STATISTICAL ANALYSIS PLAN

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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Study 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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LIST OF ABBREVIATIONS

AE	Adverse Event
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero extrapolated to infinity
AUC_{0-t}	Area under the concentration-time curve from time zero (pre-dose) to time of last observed concentration
AUC_{extr}	Proportion of area under the concentration-time curve from time zero extrapolated to infinity due to extrapolation
AUC_{τ}	Area under the plasma concentration-time curve over the 8-hour dosing interval
BMI	Body mass index
CL/F	Apparent oral clearance
C_{last}	Last temporal predicted plasma concentration
C_{max}	Peak concentration
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough plasma concentration
CV	Coefficient of variation
DCR	Disease control rate
DLT	Dose limiting toxicity
DOR	Duration of response
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of Study
FAS	Full analysis set
FDA	Food and Drug Administration

GCP	Good Clinical Practice
HR	Heart rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMI	ICON Medical Imaging
IRB	Institutional Review Board
LLOQ	Lower limit of quantitation
λ_z	Terminal phase elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MRI	Magnetic resonance imaging
MSAP	Modeling and simulation analysis plan
NCA	Noncompartmental pharmacokinetic analysis
NR	No result
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PopPK	Population-based pharmacokinetic(s)
PPS	Per-protocol set
PR	Partial response
PRO	Patient Reported Outcome
QLQ	Quality of Life Questionnaires
QoL	Quality of Life
QTc	Corrected QT
R_{AUC}	Accumulation ratio for the area under the plasma concentration-time curve over the 8-hour dosing interval
RECIST	Response Evaluation Criteria in Solid Tumors

R_{sq}	Adjusted coefficient of determination
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCLC	Small cell lung cancer
SD	Stable disease
STD	Standard Deviation
TEAE	Treatment-emergent adverse event
τ	Dosing interval duration
$T_{½}$	Terminal half-life
$T_{½,eff}$	Effective half-life
TFLs	Tables, Figures, and Listings
T_{max}	Peak time
t.i.d.	Three-times-a-day
TTP	Time to progression
V_z/F	Apparent volume of distribution during elimination

1. INTRODUCTION

The purpose of this document is to describe the statistical methods, data derivations and data summaries to be employed in 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.

The preparation of this Statistical Analysis Plan (SAP) has been based on International Conference on Harmonisation (ICH) E3[1] and E9[2] Guidelines and in reference to Clinical Study Protocol v3, draft dated 26 February 2014.

In accordance with ICH E9, prior to locking the database and before executing the statistical analysis a Data Review Meeting will be held. The purpose of this meeting will be to

1. Determine the evaluability of patients and finalize the analysis populations as defined in the protocol and/or the statistical analysis plan (SAP)
2. Assess protocol deviations
3. Review completeness and reliability of the data

2. STUDY OBJECTIVES

2.1 Objectives

2.1.1 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.

2.1.2 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.

2.1.3 Exploratory Objective

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

3. STUDY DESIGN

3.1 Study Design and Population

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. 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). An evaluable patient will have received at least one dose of antroquinonol and have a valid baseline tumor assessment. Enrollment will continue until the target number of evaluable patients has been enrolled.

3.2 Study Treatments and Assessments

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 or, in the opinion of their investigator, still deriving clinical benefit, will continue to receive up to three further (12 week) treatment cycles with antroquinonol (Extension Phase). After completion of the fourth and last treatment cycle, patients will be eligible to receive further cycles of treatment with antroquinonol in a rollover protocol. Investigators should wait at least 7 days 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 and every 4 weeks during subsequent cycles (Extension Phase). The following procedures will be performed according to the schedule of assessments: physical examination, vital signs, 12 lead ECG, performance status, clinical laboratory tests, AEs, concomitant medication and patient compliance.

Patients completing the 12 week treatment period (or the Extension Phase), and those discontinuing the study before Week 12 (or during the Extension Phase), will attend an End of Study (EOS) 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 withdraw from the study before Week 12 (or during the Extension Phase) or who complete the 12 week treatment period (or the Extension Phase) will be followed up for survival status until 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. 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 primary and secondary efficacy analyses will be conducted based on independent centralized assessment of ICON Medical Imaging (IMI).

The details of the assessment schedule are described in the protocol and in the flow chart below.

Table 1 Flow Chart

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		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
EORTC QLQ[13]		X			X		X	X	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 completing the 12-week treatment period (or the Extension Phase) and those discontinuing the study before Week 12 (or during the Extension Phase) will attend an EOS Visit 4 weeks after the last administration of study drug. 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 or, in the opinion of their investigator, still deriving clinical benefit, will continue to receive up to three further (12-week) treatment cycles with antroquinonol. After completion of the fourth and last treatment cycle, patients will be eligible to receive further cycles of treatment with antroquinonol in a rollover protocol. Investigators should wait at least 7 days before initiating alternative treatment is administered. Patients completing or discontinuing the study during the Extension Phase will attend an EOS Visit 4 weeks after last administration of study drug. Patients will attend visits every 4 weeks (±7 days) during the Extension Phase.

