1.3.6 Visit 5 (Day 56 ± 3)

- Record concomitant medications
- Perform physical examinations
- Obtain vital signs
- Perform ECOG performance status evaluation
- Perform 12-Lead ECG examinations
- Perform clinical laboratory tests (hematology, biochemistry, and urinalysis)
- Dispense study drug
- Perform drug accountability
- Collect pre-dose blood sample 30 minutes prior to dosing (Stage 2 only; approximately 8 hours after the prior dose)
- Administer study drug at site and collect random PK blood sample (Stage 2 only)
- Record AE and grade possible toxicity
- Calculate patient compliance

9.1.3.7 Visit 6 (Day 84 ± 3)

- Record concomitant medications
- Perform physical examinations
- Obtain vital signs
- Perform ECOG performance status evaluation
- Perform 12-Lead ECG examinations
- Perform clinical laboratory tests (hematology, biochemistry, and urinalysis)
- Tumor assessments (radiological and clinical tumor assessments)
- Dispense study drug
- Perform drug accountability
- Record AE and grade possible toxicity
- Calculate patient compliance
- Perform EORTC QLQ

9.1.3.8 End of Study (EOS) Visit (± 7 days)

Patients will attend an EOS Visit, 4 weeks after the last administration of study drug. In the event that a patient is scheduled to start a new treatment earlier than 3 weeks after the last dose of study drug, the EOS Visit should occur before the start of the new treatment and the reason documented.

- Record concomitant medications
- Perform physical examinations
- Obtain vital signs
- Perform ECOG performance status evaluation
- Perform 12-Lead ECG examinations
- Perform clinical laboratory tests (hematology, biochemistry, and urinalysis)
- Tumor assessments (radiological and clinical tumor assessments). Tumor assessment does not need to be performed at the EOS Visit if this was conducted at the Day 84 Visit. For patients participating in the Extension Phase, the tumor assessment does not need to be performed at the EOS Visit if it has been assessed within 8 weeks of the EOS Visit.
- Perform drug accountability
- Record AE and grade possible toxicity. Safety follow-up data may be collected by telephone contact every 3 months after the EOS Visit.
- Calculate patient compliance
- Perform EORTC QLQ

- All patients who withdraw from the study drug, but consent to be followed up for survival status, will be followed up by telephone contact every 3 months, for a maximum of 6 months from the date of last administration of study drug or death, whichever occurs first.

9.1.3.9 Extension Phase Visits (± 7 days)

Patients will attend visits every 4 weeks (± 7 days) during the second, third, and fourth treatment cycles. After completion of the fourth treatment cycle, patients will attend visits every 12 weeks (± 7 days).

- Record concomitant medications
- Perform physical examinations
- Obtain vital signs
- Perform ECOG performance status evaluation
- Perform 12-Lead ECG examinations
- Perform clinical laboratory tests (hematology, biochemistry, and urinalysis)
- Tumor assessments (radiological and clinical tumor assessments)
- Dispense study drug
- Perform drug accountability
- Record AE and grade possible toxicity
- Calculate patient compliance
- Perform EORTC QLQ

9.2 Discussion of Study Design

9.2.1 Rationale for Single-Arm, Open-Label Phase II Study

This is a single-arm, open-label, Phase II study in KRAS-positive and KRAS-negative patients with stage IV (including pleural effusion) non-squamous NSCLC who have failed two lines of anti-cancer therapy. This is defined as patients with radiologically confirmed disease progression following greater than or equal to two, but less than or equal to four, prior lines of systemic anti-cancer therapy (see Section 9.3.1 for a detailed description of the eligibility criteria). The rationale for this study is outlined in Section 7.5 and described in more detail below.

The subject population of patients with stage IV (including pleural effusion) non-squamous NSCLC who have failed two lines of anti-cancer therapy was chosen for this study as there is a current unmet need to treat this population and results from the first-in-man Phase 1 study indicate that the tumor overall response at the end of treatment showed stable disease for all three patients (one patient in the 200 mg dose group and two patients in the 600 mg dose group) included in the per-protocol set (PPS). The PPS was defined in the Phase 1 study as all patients who completed at least three cycles of treatment with proper imaging assessment

(RECIST v.1.1). Furthermore, antroquinonol at 50, 100, 200, 300, 450, and 600 mg dose levels, given daily for 4 weeks, was generally safe and well tolerated, with no particular safety concerns or DLT being identified in the study.

Preclinical data (see Section 7.3) suggest that patients with KRAS mutation positive tumors may derive greater benefit from antroquinonol therapy. Hence, patients will be stratified according to KRAS mutation status.

An open-label design was selected as this was considered the most suitable design for evaluation of antroquinonol as a single agent in the patient population eligible for participation in this study.

A two-stage, single-arm design was chosen as this was considered most suitable for assessing the safety, tolerability, PK and efficacy of antroquinonol in patients who have previously failed two lines of anti-cancer therapy.

Antroquinonol will be administered as a single agent in this study at a dose of 600 mg per day (200 mg t.i.d. administered at 8-hour intervals). This dose regimen was chosen based on results from the Phase 1 clinical study (GOLANTA20090911) involving NSCLC patients refractory to conventional treatment modalities, which reported good tolerability of antroquinonol up to 600 mg/day. The area under the plasma concentration-time curve from 0 to 24 hours (AUC_{0-24}) after single dose administration on Day 1 of the first treatment cycle (Cycle 1) increased by 18.79%, 200.1%, 215.16%, 265.19% and 396.61% at the 100, 200, 300, 450, and 600 mg dose levels, respectively, when compared with the 50 mg dose level; whereas on Day 28 of Cycle 1, the AUC_{0-24} decreased by 34.88% at the 100 mg dose level and increased by 133.58%, 141.87%, 680.65% and 562.54% at the 200, 300, 450, and 600 mg dose levels, respectively. Thus, the AUC_{0-24} was not linearly proportional to the antroquinonol dose on Day 1 and Day 28. There were no significant differences in AUC_{0-24} in the 100-300 mg dose range on Day 1 and Day 28. The highest peak concentration (C_{max}) over the 100-300 mg dose range was observed with the 200 mg dose on Day 28. One patient in the 200 mg dose group and two patients in the 600 mg dose group exhibited stable disease at the end of treatment.

Thus, in order to maintain a high drug concentration and enhance the efficacy of antroquinonol 200 mg t.i.d. (every eight hours) has been chosen as the dosage regimen for this study.

The study design is based on the assumption that within each of the KRAS tumor mutation positive and negative strata, a PFS rate at 12 weeks of 40% and 35% overall would be of interest. Further testing would not be pursued if the PFS rate at 12 weeks was less than 15%. See Section 14.1 for further details.

The study drug will be administered until disease progression, occurrence of unacceptable toxicity, non-compliance or withdrawal of consent by the patient, or investigator decision to stop study drug, whichever comes first.

9.2.2 Appropriateness of Measurements

The primary efficacy endpoint in this study is the PFS rate, defined as the proportion of patients alive and progression-free at Week 12. Patients will be progression-free if they have no evidence of progressive disease (per RECIST version 1.1) from the start of treatment to Week 12. The RECIST guidelines recognize that the proportion progression-free at a pre-specified time point is an appropriate to assess the anti-tumor activity of agents such as antroquinonol, where biological activity is more likely to translate into stabilization of disease.[25]

Tumor response, based on radiological measurement, is a standard and well accepted efficacy endpoint in clinical development. Response to study drug will be assessed in this study using RECIST version 1.1 (see Appendix 1), an internationally standardized and widely accepted standard for measuring response to treatment in cancer.[25]

The secondary efficacy measures of objective response rate (ORR), disease control rate (DCR), duration of overall tumor response (DR), PFS, overall survival (OS) and time to progression (TTP) are also well accepted efficacy endpoints in clinical development for oncology studies and in line with recommendations in the European Medicine's Agency (EMA), Committee for Medicinal Products for Human Use (CHMP) Guideline on the Evaluation of Anticancer Medicinal Products in Man (EMA/CPMP/205/95/Rev.4, 2012)[26]; and the United States (US) Food and Drug Administration (FDA) Guidance for Industry on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (US Department of Health and Human Services, May 2007).[27]

The safety and PK endpoints in this study are standard and well understood endpoints in clinical oncology. The corrected QT (QTc) assessment strategy for this study is based on recommendations in the International Conference on Harmonisation (ICH) E14 guideline[28] and is designed to focus on the collection of cardiac safety information. There are no concerns for cardiotoxicity based on the mechanism of action, the nonclinical toxicology studies, or the limited clinical information available to date. Twelve-lead ECGs are required during Screening, during treatment, and at the End of Treatment Visit, and as clinically indicated.