[4] Tumor tissue blocks 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. 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.

[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 (± 3) days of enrollment into the study. 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 at least 6 months after last dose of study drug or alternative treatment for NSCLC is started, 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 2 months after the EOS Visit.

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

4. ANALYSIS VARIABLES

The detailed derivation rules and/or censoring rules for each variable are specified in section 6 along with analysis methods. Variables not referred to in this section, but collected throughout the study period, such as patient demographic data, study drug exposure, concomitant medication, will be summarized descriptively.

The primary and secondary efficacy analyses will be based on the independent centralized assessment of medical images conducted by IMI. Tumor response, as assessed by the investigator at each site during the study, will be supportive.

Primary Efficacy variable:

The primary efficacy endpoint is PFS rate at 12 weeks. It is defined as the proportion of patients alive and progression-free to evaluable subject at 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.

Secondary Efficacy variable:

The following secondary efficacy variables are defined in accordance with the RECIST guidelines, version1.1:

Objective Response Rate (ORR): The ORR is defined as the proportion of patients whose best overall response is either CR or PR during the first 12-week treatment cycle.

Disease Control Rate (DCR): The DCR is defined as the proportion of patients with a documented complete response (CR), partial response (PR) and stable disease (SD) during the first 12-week treatment cycle.

Duration of Response (DOR): DOR 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.

Progression Free Survival (PFS): PFS is the time from date of first administration of study drug to date of first documentation of progression or death due to any cause, whichever occurs first.

Overall survival (OS): Survival time will be calculated for all patients from the date of first administration of study drug to the date of death from any cause.

Time to progression (TTP): Time to progression will be calculated for all patients from the date of first administration of study drug to the date of the first documented tumor progression.

Pharmacokinetic variables:

For stage 1, PK endpoints will be derived for intensively sampled PK profiles by noncompartmental 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

- V_z/F: apparent volume of distribution during elimination
- CL/F: apparent oral clearance
- $T_{½,eff}$: effective half-life

Safety variables:

- Adverse Events recording and follow up
- Vital Signs : blood pressure, heart rate, body temperature, respiratory rate

ECOG performance status score

- 12-lead electrocardiogram (ECG)
- Physical Examinations
- Safety laboratory assessments : hematology, chemistry, urinalysis

Patient Reported Outcome:

Quality of life will be assessed using European Organization for Research and Treatment of Cancer (EORTC) 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
- 5 functional scales(physical, role, emotional, cognitive, and social)
- 3 symptom scales(fatigue, nausea and vomiting, and pain)
- Other single items from QoL questionnaire
- Module designed specifically for lung cancer

5. 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)[3], von Mehren et. al. (2012)[4] and Hoang et. al. (2013)[5] 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 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 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 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 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).

6. METHODS OF ANALYSIS AND PRESENTATION

6.1 General Principles and Considerations

Section 6 describes the algorithms, imputations and conventions that will generally apply to program manipulations of the data in order to prepare the proposed summary tabulations, and individual patient data listings. Unless otherwise indicated, these specifications apply to all analyses.

Full details of the table, figure and listing outputs that will be produced are given in the document entitled "Golden Biotech-GHNSCLC-2-001_TFL Final v1 0 06Aug2014". Appendix I lists the Tables (T), Figures (F) and Listings (L) (collectively TFLs) that will be generated for the DSMB (Data and Safety Monitoring Board).

6.2 Presentation of Output

Summaries will use the following descriptive statistics for continuous variables (n, mean, standard deviation [STD], median, minimum and maximum). The number of decimal places displayed for each statistical analysis will be determined as follows:

1. Mean and median: one more than the number of decimal places allotted in the CRF
2. Standard deviation: two more than the number of decimal places allotted in the CRF
3. Minimum and Maximum: equal to the number of decimal places allotted in the CRF

Qualitative variables will be presented as category counts and percentages. Percentages will be presented to one decimal place throughout.

All dates will be displayed in DDMMMYYYY format. Visits will be referred to as shown in the protocol: "Baseline", 'Cycle1 Day1", etc.

Study day is defined relative to date of first administration of study drug.

Data will be listed for all subjects. Individual subject data listings provide support for summary tables and serve as a data source substitute when a summary table is deemed either inappropriate or unnecessary. All data listings will be sorted by site number, subject number, visit date or study day unless otherwise specified. Throughout all data listings and summary tables, treatment will be labeled as Antroquinonol.

6.2.1 Definition of Baseline and Visit Windows

The baseline will be defined as the last value or measurement taken up to the first dosing of study drug, unless otherwise specified.

Baseline tumor assessment is defined as a readable scan performed within 14 (± 3) study days prior to enrollment into the study by investigator at the site. Last Visit (Endpoint) is defined as the last on-therapy visit. Study day is defined relative to the date of the first administration of study drug as:

Study day = date of assessment – date of first administration of study drug.

The date of first administration of study drug will be Day0 as specified in the study protocol.

For safety data (e.g. laboratory tests, vital signs, ECG etc.), nominal visit times will be used regardless of the study day.

Allowed windows for PK samples:

Day	Scheduled Time Relative to Dose (hour)	Time Window	Comment
Stage 1			
0	-0.5		Pre-dose sample
0	0.5	± 5 min	
0	1	± 10 min	
0	2	± 15 min	
0	3	± 20 min	
0	4	± 20 min	
0	6	± 20 min	
0	8	± 20 min	
28	-0.5*		Pre-dose sample
28	0.5	± 5 min	
28	1	± 10 min	
28	2	± 15 min	
28	3	± 20 min	
28	4	± 20 min	
28	6	± 20 min	
28	8	± 20 min	
Stage 2			
28	-0.5*		Trough
28	3	± 1 hr	Peak
42	-0.5*		Trough
42	N/A		Random**
56	-0.5*		Trough
56	N/A		Random**

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

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

Samples taken outside these windows may be used in the PK analyses provided that accurate dosing and sample time data are recorded and that any sampling time deviation does not meaningfully bias the PK parameters.

6.2.2 Missing data or partial date handling

In the event that a partial date is provided for a tumor assessment conducted during the first 12-week treatment phase and/or the extension phase the following rules will be adopted:

- If day is missing, then the 15th day of the month will be assumed
- If month or year are not available, the assessment will not be used

Imputation Rules for Partial or Missing Stop Dates for adverse events and concomitant medications are detailed below.

- If the month and year are present, impute the last day of that month.
- If only the year is present, impute December 31 of that year.
- If the stop date is entirely missing, assume the event or medication is ongoing.

If a partial or complete stop date is presented along with checking the 'ongoing' or 'continuing' box, then it will be assumed that the adverse event or concomitant medication stopped and the stop date will be imputed if partial.

Imputation Rules for Partial or Missing Start Dates for adverse events and concomitant medications are detailed in Table 2. The following imputation rule will be applied, where applicable.

Table 2 Imputation rules for partial or missing start dates

Rule no.	Criteria 1	Criteria 2	Imputation rule
1	partial start date (mmmyyyy) = 1st dose (mmmyyyy) or partial start date (yyyy) = 1st dose (yyyy)	partial stop date (yyyy) < 1st dose yyyy	NA
2	partial start date (mmmyyyy) = 1st dose (mmmyyyy) or partial start date (yyyy) = 1st dose (yyyy) or start date = missing	complete stop date (ddmmmyyyy) ≥ 1st dose (ddmmmyyyy) or partial stop date (mmmyyyy) ≥ 1st dose (mmmyyyy) or partial stop date (yyyy) ≥ 1st dose (yyyy) or stop date = missing	Impute the date of first dose
3	partial start date (mmmyyyy)	not applicable to rule 2	Impute the first day, i.e. 1, of the month
4	partial start date (yyyy)	not applicable to rule 2	Impute January 1 of the year

Rule no.	Criteria 1	Criteria 2	Imputation rule
5	start date = missing	complete stop date (ddmmmyyyy) < 1st dose (ddmmmyyyy) or partial stop date (mmmyyyy) < 1st dose (mmmyyyy) or partial stop date (yyyy) < 1st dose (yyyy)	Impute January 1 of the stop year

In all other instances, missing values will not be imputed.

6.2.3 Version Numbers

All analyses will be carried out using SAS® Version 9.13 or later. Data will be stored in Inform database. Adverse event and body/organ system coding will be performed using MedDRA version 17.0. Prior/concomitant medication coding will utilize WHO Drug March 2014E.

6.3 Analysis Sets

6.3.1 Safety Population

The safety population includes all patients who received at least one dose of study drug.

This population will be used for the analysis of safety data.

6.3.2 Evaluable Population

The evaluable population will include patients who in safety population and meet all eligibility criteria as well as having 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 (± 3) days prior to enrollment into the study.

This will be the primary analysis population for primary efficacy analysis.

6.3.3 Full Analysis Set (FAS)

The FAS will consist of patients in the evaluable population who has at least one post-baseline tumor assessment.

This analysis population will be used for supportive population of primary efficacy analyses and used for all secondary efficacy analyses.

6.3.4 Per-Protocol Set (PPS)

The PPS is a subset of patients in FAS who do not have major protocol violations. Major protocol violations will include (but are not limited to) the following:

- Subject did not meet all inclusion/exclusion criteria
- Use of prohibited/excluded concomitant medication/procedure that may impact patient safety or the primary study objective
- Error in administration of study drug – Potential impact on subject safety or primary study objective

Major protocol deviations will be discussed and agreed during the Data Review Meeting.