Quality of life will be assessed using EORTC QLQ C30 (QLQ-C30) and the Module on Lung Cancer (QLQ-LC13), which is a validated instrument for assessing quality of life (QoL) in patients with lung cancer.

The EORTC QLQ-C30 / EORTC QLQ-LC13 is comprised of a global health status scale, five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), and several single items, as well as a module designed specifically for lung cancer. These QoL assessment tools are included in this study in order to evaluate the side effects of antroquinonol as well as the impact of treatment on patients' disease-related symptoms.

9.2.3 Risk/Benefit and Ethical Assessment

As known to the sponsor, no fatal or severe/serious adverse drug reaction has been reported by the marketed product (food supplement) of *Antrodia camphorata*.

Patients anticipated to be enrolled into the study will be non-squamous NSCLC patients with confirmed disease progression following two prior lines of systemic anti-cancer therapy for recurrent/metastatic disease (one of which should be a platinum-based **regimen**). As the dose utilized for this study is considered conservative and acceptable, and the patients targeted are mainly patients with rather limited treatment options, the risk and benefit assessment is deemed justifiable.

9.2.4 Early Termination

This study may be terminated at the discretion of the sponsor or any regulatory agency. A principal investigator (PI) may elect to discontinue or stop the study at his or her site for any reason including safety or low enrollment.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Patients eligible for enrollment in the study must meet all of the following criteria:

1. Cytologically or histologically confirmed non-squamous NSCLC Stage IV (including pleural effusion)
2. Radiologically confirmed disease progression following greater than or equal to two, but less than or equal to four, prior lines of systemic anti-cancer therapy, one of which should be a platinum-based regimen, OR the patient has refused treatment with approved treatment modalities, OR the investigator feels that the patient is not a candidate for other systemic therapy. Patients with epidermal growth factor receptor (EGFR)-positive mutations should have been offered treatment with an EGFR-TK inhibitor prior to enrolment in this study. Adjuvant therapy with or without maintenance therapy would count as one line of systemic therapy. A line of therapy requires at least two 3-4 week complete cycles unless it was stopped due to toxicity, in which case it would count as one line of therapy
3. At least one radiologically measurable target lesion per RECIST version 1.1
4. Fresh or archival biopsy tissue available to determine KRAS tumor mutation status
5. At least 18 years of age at the time of signing informed consent
6. Life expectancy of at least 3 months
7. Written informed consent that is consistent with ICH Tripartite Guideline on Good Clinical Practice (GCP) guidelines
8. Patient or legally acceptable representative has granted written informed consent before any study-specific procedures (including special Screening tests) are performed
9. Eastern Cooperative Oncology Group (ECOG) performance score of 0, 1 or 2

10. Hemoglobin ≥ 9.0 g/dL; platelets ≥ 100 x 10^9/L; ANC ≥ 1.5 x 10^9/L without the use of hematopoietic growth factors
11. Bilirubin and creatinine less than 2 × upper limit of normal (ULN) for the institution
12. Albumin ≥ 2.5 g/dL
13. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) less than 5 × ULN for the institution
14. Prothrombin time less than 1.5 × ULN for the institution
15. Potassium, magnesium and phosphorus within the normal range for the institution (supplementation is permissible)
16. Willing to use two medically accepted and effective methods of contraception from the list below during the study (both men and women as appropriate) and for 3 months after the last dose of study drug:
    - Established use of oral, injected or implanted hormonal methods of contraception.
    - Placement of an intrauterine device or intrauterine system.
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
    - Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
    - True abstinence: When this is in line with the preferred and usual lifestyle of the patient.
17. Recovery to ≤ Grade 1 or baseline of any toxicities due to prior treatments, excluding alopecia

9.3.2 Exclusion Criteria

Patients meeting any of the following criteria must not be enrolled in the study:

1. Chemo-, hormone- or immunotherapy, within 4 weeks or within less than four half-lives of the date of first administration of study drug and/or persistence of toxicities of prior anti-cancer therapies which are deemed to be clinically relevant
2. Radiotherapy within the past 2 weeks prior to the date of first administration of study drug.
3. Previous treatment with a histone deacetylase (HDAC) inhibitor or an EGFR inhibitor within at least 4 weeks of the date of first administration of study drug
4. Treatment with any drug(s) known to be a strong inhibitor or inducer of CYP2C19, CYP3A4, CYP2C8, and CYP2E1, within 14 days of the date of first administration of study drug

5. Brain metastases which are symptomatic; patients with treated brain metastases are eligible with stable brain disease for at least 4 weeks without the requirement for steroids or anti-epileptic therapy
6. Inability to swallow oral medications or a recent acute gastrointestinal disorder with diarrhea e.g., Crohn's disease, malabsorption, or Common Terminology Criteria for Adverse Events (CTCAE) Grade > 2 diarrhea of any etiology at baseline
7. Other malignancies diagnosed within the past 5 years (other than curatively treated cervical cancer *in situ*, non-melanoma skin cancer, superficial bladder tumors Ta [non-invasive tumor] and TIS [carcinoma *in situ*], or non-metastatic prostate cancer stage 1 to 2, which has been previously treated with surgery or radiation therapy, and serum prostate-specific antigen is within normal limits [test performed within the past 12 months prior to the date of first administration of study drug])
8. Patients with any serious active infection (i.e., requiring an intravenous antibiotic, antifungal, or antiviral agent)
9. Patients with known HIV, active hepatitis B or active hepatitis C
10. Patients who have any other life-threatening illness or organ system dysfunction, which in the opinion of the investigator, would either compromise patient safety or interfere with the evaluation of the safety of the study drug
11. Known or suspected substance abuse or alcohol abuse
12. Women of child-bearing potential or men who are able to father a child unwilling to use two medically accepted and effective methods of contraception during the study (as specified in the inclusion criteria)
13. Pregnancy or breast feeding
14. Patient unable to comply with the protocol
15. History of clinically significant or uncontrolled cardiac disease, including congestive heart failure, angina, myocardial infarction, arrhythmia, including New York Heart Association functional classification of 3

9.3.3 Removal of Patients from Study or from Study Treatment

Patients may withdraw their consent to participate in the study and investigators may withdraw patients at any time without prejudice. Patients will be withdrawn from the study or study treatment if any of the conditions set below has occurred:

1. Documented disease progression according to the response criteria
2. Unacceptable toxicity
3. Patient decides to withdraw his/her informed consent
4. Investigator considers that the patient is no longer physically and/or psychologically able to remain in the study

5. Patient has developed a condition that requires treatment with a medication prohibited by the protocol
6. Patient develops adverse effects that the investigator considers a permanent cessation of the study drug is necessary
7. Non-compliance with study drug, protocol requirements, or study-related procedures
8. Patient's treatment is interrupted for more than 1 week and the investigator and Medical Monitor considers a permanent cessation of the study drug is necessary

The investigators should complete the evaluation items for the EOS Visit upon a patient's withdrawal. Tumor assessment does not need to be performed at the EOS Visit if this was conducted at the Day 84 Visit. For patients participating in the Extension Phase, the tumor assessment does not need to be performed at the EOS Visit if it has been assessed within 8 weeks of the EOS Visit. This does not include a patient who has not been treated by the study drug, such as withdrawal at Screening or at Baseline. Only the electronic Case Report Form (eCRF) required data should be completed. All patients who are withdrawn or removed will not be replaced in this study.

9.3.4 Follow-Up for Drug Discontinuation/Patient Withdrawal from Study

If a patient discontinues study drug and is withdrawn from the study for any reason, the study center must immediately notify the monitor. The date and the reason for study drug discontinuation or patient withdrawal from the study must be recorded on the eCRF. Patients who withdraw from the study are to complete all evaluations for the EOS Visit. If the PI is unable to complete the visit assessments, the reason(s) must be recorded in the eCRF.

10 TREATMENT OF PATIENTS

10.1 Study Drug Treatment and Dosing

Antroquinonol should be taken every 8 hours approximately 15 minutes after a meal or light snack and not within ± 1 hour of drinking an ethanol-containing beverage e.g. an alcoholic drink.

Subjects who forget or are unable to take a dose at the scheduled time should be instructed to take the dose as soon as possible. If they do not remember or are unable to take the dose prior to the next scheduled dose, they should take the scheduled dose and the missed dose will not be made up.

The date and time of each study drug administration should be recorded in the patient diary.

10.2 Treatment for Study Drug Overdose

Treatment of study drug overdose is at the discretion of the investigator.