This analysis population will be used for supportive population of primary efficacy analyses and used for all secondary efficacy analyses.

6.3.5 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.

6.3.6 Population-Based PK (PopPK) Population

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

6.3.7 Patient Reported Outcome (PRO) Population

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.

This population will be used for the analysis of patient reported outcome data.

6.4 Major Protocol Violations/Deviations

Major protocol violations/deviations will be defined as any event or behavior of the patient or the investigator, which makes the evaluation of the primary objective of the protocol impossible or unreliable. Protocol deviation criteria will be described in the document entitled “Golden Biotech_Protocol Deviations Criteria_v1.0_28Jul14”.

Protocol violations/deviations will be defined during the Data Review Meeting of the study before final database lock.

6.5 Disposition

The number of patients screened, enrolled, treated, on-going, completed or discontinued for first 12-week treatment phase and extension phase will be summarized for the overall (unselected) population and by KRAS mutation status(positive/negative)..

Patients who discontinue from the treatment phase and/or the extension phase will be summarized by their primary reason for discontinuation for the overall population and by

KRAS mutation status.

Screen failures (reason for failure) will be summarized. Supportive listings will be provided. Data on inclusion/exclusion criteria and protocol deviations will also be reported.

A listing of protocol violations will be summarized by KRAS mutation status. The listing will include a variable indicating whether the violation is considered as key or non-key.

6.6 Demographics and Baseline Characteristics

Patient demographics and baseline characteristics will be summarized for the safety and the all evaluable population.

Demographic data (age at consent as continuous and categorized into <40 years, ≥40-<65 years and ≥65 years, sex, race, ethnicity, region, smoking status, disease stage at initial diagnosis) will be summarized.

ECOG Performance Status at screening will be summarized.

Medical history and baseline signs and symptoms and previous therapy for treatment of NSCLC will also be summarized by KRAS mutation status. An overall summary of prior therapy will be produced which will include the number of prior chemotherapy and whether subject had prior surgery, radiotherapy and other regimens will be summarized by KRAS mutation status.

Number of patients and percentage of biomarker data including KRAS mutation status, EGFR, ALK and ROSI will be summarized for overall stratum.

6.7 Prior and Concomitant medication

Medication history and concomitant medication will be summarized by KRAS mutation status and WHO Drug preferred term for the Safety population.

Medication will be classified as:

- Prior medications :
  - Those started and stopped prior to the first dosing (Day 0)
- Concomitant medications :
  - Those started prior to and on-going at the first dosing (Day 0), or
  - Those started after or equal to the first dosing (Day 0).

If medication could not be classified due to incomplete or partial start and/or stop dates, it will be assumed to be concomitant medication.

6.8 Treatment Compliance and exposure

Study drug compliance and exposure during treatment phase and extension phase will be summarized by KRAS mutation status.

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

[(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:

[Date of last dose -Date of first dose + 1].

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

(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)])

The extent of exposure to Antroquinonol will be characterized by the number of administered cycles, cumulative dose (mg), dose intensity (mg/week). Dose intensity will be calculated by dividing the total received dose (mg) of the study drug by the number of weeks of treatment. The number of dose adjustments together with each reason will be summarized by KRAS mutation status.

6.9 Efficacy Analysis

Except for the primary efficacy analysis, there will be no formal statistical testing. All data will be summarized and listed descriptively. All efficacy endpoints will be evaluated for the overall population and by KRAS mutation status.

The primary and secondary efficacy analyses will be based on the independent centralized assessment of medical images conducted by IMI. The Independent Review Charter is provided in the Appendix II.

A sensitivity analysis, based on the local (investigator) assessment will also be conducted and summarized.

The same response assessment rule will be used for the centralized and local (investigator) review. For example, tumor assessment dates are defined as:

- Progression date: Radiological assessments for a given visit occur over a series of days rather than the same day. The Date of Progression will be the date of the first scan, regardless of modality.
- Response date: Date of Initial Response is defined as the date when either level of response (PR or CR) first appears as a timepoint response on CT or MRI tumor assessment imaging. When multiple scan dates are associated with the timepoint for which a response was first recorded, the latest scan date associated with that timepoint will be the Date of First Response

6.9.1 Primary Endpoint

As stated in section 4, the primary endpoint is the PFS rate at 12 weeks. It is defined as the proportion of patients alive and progression-free to evaluable subject 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 date of first administration of study drug to Day 84 (±3). Study day will be computed by [date of assessment – the first date of administration of study drug]. 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 centralized review for the evaluable population will be primary for hypothesis testing. The PFS rate at week 12 along with a two-sided 95% Clopper–Pearson exact confidence

interval will be provided for the overall evaluable population and each KRAS mutation stratum.

The supportive analysis will performed on the FAS and PPS, as for the evaluable population. The time window used for the evaluable population will be applied.

6.9.2 Secondary Endpoint(s)

All secondary efficacy endpoints will be evaluated for the FAS and PPS. Analyses based on the both central and local (investigator) review will be summarized.

Objective Response Rate (ORR)

Tumor response will be evaluated according to the RECIST guidelines version1.1. The response assessment categories are CR, PR, SD, and progressive disease (PD), not evaluable (NE). The best overall response will be the best response achieved during the first 12-week treatment phase.

The ORR is defined as the number of patients whose best overall response is either CR or PR according to RECIST 1.1 divided by the number of patients in the analysis population. For the analysis of response, patients with missing response data will be reported and distinguished from non-responders, and included in the denominator when calculating percentages.

Exact Pearson-Clopper 2-sided 95% confidence limits for the tumor response rates in each arm will be calculated.

The number and percentage of patients assigned to each best overall response category (CR, PR, SD, PD, NE) will be summarized.

For each patient, the maximum decrease in sum of longest diameter of target lesions will be plotted. Patients in each category of best overall response (i.e. CR, PR, SD, and PD) will be represented in different colors. A separate plot will be produced by KRAS mutation status.

Disease Control Rate (DCR)

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 RECIST 1.1.

DCR will be analyzed and presented together with ORR.

Duration of Response (DOR)

DOR is defined as the time from first documented evidence of CR or PR (whichever status is recorded first) until the first documented sign of disease progression or death due to any cause. For patients in the subset of responders who do not progress or die, DOR will be censored.

DOR (days) = Date of progression/ death/ censoring – Response date +1.

The table below will be used for calculating the DOR.

Situation	End Date	Outcome
Documented PD during the study	Date of the first assessment of the series of the tests that determined PD	Event[a]
Death during the study before PD	Date of death	Event[a]
Discontinued due to PD, but no documented PD	Date of last tumor assessment before discontinuation	Censored
Discontinued due to clinical progression per investigator	Date of last tumor assessment before discontinuation	Censored
Treatment discontinuation for reason other than PD or death	Date of last tumor assessment	Censored
New anticancer treatment started	Date of last tumor assessment before start of new treatment	Censored
Death or PD after one or more missed tumor assessments	Date of the last assessment before missed assessments	Event[a]
Patients still on treatment without PD as of data cut-off	Date of last tumor assessment	Censored

a - Earliest date among the three dates is used in calculating the DOR.

DOR will be summarized using Kaplan-Meier method. The Kaplan-Meier estimate of the median DOR and first and third quartiles will be presented with 95% confidence intervals for the subset of responders. Kaplan-Meier curve will be presented.

If the number of patients with a documented CR or PR is less than 10 subjects for each stratum then only descriptive statistics or listings will be presented.

Progression Free Survival (PFS)

PFS is the time from date of first administration of study drug to date of first documentation of progression or death due to any cause. Date of first documentation of progression can be based on the centralized or local (investigator) review.

PFS (days) = Date of progression/ death/ censoring – Date of first administration of study drug + 1.

The table below will be used for calculating the PFS.

Situation	End Date	Outcome
Documented PD during the study	Date of the first assessment of the series of the tests that determined PD	Event[a]
Death during the study before PD	Date of death	Event[a]
Discontinued due to PD, but no documented PD	Date of last tumor assessment before discontinuation	Censored
Discontinued due to clinical progression per investigator	Date of last tumor assessment before discontinuation	Censored
No baseline assessments	Date of first administration of study drug	Censored
Treatment discontinuation for reasons other than PD or death, and no post-baseline tumor assessments	Date of first administration of study drug	Censored
Treatment discontinuation for reasons other than PD or death with post-baseline tumor assessments	Date of last tumor assessment	Censored
New anticancer treatment started prior to disease progression	Date of last tumor assessment before start of new treatment	Censored
Death or PD after one or more missed tumor assessments	Date of the last assessment before missed assessments	Event[a]
Patients still on treatment without PD as of data cut-off	Date of last tumor assessment	Censored

a - Earliest date among the three dates is used in calculating the PFS.

PFS will be summarized using the Kaplan-Meier method. The Kaplan-Meier estimate of the median PFS time and first and third quartiles will be presented with 95% confidence intervals. The 12, 24, 36, and 48 week PFS rates will also be provided with 95% confidence intervals. Kaplan-Meier curve will be presented.

The number and percentage of subjects in the overall (unselected) group and by KRAS mutation status who have progressed or died at 12 weeks, 24 weeks, 36 weeks and 48 weeks will be summarized along with the number and percentage of censored subjects (follow-up ended or follow-up ongoing).

Overall Survival (OS)

OS is defined as the time from date of first administration of study drug until the date of death due to any cause. For patients who are lost to follow-up or who are alive at the date of data cut-off, the time to death will be censored at the time of last contact.

OS (days) = Date of death/censoring – Date of first administration of study drug + 1.