10.3 Administration on Pharmacokinetic Sampling Days

On the days in Stage 1 when PK sampling will be performed, namely, Days 0 and 28, patients will eat a meal at the study site and then take their next dose of antroquinonol 15 minutes (± 3 minutes) after completion. Patients should take their last dose of antroquinonol on Day 27, approximately 8 hours before the scheduled time of dosing at the study site.

Study drug should be taken at 8-hour intervals, approximately 15 minutes after a meal or light snack, and not within ± 1 hour of drinking an ethanol-containing beverage, e.g. an alcoholic drink. The exact time of study drug administration should be recorded in the patient diary. All capsules must be swallowed within 2 to 3 minutes. On Days 0 and 28 patients will remain at the site for 8 hours after study drug administration if required for PK.

On days of PK sampling in Stage 2, namely, Days 28, 42, and 56, patients will eat a meal at the study site and then take their next dose of antroquinonol 15 minutes (± 3 minutes) after completion. Patients should take their last dose of antroquinonol on Days 27, 41, and 55 approximately 8 hours before the scheduled time of dosing at the study site.

10.4 Extension Phase

After the first 12-week treatment cycle, patients who are progression-free will be eligible to receive further (12-week) treatment cycles with antroquinonol in the Extension Phase.

Patients participating in the Extension Phase will follow a schedule similar to that of the first 12-week treatment cycle, except no PK samples will be drawn. Patients will attend visits every 4 weeks (± 7 days) during the second, third, and fourth treatment cycles. After completion of the fourth treatment cycle, patients will attend visits every 12 weeks (± 7 days).

Patients may continue in the Extension Phase until documented evidence of disease progression, unacceptable toxicity, non-compliance or withdrawal of consent by the patient, or the investigator decides to discontinue treatment, whichever comes first.

If there is Grade 3 or 4 toxicity, the patient's dose will drop down to the next lower dose according to the Dose Modification and Toxicity Management Guidelines in Section 10.5.

10.5 Dose Modification

The guidelines for dose modification and management of drug toxicity are as follows:

Table 10.1 Dose Modification and Management of Drug Toxicity Guidelines

Event	Grade	Management/Action
All non-hematologic and hematologic adverse events that are study drug-related	1 or 2	No change.
	3	Suspend treatment. Treatment may resume if toxicity is resolved to grade ≤ 1 or returns to baseline within 7 days. Treatment should resume at a reduced dose (100 mg t.i.d). If toxicity lasts more than 7 days, study drug will be permanently discontinued (subject to investigator and Medical Monitor agreement); if a patient experiences another grade ≥ 3 toxicity at the reduced dose, then study drug will be permanently discontinued.
	4	

Treatment may be withheld for up to 7 days due to study drug-related toxicities. Patients will be permanently discontinued from the study drug if treatment interruption is more than 7 days and the investigator and Medical Monitor consider that permanent cessation of study drug is necessary. If a patient resumes treatment before the end of a cycle, the patient will have to complete the rest of the treatment of that cycle.

When patients are suspected to experience Grade 3 or more AEs, they should contact the site as soon as possible for an appointment and bring back any unused study drug to the site. Treatment should only be withheld for nausea, vomiting, and diarrhea of Grade ≥ 3 if symptoms remain at Grade ≥ 3 despite adequate treatment. If dose modification is deemed necessary, the unused study drug will be retrieved and a new bottle with quantity of study drugs calculated based on the modified dose will be dispensed. Sufficient study drug should be dispensed for the period from the day of dose modification to the next dispensing visit.

The quantity given will be recorded in the eCRF and the drug accountability log. At the time the patient returns the unused study drug, they will be counted at the site and recorded in the eCRF. The dates and durations of any dosing interruptions will be recorded in the eCRF.

10.6 Packaging and Labeling

The study drug for this study will be supplied by Golden Biotechnology Corporation for active ingredient and for final formulation and packaging. The physicochemical properties and the pharmaceutical specifications of the study drug for this study are provided in the Investigator's Brochure.[29] The sponsor is responsible for shipping the study drug to the study site and implementing strict inventory control for drug accountability.

The study drug will be filled in # 2 capsules (100 mg) and then packed in a light-protected polyethylene bottle and closed with a piece of polyethylene cap liner fitted in the cap for each

dispensation at Visit 1 (Day 0), 3 (Day 28), 4 (Day 42), 5 (Day 56) and 6 (Day 84), and subsequent visits for patients entering the Extension Phase. The study drug will be labeled in accordance with country-specific requirements.

10.7 Dispensing and Return of Study Drug

The study investigator and/or the designated pharmacist will be in charge of the management and dispensation of the study drug. All unused study drug must be returned to investigator at each visit. Drug accountability and inventory will be recorded in the eCRFs and the relevant study log.

Patients who participate in the Extension Phase will be given enough study drugs for one cycle. Study drug will be returned to the pharmacy if the patient discontinues study drug early.

10.8 Storage and Reconciliation of Supplies

The available stability data supports a 3-year shelf-life for antroquinonol capsules when stored below 28ºC and in the original package.

Antroquinonol capsules are packaged in a light-protected polyethylene bottle. Investigational drug must be stored at the study site in a dry place below 28ºC and protected from direct light and excessive humidity, as stated in the Investigator's Brochure.[29] Antroquinonol will be shipped to the study site by Golden Biotechnology Corporation by express delivery. During shipping, the study drug will be packaged to maintain the temperature below 28 ºC.

Patients will be instructed to store the drug at room temperature and to protect the study drug from light and excess humidity.

10.9 Concomitant Medications

The investigators may prescribe additional medications during the study, as long as these are not prohibited by the protocol (Section 10.10).

Any use of concomitant treatment must be recorded on the eCRF.

10.10 Prohibited Medications, Foods and Tobacco Use

Except for antroquinonol, no other cytotoxic agents (examples listed in next paragraph), investigational drugs, active or passive immunotherapy, chemotherapy, and radiotherapy will be permitted during the study period. Simultaneous participation in other clinical treatment study protocols is not allowed.

1. Small molecule inhibitors of the tyrosine kinase of EGFR, e.g., gefitinib or erlotinib
2. Monoclonal antibody binding specifically to EGFR, e.g., cetuximab or panitumumab
3. Recombinant humanized monoclonal antibody targeting vascular endothelial growth factor, e.g., bevacizumab
4. Folate analogue metabolic inhibitor, e.g., pemetrexed

Levonorgestrel will be prohibited during the conduction of this study because it is used as internal standard in bioanalysis.

Drugs/articles known to be strong inhibitors or inducers of CYP2C19, 3A4, 2C8, and 2E1 are prohibited. Drugs with a narrow therapeutic index that are substrates of 1A2, 2B6, 2C8, 2C9, 2C19, 3A and 2D6 are also prohibited. A list of commonly known substrates, inhibitors and inducers is given in Appendix 4. It should be noted that this is not an exhaustive list.

Foods which may affect the assessment of the study drug should be prohibited during the study. These foods include charbroiled food, star fruit, and grapefruit juice. Smoking is also prohibited during the study.

10.11 Treatment Compliance

A patient's treatment compliance will be assessed by the following formulae:

For each visit**,** except Visit 2, the compliance will be calculated:

[(Capsules actually used) ÷ (number of days patients exposed to study drug * planned number of capsules per day)]

The number of days patients exposed to study drug is calculated as:

[Day of last dose -Day of first dose + 1]

Patients who undergo dose modifications will have their treatment compliance calculated by this formula:

(Original dose [(Capsules actually used) ÷ (number of days patients exposed to study drug* planned number of capsules per day for each day patient was on original dose)]) + (Modified Dose [(Capsules actually used) ÷ (number of days patients exposed to study drug* planned number of capsules per day for each day patient was on modified dose)])

Site staff will record compliance of patients with their assigned regimen. Patients are to be instructed to bring their partially used or empty bottles back for inspection at each study visit. All patients are to be reminded of the importance of compliance with their assigned regimen with an emphasis on taking their study drug on schedule (i.e., every 8 hours), and contacting the site for an appointment as soon as possible if they think they are experiencing significant toxicity.

11 ASSESSMENT OF EFFICACY

The primary and secondary efficacy analyses will be based on the independent centralized assessment of medical images. A detailed description of the process is provided in the Independent Review Charter.

11.1 Efficacy Variables

Primary endpoint

The primary endpoint is the PFS rate at 12 weeks, defined as the proportion of patients alive and progression-free at Week 12. Patients will be progression-free if they have no evidence of progressive disease (defined according to RECIST guidelines, version 1.1) from the start of treatment to Week 12.