The table below will be used for calculating the OS.

Situation	End Date	Outcome
Death during study	Date of death	Event
Patient still alive at data cut-off	Date last known to be alive	Censored
Patient lost to follow-up before data cut-off	Date last known to be alive	Censored

OS will be summarized using the Kaplan-Meier method. The Kaplan-Meier estimate of the median survival time and first and third quartiles will be presented with 95% confidence intervals. The 12 and 48 week OS rates will also be provided with 95% confidence intervals. Kaplan-Meier curve will be presented.

Time to Progression (TTP)

The analysis and censoring rule for TTP will be performed as explained under DOR.

TTP (days) = Date of disease progression/ censoring – Date of first administration of study drug + 1.

TTP will be summarized using the Kaplan-Meier method. The Kaplan-Meier estimate of the median TTP and first and third quartiles will be presented with 95% confidence intervals. Survival rate of 12, 48 weeks will also be provided with 95% confidence intervals. Kaplan-Meier curve will be presented.

6.10 PK Analysis

6.10.1 Noncompartmental Pharmacokinetic Analysis (NCA)

For intensively sampled PK profiles from the PK population, pharmacokinetic parameters will be calculated from the concentration-time data using noncompartmental techniques (Phoenix WNL® Version 6.2.1 [or later], Pharsight Corp, St. Louis, MO). Calculation will be based on the actual sampling times recorded during the study.

The following PK parameters will be determined after doses of antroquinonol on Days 0 and 28, as appropriate:

Variable	Definition
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval (τ)
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero extrapolated to infinity, calculated as $AUC_{0-t} + (C_{last} / \lambda_z)$ where AUC_{0-t} is AUC from time zero (pre-dose) to time of last quantifiable concentration, C_{last} is the last temporal predicted plasma concentration (Day 0 only), and λ_z is the terminal phase elimination rate constant
C_{max}	Maximum observed plasma concentration
T_{max}	Time at which the C_{max} was observed
$T_{½}$	Apparent elimination half-life, calculated as $\ln(2)/\lambda_z$
$T_{½,eff}$	Effective half-life calculated as $\tau \times \log(2)/\log(R_{AUC}/(R_{AUC}-1))$ (Day 28 only)

CL/F	Apparent oral clearance, calculated as Dose/$AUC_{0-\infty}$ on Day 0 and Dose/AUC_{τ} on Day 28
V_z/F	Volume of distribution during elimination, calculated as $(CL/F)/\lambda_z$
C_{trough}	Trough concentration at the end of each dosing interval (i.e. τ hours after dosing)
R_{AUC}	accumulation ratios for AUC_{τ}, calculated as AUC_{τ} on Day 28 divided by AUC_{τ} on Day 0

Following administration, C_{max} and T_{max} will be obtained directly from the experimental observations. If multiple maxima occur at equal concentrations, the first temporal value will be taken.

AUC will be calculated using the linear/log trapezoidal rule, using actual elapsed time values.

The number of data points included in the regression for determination of λ_z and $T_{½}$ will be determined by visual inspection, but a minimum of 3 data points in the terminal phase, excluding C_{max}, will be required to estimate λ_z. The λ_z values (and consequently $T_{½}$, CL/F, V_z/F, and $AUC_{0-\infty}$ values) will be considered unreliable estimates if the time period over which an individual λ_z was estimated is less than twice the resultant $T_{½}$ or if the adjusted coefficient of determination 'R_{sq}' is less than or equal to 0.8.

The proportion of $AUC_{0-\infty}$ due to extrapolation (AUC_{extr}) will also be calculated, and expressed as a percentage. The value of AUC_{extr} should be less than or equal to 20% of the $AUC_{0-\infty}$ to be considered to be well estimated. If this proportion is any higher, then the values of $AUC_{0-\infty}$, CL/F, and V_z/F will be considered unreliable and therefore excluded from the analysis.

6.10.2 Treatment of Outliers

Individual antroquinonol plasma concentration-time points, if considered anomalous, may be excluded from the analysis at the discretion of the pharmacokineticist following a review of the available documentation (bioanalytical report, CRF, etc.). Any such exclusion will be discussed with the sponsor and clearly outlined in the study report.

Entire individual treatment profiles for a subject may be excluded following review of the available documentation and discussion with the sponsor. However, results of analysis with and without the excluded profiles will be presented in the study report. Any such exclusion will be clearly listed in the study report along with justification for exclusion.

6.10.3 Non-Quantifiable Concentrations

All plasma concentrations reported as No Result (NR) values will be treated as missing and will appear in the data set as ".".

For the purpose of calculating AUC, when 2 consecutive values less than the lower limit of quantification (LLOQ) are encountered after T_{max}, these and all subsequent values will be excluded from the analysis. Values less than LLOQ that are encountered prior to T_{max} will be set to 0. When single embedded missing values occur, they will be excluded from the analysis. For calculation of summary concentrations, <LLOQ will be set to 0.

6.10.4 PopPK Analysis

If possible, PK data from all patients (Stages 1 and 2) in the PopPK population will be analyzed using nonlinear, mixed-effects methods and post hoc estimates of antroquinonol exposure (i.e., C_{max}, C_{trough}, and AUC_{τ}) 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). If performed, results from the PopPK analysis will not be reported in the clinical study report (CSR), but will be the subject of a separate PopPK report.

6.10.5 Reporting of Concentrations and PK Parameters

Intensively sampled plasma concentration-time data for antroquinonol will be listed and summarized descriptively. The following descriptive statistics will be calculated at each of the sampling times: n, mean, median, standard deviation (STD), geometric mean, coefficient of variation (CV[%]), 25th percentile, minimum, 75th percentile, and maximum.

Individual and mean (+STD) plasma concentration-time profiles of antroquinonol will be presented graphically on a semi-logarithmic and a linear scale.

Pharmacokinetic parameters of antroquinonol will be listed by subject and summarized descriptively by study day for the PK population. The following descriptive statistics will be provided: n, arithmetic mean, STD, median, min and max and 95% confidence interval. Only n, median, min and max will be reported for T_{max}. In addition, geometric means and between-subject CV will be calculated for AUC_{τ}, $AUC_{0-\infty}$, C_{max}, C_{τ}, $T_{½}$, $T_{½,eff}$, CL/F, V_z/F, and C_{trough}. A box plots will be used to graphically compare C_{max} and CL/F on Days 0 and 28.

Sparsely sampled plasma concentration data will be listed. Nominal trough concentrations within subject will be summarized as the arithmetic mean and listed along with observed concentration data.

6.11 Patient Reported Outcome

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 and changes from baseline (Day 0) for EORTC QLQ-C30 and QLQ-LC13 at each nominal time. Scores will be plotted for Dyspnea from QLQ-LC13.

The questionnaire will be scored according to the algorithm described in the QLQ-C30 scoring manual[6]. All scales are scored on categorical scales and linearly transformed to 0-100 scales where:

- a high score for a functional scale represents a high or healthy level of functioning
- a high score for the global QoL scale represents a high level of quality of life

- a high score for a symptom scale or item represents a high level of symptomatology or problems

Details of the scoring algorithms can be seen in Appendix III

6.12 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 by KRAS mutation status. There will be no formal statistical analysis of safety data.

6.12.1 Adverse Events

Adverse Events (AEs) collected for the duration of the study from the time the subject signs the informed consent will be classified as per the MedDRA, graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Based on the timing of each AE relative to the date of the first study procedure or first dose of study drug, whichever occurs first, it will be classified as being a Pre-Treatment AE or a Treatment-Emergent AE, according to the following definitions:

- Pre-Treatment Adverse Events are defined as any AE, whose onset occurs prior to undergoing the first study procedure or receipt of first dose of study drug (whichever occurs first)
- Treatment-Emergent Adverse Events (TEAE) are defined as any AE whose onset occurs or intensity worsens after undertaking the first study procedure or first dose of study drug (whichever occurs first).

AEs will be coded using the MedDRA AE dictionary, which is an adverse event reporting system which allows the grouping of adverse events and the classification of adverse events into a system organ class and preferred term. Events will be graded for severity using NCI-CTCAE, version 4.03. In addition, the relationship of each AE to study drug, study drug will also be assessed by the investigator. For each of these categories, the causality will be assumed as "Related" where the causality outcome is missing or where it cannot be determined.

The following summary tables will be prepared:

- Overview of AEs:
    - Number of subjects with any treatment-emergent AEs, related study drug treatment-emergent AEs, Grade 3 or 4 or 5 treatment emergent AEs, treatment-emergent AEs leading to withdrawal.
    - Serious treatment-emergent AEs, related study drug serious AEs, treatment-emergent AEs leading to withdrawal.
    - Deaths.
- Incidence of treatment-emergent AEs
- Incidence of treatment-emergent AEs related to study drug
- Drug-related treatment-emergent AEs
- Treatment-emergent AEs leading to discontinuation

- Incidence of serious treatment-emergent AEs
- Incidence of serious AEs related to study drug

All AEs will be presented in a listing, with a flag to indicate their classification based on the categories as pre-TEAE and TEAE as described earlier in this section. In addition, separate listings for TEAEs leading to study drug discontinuation, serious TEAEs and AEs resulting in death will be presented.

All AE data will be presented using the Safety population. All summaries of AEs will include counts subjects. For counts of subjects, subjects will only be counted once per preferred term and once per system organ class. In the case that a patient has multiple events with different intensity, severity etc., the worst case will be used in data presentation.

6.12.2 Deaths

The incidence and reasons for death will be presented using frequency counts and percentages.