Tumor response will be assessed at 6-week intervals during the first treatment cycle using the RECIST criteria version 1.1. Each patient will be assigned one of the following categories: 1) complete response (CR), 2) partial response (PR), 3) stable disease (SD), or 4) progressive disease (PD). Patients who died from any cause or discontinued the study for any reason without a post-screening or Week 12 tumor assessment will be considered as failing to respond to treatment.

Secondary efficacy endpoints

Secondary efficacy endpoints are as follows:

- Objective response rate, defined as the proportion of patients whose best overall response is either CR or PR according to RECIST version 1.1. The best overall response is the best response recorded during the first 12-week treatment cycle.
- Disease control rate, defined as the proportion of patients with a documented CR, PR and SD during the first 12-week treatment cycle according to RECIST version 1.1.
- Duration of overall tumor response, defined as the interval between the date of the first observation of tumor response (CR or PR) and the date of disease progression or death.
- Progression free survival, defined as the time from the date of first administration of study drug to objective tumor progression by RECIST version 1.1 or death due to any cause, whichever occurs first.
- Overall survival, defined as the time from the date of first administration of study drug to death from any cause.
- Time to progression, defined as the time from the date of first administration of study drug to objective tumor progression by RECIST version 1.1.

Patient Reported Outcome endpoint:

The PRO endpoint is as follows:

- European Organization for Research and Treatment of Cancer QLQ-C30 and the EORTC QLQ-LC13.

Pharmacokinetic endpoints:

For Stage 1, PK endpoints will be derived for intensively sampled PK profiles by non-compartmental methods and include:

- C_{max}: peak concentration
- C_{trough}: trough plasma concentration
- T_{max}: peak time
- AUC_{τ}: area under the plasma concentration-time curve over the 8-hour dosing interval
- $T_{½}$: terminal half-life
- Vz/F: apparent volume of distribution during elimination
- CL/F: apparent oral clearance
- $T_{½, eff}$: effective half-life

If possible, PK data from all patients will be analyzed using PopPK methods and *post hoc* estimates of antroquinonol exposure (i.e., C_{max}, C_{trough}, and AUC_{τ}) will be computed for exploration of potential exposure-response relationships.

Tumor biomarkers:

Subgroup analyses will assess the predictive value of tumor biomarkers.

11.2 Efficacy Assessments

11.2.1 Tumor Measurement

Tumor assessment will be performed during the 12 week treatment period using computed tomography (CT) scan or magnetic resonance imaging (MRI) according to RECIST guideline, version 1.1 (see Appendix 1) at the Screening Visit, Visit 4 (42), and Visit 6 (84). Tumor assessments will be performed every 12 weeks during the Extension Phase. The tumor assessment does not need to be performed at the EOS Visit if this was conducted at the Day 84 Visit. For patients participating in the Extension Phase, the tumor assessment does not need to be performed at the EOS Visit if it has been assessed within 8 weeks of the EOS Visit. The preferred scan is a CT of the chest, abdomen, and pelvis, performed with IV contrast. If patients have a contraindication to iodinated contrast, such as a documented allergy or impaired renal function, a non-contrast CT of the chest and MRI of the abdomen and pelvis is permitted (MRI preferably with gadolinium contrast, though this may be omitted if renal impairment is severe). Imaging evaluation at the Screening Visit must be performed within 14 (± 7) days of the date of first administration of study drug.

The same method of assessment will be used at each tumor assessment visit as used at the baseline visit.

11.2.2 Clinical Response – Solid Tumors

Clinical response will be evaluated according to RECIST criteria[25] in evaluable patients, by comparing the measurements and number of target lesions at baseline and during the study.

The RECIST version 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumor response criteria are in Appendix 1.

11.2.3 Tumor Biomarkers

Formalin fixed paraffin embedded (FFPE) tumor tissue will be submitted for analysis of tumor biomarkers. Next-generation sequencing will be used to screen a panel of 236 genes commonly mutated in tumors, including KRAS, EGFR, and ALK. Patients will be stratified according to KRAS mutation status to test for possible differences in sensitivity/resistance to the study drug. In addition, selected samples may also have ALK and ROS1 status determined by immunohistochemistry.

Refer to the Laboratory Manual for details of the mutation assays, and instructions for sample collection, handling, and shipment.

12 PHARMACOKINETICS

12.1 Pharmacokinetic Sampling

PK sampling will be performed on Day 0 and Day 28 in all patients enrolled in Stage 1 at the following time points:

Day 0: (Approximately 5 mL per sample, 60 mL in total) 30 minutes prior to and 0.5, 1, 2, 3, 4, 6, and 8 hours after the first dose.

Day 28: (Approximately 5 mL per sample, 60 mL in total) immediately before and 0.5, 1, 2, 3, 4, 6, and 8 hours after the first dose on Day 28.

Sparse PK sampling will be performed on Days 28, 42, and 56 in all patients enrolled in Stage 2. At least two samples will be collected on each occasion, one of which will be a trough concentration (30 minutes prior to the first dose on Days 28, 42, and 56 and approximately 8 hours after the last dose on the prior day). At least one sample per patient will be timed to coincide with the peak concentration (3 hours after the first dose). The remainder may be taken at any time during the dosing interval.

Each blood sample will be analyzed for antroquinonol plasma concentration to determine PK parameters after administration of antroquinonol using a fully validated bioanalytical method (a copy of the analytical method validation report and bioanalytical report will be included in the clinical study report).

12.2 Pharmacokinetic Sampling Procedures

12.2.1 Blood Samples

Samples of venous blood will be obtained in 5 mL sodium heparin Vacutainer® tubes at the sample times listed above in Section 12.1. Immediately after collection the tube will be gently inverted 8 to 10 times to mix the anticoagulant with the blood sample. All samples will be processed and placed into a freezer within one (1) hour after collection. The plasma fraction will be separated by placing the collection tube into a refrigerated centrifuge (4°C) for 10 minutes at 3000 rpm. The plasma fraction will be withdrawn by pipette and divided into two polypropylene freezing tubes (with each tube receiving approximately equal aliquots). All sample collection and freezing tubes will be clearly labeled with the patient number, the study period, and the collection time. Labels will be fixed to freezing tubes in a manner that will prevent the label from becoming detached after freezing. All plasma samples will be placed into a freezer at -70°C within 1 hour after collection.

12.2.2 Sample Storage and Shipping

All plasma samples will be stored frozen (at -70°C) until they are shipped to the Central Laboratory Facility. Prior to shipping, the samples will be packed into thermal insulated containers and packed in sufficient dry ice to assure they remain frozen, and are protected from breakage during shipment. Samples will be shipped by overnight, priority courier. The samples will be divided into two shipments, each containing one aliquot of plasma for each time point. After receipt of verification that the first shipment was received by the Central

Laboratory Facility in good condition, the second shipment will be sent to the Central Laboratory Facility.

Samples will be shipped monthly to the Central Laboratory Facility. The shipping address and contact information will be provided in a separate document.

12.2.3 Analytical Methodology

The concentration of study drug will be determined from the plasma samples using a validated analytical method. Details of the method validation and sample analysis will be included in the final clinical study report.

13 ASSESSMENT OF SAFETY

Safety will be assessed based on AEs, clinical laboratory results (routine hematology and biochemistry), physical examination, vital signs, and ECG recording.

13.1 Height and Weight

Height is to be measured for the patient not wearing shoes at the Screening Visit and will be rounded to the nearest centimeter. Weight and BMI will be measured at Screening Visit only.

13.2 Demographics

Demographic data including date of birth and gender information will be obtained at Screening.

13.3 Medical History

General medical history should be recorded at the Screening Visit. The medical history should include procedural and surgical history within the past year. Cancer history should be recorded on a life-time basis.

13.4 Previous and Concomitant Medications

All previous medications taken by the patient during the 6-week period prior to study enrollment should be recorded at the Screening Visit. Cancer therapies should be recorded on a life-time basis. All concomitant medications starting from enrollment of patients should be recorded.

13.5 Physical Examination

Patients will be examined at every visit by standard physical examination including general appearance, skin, eyes, ear/nose/throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, and other body systems if applicable for describing the status of their health.

13.6 Vital Signs

Vital signs will be measured for all patients at every visit and include blood pressure, pulse rate, respiratory rate, and body temperature.

13.7 Electrocardiograms

Electrocardiograms will be performed at every visit, except Visit 2. The evaluation items for all ECGs will include heart rate, QRS complex, QT interval, QTc, and RR intervals. At Screening the investigator should examine the ECG for signs of cardiac disease that could exclude the patient from the study. An assessment of normal or abnormal will be recorded and if the ECG is considered abnormal, the abnormality will be documented on the eCRF.

13.8 Eastern Cooperative Oncology Group Performance Status

The performance status of patients will be graded by their ECOG performance status score at every visit**,** except Visit 2. The description of ECOG performance status scale is defined as follows:

0: Normal activity. Fully active, able to carry on all pre-disease performance without restriction.

1: Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).

2: In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.

3: In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4: 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

5: Dead.

13.9 Laboratory Variables

Blood laboratory tests including red blood cells, white blood cells with differential counts, platelet count, hemoglobin, hematocrit, sodium, potassium, calcium, magnesium, phosphorus, glucose, blood urea nitrogen, creatinine, uric acid, albumin, total protein, alkaline phosphatase, ALT, AST, total bilirubin, gamma glutamyltransferase, and C-reactive protein will be taken at every visit. Urinalysis including pH, erythrocyte, leukocyte, glucose, and protein will be conducted at the same visits at which blood laboratory tests are performed. All tests will be performed at the Central Laboratory Facility.

All Screening laboratory results must be available and reviewed before the patient receives the first dose of study drug at Visit 1 (Day 0). After the test results are evaluated, the investigators should judge whether patients are still eligible to stay in the study. Significant abnormal values occurring during the study will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant.

13.10 Adverse Events

An AE is any untoward medical occurrence in a patient during participation in the study, regardless of the relationship of the occurrence to the treatment with the study drug. An AE can be any unfavorable sign or symptom or diagnosed new disease or deterioration of existing chronic or intermittent diseases, significantly unexpected deteriorated condition of the study indication, which is associated with the use of the study drug. Abnormal can be considered as aforementioned signs and can be considered an AE. However, hospital admissions and/or surgical operations scheduled prior to the participation in this study for a pre-existing illness or disease to be performed during participation in this study are not to be considered an AE. The investigators are responsible for the detection, reporting, and documentation of AEs.

13.10.1 Disease-Related Events

A disease-related event is defined as an event that can be explained by the study indication. Considering the nature of the study patients to be late-stage cancer patients, the natural course of the disease leading to death or life-threatening conditions is considered as AEs or SAEs. The investigator must judge whether the event is a consequence or progression of the pre-existing disease(s). Disease-related events, like any other events that are life-threatening, or result in death, must be reported as SAEs.

13.10.2 Lack of Efficacy

Lack of efficacy is not to be considered as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definitions of AE or SAE.

13.10.3 Clinical Laboratory Abnormalities

Abnormal laboratory findings and/or assessments that are judged by the investigator to be clinically significant will be reported as AEs or SAEs if they meet the definitions set forth. For the conditions that the abnormal laboratory and/or assessment findings are considered as the underlying disease-related, and are not unexpectedly worsened during the study, no AE or SAE should be reported.

13.10.4 Recording AEs and SAEs

All AEs and SAEs should be documented in the source documents and the relevant eCRF and SAE form when applicable. The investigator may be asked to provide photocopies of the medical records for completing the AE or SAE report. The medical records submitted to the relevant parties will be concealed of the patients' names. It is the responsibility of the investigator to report AEs or SAEs by diagnosis terminologies, if possible. When the diagnosis is possible for the reported AE or SAE, no signs and symptoms used to establish that particular diagnosis should be reported. The investigator will be asked to determine the severity and causality of each AE and SAE based on the investigator's clinical judgment. Five levels of intensity and two levels of causality are used to evaluate each AE and SAE as shown below:

Severity based on the National Cancer Institute (NCI) CTCAE version 4.03:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

*There is no direct relationship for severity and seriousness of an AE.

Causality:

- Possibly related: The suspected AE may follow a reasonable temporal sequence from test drug administration but could have been produced or mimicked by the patient's clinical state or by other modes of therapy concomitantly administered to the patient.
- Unrelated: Should be reserved for those events which occur prior to unrelated test drug administration (i.e., washout or single-masked placebo) or those events which cannot be even remotely related to study participation (e.g., injuries sustained in an automobile accident).

It is important for the investigators to take information of underlying diseases, concomitant drugs, and temporal relationship of the onset of the event to the time of dosing the study drug, and re-challenging outcomes, into account when making a causal relation decision. It is the investigators' responsibility to follow proactively the outcome of each AE until resolution or stabilization of the condition, alternative treatment for NSCLC is started, 6 months after last dose of study drug, or loss to follow-up, whichever occurs first. In the event of serious or study drug-related toxicities, the patient will be followed until resolution or stabilization. Safety follow-up data may be collected by telephone contact every 3 months after the EOS Visit.

13.10.5 Serious Adverse Events

An SAE is an AE that leads to any of the following medical occurrence:

- Results in death
- Is life-threatening, meaning the patient is at risk of death at the time of event
- Requires hospitalization or prolongation of existing hospitalization. Emergency room visits that do not result in admission to the hospital should not be considered as a SAE requiring hospitalization or prolongation of existing hospitalization, and such emergency room visits should be evaluated for one of the other serious outcomes instead
- Results in disability/incapacity
- Is a congenital anomaly/birth defect
- Events requiring medical and/or surgical intervention to prevent one of the other outcomes listed in the definition above or, based on medical and/or scientific judgment of investigator, are important and should be considered serious

Any hospitalization only for the purpose of diagnostic or study-related procedures is not to be considered as a serious AE.

Any SAE, including death from any cause that occurred during the study, whether or not related to the study drug, must be reported to the Safety Desk immediately (within 24 hours) via telephone, fax, or e-mail. If initially reported via telephone or e-mail, this must be followed up by a written report to be submitted within 24 hours of its occurrence.

Serious Adverse Event Reporting

ICON Clinical Research

Medical & Safety Services

United States of America - Serious Adverse Event Reporting

Phone: +1 888 723 9952

Fax: +1 215 616 3096

e-mail: ICR-MA-SAE-USA@iconplc.com

Taiwan - Serious Adverse Event Reporting

Phone: +65 6896 0378

Fax: +65 6565 7939

e-mail: ICR-MA-SAE-Singapore@iconplc.com

It is imperative to report the SAE within 24 hours of its occurrence so that reporting to the Regulatory Agencies can be met within the required time frame (7 or 15 calendar days). Because of the need to report to health authorities all SAEs in a timely manner, it is vitally important that an investigator report immediately any AEs that would be considered serious, even if the PI does not consider the AE to be clinically significant or drug-related. Should the PI become aware of an SAE (regardless of relationship to study drug) that occurs within 30-days after stopping the study drug, the SAE must be reported in accordance with the procedures specified in this protocol. There is no time limit on the collection of SAEs that are considered related to study drug. All SAEs that are not resolved by the end of the study, or that were not resolved upon discontinuation of the patient's participation in the study, are to be followed until either: the AE resolves, the AE stabilizes, the AE returns to baseline values (if a baseline value is available), or it is shown that the AE is not attributable to the study drug or study conduct. Medical and scientific judgment is to be exercised in deciding whether expedited reporting is appropriate in other situations, such as for important medical events that were not immediately life-threatening or did not result in death or hospitalization but are jeopardizing the patient or require intervention to prevent one of the outcomes listed above.

13.10.6 Pregnancy

Patients with child-bearing potential must be confirmed as not being pregnant at Screening and willing to use effective methods of contraception during the study and for 3 months after the last dose of study drug (as defined in Section 9.3.1, Inclusion Criterion 16). Following administration of study drug, pregnancy cases in any female patient will be reported if known until the patient completes or withdraws from the study. The pregnancy will be reported immediately by phone and by faxing a completed Pregnancy Report to the sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however the investigator will follow the patient until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy.

The investigator should notify the sponsor (or designee) of the pregnancy outcome by submitting a follow-up Pregnancy Report. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the investigator will report the event by phone and by faxing a completed SAE form to the sponsor (or designee) within 24 hours of knowledge of the event.

14 STATISTICAL EVALUATION

14.1 Sample Size and Power

The study uses a two-stage design. Thirty evaluable patients (15 in each stratum) will be treated initially (Stage 1), with expansion to a maximum of 60 evaluable patients (Stage 2). Enrollment will continue until the target number of evaluable patients has been enrolled.

The statistical design is based on literature published by Green and Dahlberg (1992)[30], von Mehren et. al. (2012)[31] and Hoang et. al. (2013)[32]. It is assumed that within each of the KRAS tumor mutation positive and negative strata, a PFS rate at 12 weeks of 40% and 35% overall (unselected) population will be of interest. Further testing will not be pursued if the PFS rate at 12 weeks is less than 15%.

Initially, 15 evaluable patients are to be accrued within each stratum. If two or more patients are alive and progression-free at Week 12 within a stratum, then an additional 15 evaluable patients will be accrued to that stratum for a total of 30 evaluable patients. If nine or more patients are alive and progression-free at Week 12 within the 30 evaluable patients in the stratum then antroquinonol will be considered worthy of further study in that cohort. This design will allow a significance level of 2.8% and a power of 90.5% within each stratum.

In addition to within-stratum hypothesis testing, this study is also designed to investigate the PFS rate at 12 weeks in the overall (unselected) population. If less than three patients are alive and progression-free at Week 12 in the first 20 evaluable patients, and the criterion for continuing the individual stratum are not met, then the accrual for all strata will be discontinued. Otherwise, a maximum of 40 additional evaluable patients will be entered (depending on whether any individual stratum is closed). Fifteen or more patients alive and progression-free at Week 12 out of the maximum 60 evaluable patients would warrant further study. The overall design has a significance level of 2.8% (probability of falsely declaring the regimen with a 15% PFS rate at 12 weeks to warrant further study) and power 95.6% (probability of declaring the regimen with a 35% PFS rate at 12 weeks in the overall population to warrant further study).

14.2 Statistical Methods

All analysis will be performed in accordance with a detailed Statistical Analysis Plan (SAP).

14.2.1 Analysis Populations

The primary analysis will be performed on the evaluable population. The evaluable population will consist of all enrolled patients who receive at least one dose of antroquinonol and have a valid baseline tumor assessment. A valid baseline assessment is defined as a readable scan (one in which the images are of high enough quality to permit accurate assessment of the tumor) performed within 14 (± 7) days of the date of first administration of study drug. For the efficacy analysis, enrollment will continue until the target number of evaluable patients has been enrolled.

The full analysis set (FAS) and PPS will be used for supportive efficacy analyses. The FAS will consist of patients in the evaluable population who have at least one post-baseline tumor

assessment. The PPS will consist of patients in the FAS who do not have major protocol violations.

The PK population will consist of patients in the first stage who have an evaluable PK profile, defined as a profile from which at least one of the PK parameters stated as endpoints can be estimated, and no protocol deviations that would affect the PK of antroquinonol.

The PopPK population will consist of patients with at least two plasma concentrations and sufficient and reliable dosing histories.

The Safety population will comprise all patients who are treated with at least one dose of study drug.

The PRO population will consist of all patients who have completed the QoL Questionnaire on Day 0 and on at least one occasion after the first administration of study drug.

14.2.2 Efficacy Analysis

Except for the primary efficacy analysis, there will be no formal statistical testing. All data will be summarized and listed as appropriate. All efficacy endpoints will be evaluated in both the overall (unselected) population and within-stratum.

The primary and secondary efficacy analyses will be based on the independent centralized assessment of medical images. A detailed description of the process is provided in the Independent Review Charter.

14.2.2.1 Primary Efficacy Analysis

The primary endpoint is the PFS rate at 12 weeks, defined as the proportion of patients alive and progression-free at Week 12. Patients will be progression-free if they have no evidence of progressive disease (defined according to RECIST guideline, version 1.1) from the start of treatment to Week 12. An evaluable patient who died from any cause or discontinued the study for any reason without a post-screening or Week 12 tumor assessment will be considered as failing to respond to treatment.

The primary analysis will be performed on the evaluable population as defined in Section 14.2.1. The FAS and PPS (as defined in Section 14.2.1) will be used for supportive efficacy analyses. The PFS rate together with a two-sided 95% exact confidence interval (CI) will be calculated for the evaluable population, FAS and PPS.

The primary analysis will follow the two-stage procedure as specified in Section 14.1.

14.2.2.2 Secondary Efficacy Analysis

The FAS and PPS will be used for the secondary efficacy analyses. The secondary efficacy endpoints comprise the following: ORR, DCR, DR, PFS, OS and TTP.

The ORR is defined as the proportion of patients whose best overall response is either CR or PR according to RECIST version 1.1. The best overall response is the best response recorded during the first 12-week treatment cycle.

The DCR is defined as the proportion of patients with a documented CR, PR and SD during the first 12-week treatment cycle according to the RECIST version 1.1. For both ORR and DCR, 95% two-sided CIs will be presented.

The DR is defined as the interval between the date of the first observation of tumor response (CR or PR) and the date of disease progression or death. The DR will be summarized using Kaplan-Meier methods and displayed graphically where appropriate. The DR will be calculated for the subgroup of patients with tumor response (CR or PR).

If the number of patients with a documented CR or PR is small then only descriptive statistics or listings will be presented.

Progression-free survival is defined as the time from the date of first administration of study drug to objective tumor progression by RECIST version 1.1 or death due to any cause, whichever occurs first. The censoring rule for PFS will be described in the SAP.

Overall survival is defined as the time from the date of first administration of study drug to death from any cause. The censoring rule for OS will be described in the SAP.

Time to progression is defined as the time from the date of first administration of study drug to objective tumor progression by RECIST version 1.1. The censoring rule for TTP will be described in the SAP.

Objective response rate and DCR will be reported with category counts, percentage and 95% CIs. PFS, OS and TTP will be evaluated using Kaplan-Meier estimates and curves will be generated based on these estimates.

Time-to-event endpoints will be re-analyzed when all patients have completed the Extension Phase.

14.2.3 Pharmacokinetic Analysis

Non-compartmental PK analysis will be performed for the PK population, which will consist of patients in the first stage who have an evaluable PK profile, defined as a profile from which at least one of the PK parameters stated as endpoints can be estimated and no protocol deviations that would affect the PK of antroquinonol. Curves of antroquinonol concentration versus time in plasma will be constructed for each patient. Descriptive statistics will be presented for all PK parameters.

The following PK parameters will be estimated by non-compartmental methods:

- C_{max}: peak concentration
- C_{trough}: trough plasma concentration
- T_{max}: peak time
- AUC_{τ}: area under the plasma concentration-time curve over the 8-hour dosing interval
- $T_{½}$: terminal half-life
- Vz/F: apparent volume of distribution during elimination
- CL/F: apparent oral clearance

- $T_{½, eff}$: effective half-life

Full details of the PK analysis will be provided in the SAP.

If possible, PK data from all patients in the PopPK population will be analyzed using PopPK methods and *post hoc* estimates of antroquinonol exposure computed for exploration of potential exposure-response relationships. Full details of the PopPK analysis will be provided in a separate modeling and simulation analysis plan (MSAP).

14.2.4 Safety Analysis

All patients who are treated with at least one dose of study drug will be evaluated for safety. Safety data will be summarized for the overall (unselected) population and within-stratum. There will be no formal statistical analysis of safety data. Demographic and Screening data will be listed and summarized, as appropriate. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), graded using the NCI CTCAE version 4.03 and listed by patient. Treatment-emergent AEs will be summarized by treatment, severity and causal relationship to study drug. Any serious AEs will be listed separately.

System organ class and preferred terms within each body system will be used for frequency summaries. CTC grades for clinical laboratory data will be derived, and changes in CTC grades will be summarized by visit. Vital signs and ECG data will be listed by patient and summarized, as appropriate.

Safety data followed up during the Extension Phase will be analyzed where all patients will complete the Extension Phase.

14.2.5 Patient Reported Outcome

PRO data will be summarized for the overall (unselected) population and within-stratum.

The EORTC QLQ-C30 is comprised of a global health status scale, five functional scales (physical, role, emotional, cognitive and social) and three symptom scales (fatigue, nausea and vomiting, pain) and six single items (dyspnea, insomnia, appetite loss, constipation, Diarrhea and financial difficulties). The QLQ-LC13 includes questions assessing lung cancer-associated symptoms (cough, hemoptysis, dyspnea and site specific pain), treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia) and pain medication.

Descriptive statistics will be presented for both absolute scores for EORTC QLQ-C30 and QLQ-LC13 and changes from baseline (Day 0) at each assessment time. Scores will be plotted for selected symptoms.

14.3 Interim Analysis

An interim analysis for safety and efficacy will be performed when 20 patients overall and when 15 patients within each stratum are evaluable for the primary endpoint, PFS rate at 12 weeks. As described in Section 14.1, if less than two patients are alive and progression-free within a stratum, then the accrual for that stratum will be discontinued. Otherwise, a maximum of 15 additional evaluable patients will be accrued to that stratum for a total of 30 evaluable patients. Furthermore, if less than three patients in the overall

(unselected) population are alive and progression-free in the first 20 evaluable patients, and the criterion for continuing the individual stratum are not met, then the accrual for all strata will be discontinued. Otherwise, a maximum of 40 additional evaluable patients will be entered (depending on whether any individual stratum is closed).

14.4 Tumor Biomarkers

Tumor tissue blocks or slides will be obtained from archival material or from fresh biopsy during the Screening period to determine the KRAS tumor mutation status before enrolling the patient into the study. A patient may be enrolled based on KRAS test results from the local laboratory. Pleural fluid cytology may be used to determine KRAS mutation status if the cytology was pathologically reviewed and reported to contain malignant cells consistent with NSCLC. Patients will be stratified according to KRAS mutation status to test for possible differences in sensitivity/resistance to the study drug. KRAS and other tumor biomarkers will be used in subgroup analyses to determine the molecular signature of patients who could benefit from antroquinonol. To that effect, tumor tissue from patients will be used to evaluate arrays of genomic and proteomic markers of interest.

Full details of this analysis will be provided in the SAP.

14.5 Data Monitoring Committee

An Independent Data Monitoring Committee will act in an advisory capacity to monitor patient safety and efficacy data from the study. The members will be selected on the basis of relevant experience and understanding of clinical research and the issues specific to the therapeutic area, as well as previous data monitoring committee experience.

A Data Monitoring Committee charter, which includes detailed processes, will be prepared before the interim analysis.

15 DATA HANDLING AND RECORD KEEPING

15.1 Informed Consent and Institutional Review

All patients in this research study should be completely informed about the purpose, duration and important procedural details of the study. Informed Consent must be obtained using a written form which has been approved by the appropriate Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

The ICF will be understood and signed by each patient prior to enrollment into the study. The investigator will keep the original signed copies of all consent forms in his/her files and will provide a duplicate copy to the patient. A copy of the letter indicating IEC or IRB approval must be provided to the study sponsor prior to the study initiations.

15.2 Confidentiality/Publication of the Study

Any information the study sponsor shares with you regarding this study, including this protocol, is considered proprietary information and should be kept confidential. Each investigator will be required to sign the signature page which affirms he/she has read/understood the obligations of investigators. Once the study has begun, the investigator will comply with the protocol as written except in instances of medical urgency. The sponsor and the IEC/IRB should be notified of these cases as soon as possible. Any other changes to the protocol must be approved by both the sponsor and the IEC/IRB prior to commencement.

The information provided by the study sponsor in this protocol and the associated Clinical Investigator's Brochure[29] and the data generated by this clinical study are to be considered as confidential property of the study sponsor. The data and information associated with this study may be used by the study sponsor now and in the future for the purposes of presentation, publication at the discretion of the study sponsor or for submission to regulatory agencies. In addition, relative to the release of any proprietary information, the study sponsor reserves the right of prior review of any publication or presentation of data from this study.

In signing this protocol, the investigator agrees to the release of the data from this study and acknowledges the above publication policy.

15.3 Data Collection

The clinical investigator must maintain detailed records on all study patients. Clinical data will be entered on eCRFs for transmission to the sponsor. The investigator will be provided a copy of all completed eCRFs.

15.4 Drug Accountability

Site staff will record compliance of patients with their assigned treatment regimen as described in Section 10.11.

The principal investigator is to keep a current record of the inventory and dispensing of all test drugs. This record will be made available to the sponsor monitor for the purpose of drug accountability checks.

Any significant discrepancy and/or deficiency should be recorded, with an explanation. All supplies to be sent to the investigator must be accounted for and the test material must not be used in any unauthorized situation.

The principal investigator, upon receipt of the clinical supplies, will conduct a drug inventory. The drug inventory record should be returned to the sponsor and be maintained for the investigator's records.

It is the principal investigator's responsibility to return all unused supplies to the sponsor at the completion of the study.

15.5 Record Retention

All records relating to the conduct of this study are to be retained by the investigator according to ICH, local regulations, or as specified in the clinical study agreement, whichever is longer. Prior to transfer or destruction of these records, the sponsor must be notified in writing and given the opportunity to further store such records. The investigator will allow representatives of sponsor’s monitoring members (and of the applicable regulatory authorities) to inspect all study records, eCRFs, and corresponding portions of the study patient’s office and/or hospital medical records at regular intervals across the study. These inspections are for the purpose of verifying the adherence to the protocol, the completeness and accuracy of the data being filled in the eCRF, and compliance with applicable regulations.

The sponsor and the investigator agree that the study patient medical records will be maintained in a confidential manner. The study report will not identify any patient by name. These reports may be submitted to the Department of Health in the Republic of China and any other applicable health authorities by the sponsor.

15.6 Case Report Forms

Clinical data will be entered on eCRFs for transmission to the sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study center. All study forms and records transmitted to the sponsor must carry only coded identifiers such that personally identifying information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by the sponsor (or designee). Access to the EDC system is available to authorized users via the study’s internet website, where an assigned username and password are required for access. The EDC system is in compliance with applicable data protection guidelines and regulations. eCRFs will be considered complete when all missing and/or incorrect data have been resolved.

15.7 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

16 MONITORING

The study will be monitored to ensure that it is conducted and documented according to the protocol, GCP, and all applicable regulatory requirements. On-site visits will be made at appropriate times during the period of the study. Monitors must have direct access to source documentation in order to check the consistency of the data recorded in the eCRFs.

The PI will make available to the monitor source documents, medical records, and source data necessary to complete eCRFs. In addition, the PI will work closely with the monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and GCP guidelines.

17 QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor or designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the sponsor lies with the PI generating the data.

The sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, Standard Operating Procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions.

18 PROTOCOL AMENDMENT AND PROTOCOL DEVIATION

18.1 Protocol Amendment

Administrative amendments to the protocol will be classed as amendment of typographical errors, clarifications of confusing wording, name changes and minor modifications that have no impact on the safety of the patient or the scientific value of the study. Administrative amendments will be submitted to the IRB/Research Ethics Board (REB) for information only. The sponsor will ensure that acknowledgement is received and filed. Otherwise, an amendment will be classed as a substantial amendment and will be submitted to the appropriate Regulatory Authorities and the IRBs/REBs for approval.

18.2 Protocol Deviations

No deviations from the protocol are anticipated. However, should a protocol deviation occur, the sponsor (and designated Clinical Research Organization personnel, such as the Medical Monitor and Clinical Research Associate) must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/REB and in accordance with applicable Regulatory Authority mandates is a PI responsibility.

19 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the Declaration of Helsinki (see Appendix 5) and its most recent amendments and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the Code of Federal Regulations (CFR), and in compliance with GCP guidelines.

Institutional Review Boards will review and approve this protocol and informed consent. All patients are required to give written informed consent prior to participation in the study. This study will be performed in accordance with GCP by qualified PIs. The study specifically incorporated the following features:

- Prospectively stated objectives and analytical plan
- Accepted, pre-specified outcome measures for safety and efficacy
- Investigator meeting prior to study start and a detailed protocol to promote consistency across sites, and
- Compliance with GCP, with assessment via regular monitoring.

Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

20 FINANCING AND INSURANCE

Financial aspects of the study are addressed in a separate clinical study agreement. The PI is required to have adequate current insurance to cover claims for negligence and/or malpractice. The sponsor will provide insurance cover for the clinical study as required by national regulations.

21 PUBLICATION POLICY

Both the use of data and the publication policy are detailed within the clinical study agreement. The PI should be aware that intellectual property rights (and related matters) generated by the PI and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the Institution and the sponsor or their designee. With respect to such rights, the sponsor or their designee will solely own all right and interest in any materials, data and intellectual property rights developed by PIs and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, PIs will be required to assign all such inventions either to their Institution or directly to the sponsor or their designee, as will be set forth in the clinical study agreement.

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23 APPENDICES

Appendix 1 Revised Response Evaluation Criteria in Solid Tumors Guidelines Version 1.1 – Adaptation from original publication with addition of supplementary explanations

Summary published by the National Cancer Institute based on the following publication: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan; 45(2):228-47.

Overview of assessment process

The tumor burden will be documented at baseline. First, reviewers will determine which lesions are appropriate for repeated quantitative assessment (these are called "measurable" lesions). From the measurable lesions, reviewers will choose a set of lesions that actually will be followed quantitatively throughout the study (these are called "target" lesions). As recommended by RECIST 1.1, the target lesions will be measured in such a way as to maximize the reproducibility and reliability of the measurement, and a value for the target tumor burden (the "sum of diameters") will be calculated. All tumor lesions that are not chosen for quantitative assessment will be documented and followed qualitatively as "non-target" lesions.

At each Follow-Up Visit, reviewers will assess the target lesions by making the appropriate measurements, calculating the sum of diameters, and comparing the sum of diameters to the values at baseline (to look for partial response) and to the smallest value seen until that point (also called the "nadir" value, to look for progression). They will also assess the non-target lesions qualitatively, and will search for new lesions. The information about target, non-target, and new lesions will be combined to produce an overall visit response for the patient. After all of the overall visit responses have been determined, information about the endpoints will be extracted from the sequence of visit responses and the dates of the visits.

Measurability of tumor at baseline

Measurement of lesions

All lesion measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Lesions other than lymph nodes are measured in their longest diameter on CT or MRI scan (or X-ray, in limited circumstances as described above). Measurements are typically made in the axial plane. Lymph nodes are normal anatomical structures which may be visible by imaging even if not involved by tumor. Only the short axis of these nodes will contribute to the sum of diameters, both at baseline and at future visits.

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable tumor lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ³ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (axial for CT, possibly coronal or sagittal for MRI). For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement.

Non-measurable tumor lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-measurable lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion, or unless the radiation took place over 6 months prior to enrollment.

Notes on measurability by method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions are measurable only when they are superficial and at least 10 mm in diameter, assessed using calipers. For skin lesions, documentation by color photography, including a ruler or size standard, is suggested.

Chest X-ray: Chest CT is preferred over chest X-ray, since CT is more sensitive than X-ray, particularly in identifying new lesions. Lesions on chest X-ray may be considered measurable (see definitions below) if they are clearly defined and surrounded by aerated lung. Still, CT is preferred over chest X-ray, even if the CT is done without contrast.

***CT, MRI*:** CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). The slice thickness for MRI (for purposes of determining measurability) is the total distance from the top of one slice to the top of the next slice (including any inter-slice gap).

If prior to enrollment it is known that a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the patient should receive non-contrast CT of the chest, and MRI of the abdomen and pelvis. If the patient develops iodinated contrast allergy during the study, the same approach (non-contrast CR of chest, MRI of abdomen and pelvis) should be used, with awareness that the change in modality may render the lesions from that point forward non-evaluable.

***Ultrasound*:** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline will be included in this protocol. Measurable disease is defined as the presence of at least one measurable lesion (as detailed above).

Baseline documentation of 'target' and 'non-target' lesions

Target lesions are a subset of measurable lesions. Measurable lesions are defined above. When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions in that organ will be recorded as non-target lesions (even if size is greater than 10 mm by CT scan). Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. Paired organs (the lungs, the kidneys, etc.) should be considered a single organ. All lymph nodes are considered a single organ.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target

lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

- *Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

***Target lesions* that become *'too small to measure'*:** while on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progressions based upon measurement error.

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked. (BML is equivalent to a less than sign <)

Lesions that split or coalesce on treatment: when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of non-target lesions, evaluated as a whole, such that it is clear that the disease is progressing regardless of the status of the target lesions.

Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease: in this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: this circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or sufficient to require a change in therapy. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions).

This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

(18)F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

FDG-PET scanning may complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
    - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
    - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT (existing disease or uncertain whether disease is present in the location where the PET is positive), additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
    - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion. If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are indicated as 'not assessed', the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 below provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 Time point response: patients with target (+/-non-target) disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease,
PD = progressive disease, and NE = inevaluable.

Table 2 Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR=complete response, PD=progressive disease, and NE=inevaluable. a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy I some trails so to assign this category when no lesions can be measured is not advised.		

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study drug until the end of treatment. Post-treatment assessments will not be considered in determination of best overall response. No new therapies are permitted by the protocol. If any other therapy is instituted during the study, the patient will be censored from the BOR assessment. Given the use of PFS as the primary efficacy endpoint, and the short timeframe of this study, confirmation of PR and CR is not required in this study.

The *best overall response* will be determined by statistical programming once all the data for the patient is known.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (eCRF). In studies where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the study must address how missing data/assessments will be addressed in determination of response and progression. For example, in most studies it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 1 and Table 2.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected**.**

Appendix 2 Eastern Co-Operative Oncology Group Evaluation

Activity Performance Description	Score
Fully active, able to carry on all pre-disease performance without restriction	0
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	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	4
Dead	5

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix 3 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and Lung Cancer Module (LC13)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Appendix 4 Reference List of Known Inducers, Inhibitors and Substrates of Selected Cytochrome P450 Enzymes

Inhibitors

2C8	2C19	2E1	3A4,5,7
Strong	fluoxetine	disulfiram	**HIV Antivirals:**
gemfibrozil	fluvoxamine		**Strong**
	ketoconazole		indinavir
	lansoprazole		nelfinavir
	omeprazole		ritonavir
	ticlopidine2		
			clarithromycin
			itraconazole
			ketoconazole
			nefazodone
			Moderate
			erythromycin
			grapefruit juice
			verapamil2
			diltiazem
			Weak
			cimetidine
			Others
			amiodarone
			NOT azithromycin
			fluvoxamine
			mibefradil
			troleandomycin
A **Strong** inhibitor is one that causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.			
A **Moderate** inhibitor is one that causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.			
A **Weak** inhibitor is one that causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.			

Inducers

2C8	2C19	2E1	3A4,5,7
		ethanol	carbamazepine
		isoniazid	phenobarbital2
			phenytoin2
			pioglitazone
			rifabutin
			rifampin1
			St. John's wort
			troglitazone1
Source: http://www.medicine.iupui.edu/clinpharm/ddis/ClinicalTable.asp			

Sensitive in vivo CYP substrates and CYP substrates with narrow therapeutic range

List (1) **of Sensitive *In Vivo* CYP Substrates and CYP Substrates with Narrow Therapeutic Range**		
CYP Enzymes	**Sensitive substrates** (2)	**Substrates with narrow therapeutic range** (3)
CYP1A2	Alosetron, caffeine, duloxetine, melatonin, ramelteon, tacrine, tizanidine	Theophylline, tizanidine
CYP2B6 (4)	Bupropion, efavirenz	
CYP2C8	Repaglinide (5)	Paclitaxel
CYP2C9	Celecoxib	Warfarin, phenytoin
CYP2C19	Lansoprazole, omeprazole, S-mephenytoin	S-mephenytoin
CYP3A (6)	Alfentanil, aprepitant, budesonide, buspirone, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, eletriptan, eplerenone, everolimus, felodipine, indinavir, fluticasone, lopinavir, lovastatin, lurasidone, maraviroc, midazolam, nisoldipine, quetiapine, saquinavir, sildenafil, simvastatin, sirolimus, tolvaptan, tipranavir, triazolam, vardenafil	Alfentanil, astemizole, (7) cisapride, (7) cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine (7)
CYP2D6	Atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, venlafaxine	Thioridazine

Source: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

(1) Note that this is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.

(2) *Sensitive CYP substrates* refers to drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a known CYP inhibitor.

(3) CYP *substrates with narrow therapeutic range* refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

(4) The AUC of these substrates were not increased by 5-fold or more with a CYP2B6 inhibitor, but they represent the most sensitive substrates studied with available inhibitors evaluated to date.

(5) Repaglinide is also a substrate for OATP1B1, and it is only suitable as a CYP2C8 substrate if the inhibition of OATP1B1 by the investigational drug has been ruled out.

(6) Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.

(7) Withdrawn from the United States market because of safety reasons.

Appendix 5 Declaration of Helsinki

World Medical Association Declaration of Helsinki:
Recommendations Guiding Physicians in Biomedical Research
Involving Human Patients

Adopted by the 18th World Medical Association (WMA) General Assembly, Helsinki, Finland, 1964 and amended by the WMA General Assembly, Tokyo, Japan in 1975, Venice, Italy in 1983, Hong Kongin 1989, Somerset West, Republic of South Africa, 1996, Edinburgh, Scotland in 2000, added with Note of Clarification on paragraph 29 by the WMA General Assembly, Washington in 2002, added with Note of Clarification on paragraph 30 by the WMA General Assembly, Tokyo 2004, and amended by the WMA General Assembly, Seoul, 2008.

A. Introduction

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human patients to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of subjects, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the subject's best interest when providing medical care.”

5. Medicalprogressisbasedonresearchthatultimatelymustincludestudiesinvolving human patients. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.

10. Physicians should consider the ethical, legal and regulatory norms and standards for

research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, and other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies.

    The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other healthcare professional and never the research subjects, even though they have given consent.
17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.

19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research

cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.

30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient’s decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.