6.12.3 Clinical Laboratory Evaluations

All laboratory parameters will be reported in SI units using the safety population. Laboratory data will be summarized at each visit for the overall (unselected) population and by KRAS mutation status. The final on therapy value (End of Study) will be summarized for the overall (unselected) population and by KRAS mutation status.

Continuous laboratory parameters will be summarized by absolute values and change from baseline.

Laboratory results will be classified according to NCI-CTCAE (version 4.03) where the grading criteria for the test are available by NCI-CTCAE. Incidence of maximum NCI-CTCAE grade under treatment and shifts in toxicity grading from treatment start to highest grade will be displayed. Only subjects with post-baseline laboratory values will be included in these analyses.

6.12.4 Vital Signs

Vital signs data (heart rate, body temperature, systolic and diastolic blood pressure) and changes from baseline (i.e. last measurement before randomization) will be summarized descriptively.

6.12.5 12-Lead ECGs

ECG data (Heart rate, RR, QRS, QT, QTc and QTc) will be summarized descriptively.

The ECG interpretation (normal, abnormal not clinically significant or abnormal clinically significant) will be summarized at each visit compared with baseline using a shift table.

6.12.6 Physical Examinations

The baseline results of the physical examination will be presented. Clinically significant, abnormal findings from the examinations will be reported as AEs. Separate summaries of the physical examination during and after treatment will therefore not be provided.

6.13 Subgroup Analysis

Exploratory subgroup analysis will be conducted to investigate if the following factors influence PFS rate at 12 weeks. Subgroup analysis will be conducted on the evaluable population for PFS.

- Sex (Male vs. Female)
- Smoking History (Yes vs. No)
- Race (Asian, American Indian or Alaska Native, Black or African American, White, Other)
- Prior chemotherapy (Yes vs. No)
- Baseline ECOG status (0 vs. 1/2)
- EGFR (positive vs. negative)
- ALK (positive vs. negative)
- ROSI (positive vs. negative)
- Stage (Stage1 vs. Stage2)

6.14 Interim Analysis and Data and Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will be established to monitor safety and efficacy. Further details are provided in the DSMB charter. Appendix I lists the outputs that will be provided.

The independent centralized review will be used for the interim analysis.

An interim analysis 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 5, if less than two patients are alive and progression-free within a stratum, and 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).

6.15 Analysis for Extension Phase

After the first 12-week treatment cycle, patients who are progression-free or, in the opinion of their investigator, still deriving clinical benefit, will continue to receive up to three further (12-week) treatment cycles with antroquinonol in the Extension Phase.

The analyses specified in this document apply to the first 12-week cycle and the Extension Phase. When all patients have completed the Extension Phase, all of the analyses specified in the SAP will be conducted, as appropriate.

6.16 Changes to Planned Analyses

None.

7. REFERENCES

1. ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95-adopted December 1995).
2. ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).
3. Green S. J. and Dahlberg S (1992). Planned Versus Attained Design in Phase II Clinical Trials. Statistics in Medicine 11:853-862.
4. von Mehren M., Rankin C., Goldblum J.R., Demetri G.D., Bramwell V., Ryan C.W., and Borden E. (2012). Phase 2 Southwest Oncology Group-Directed Intergroup Trial (S0505) of Sorafenib in Advanced Soft Tissue Sarcomas. Cancer 118:770-776.
5. Hoang T, Campbell TC, Zhang C, Kim KM, Kolesar JM, Oettel KR, et al. Vorinostat and bortezomib as third-line therapy in patients with advanced non-small cell lung cancer: a Wisconsin Oncology Network Phase II study. Invest New Drugs. 2013 June; DOI 10.1007/s10637-013-9980-5.
6. EORTC QLQ-C30 Manuals, Reference Values and Bibliography http://www.eortc.be/home/qol/

APPENDIX I: DSMB TFLS SPECIFICATIONS

The following outputs will be produced for the DSMB for safety monitoring:

	Table Number*
Subject Disposition, All subjects	14.1.1.2
Subject Discontinuation, Safety population	14.1.1.3
Demographic and Baseline Characteristics, Evaluable population	14.1.2.1.1
Demographic and Baseline Characteristics, Safety population	14.1.2.1.2
Discontinuation Due to Adverse Events , Safety population	14.3.3.3
Progression Free Survival rate at 12 week, Evaluable population	14.3.2.1
Progression Free Survival Rate at 12 Week by Region, Evaluable Population	14.3.2.1.3.7
Progression Free Survival Rate at 12 Week by Race, Evaluable Population	14.3.2.1.3.8
Kaplan-Meier Plot of Progression Free Survival (PFS), Full Analysis Set	14.2.2.1
Objective Response Rate, Evaluable population	14.3.2.2.1
Summary of Treatment-Emergent Adverse Events (All Causality) , Safety population	14.3.3.1.1
Treatment-Emergent Adverse Events by System Organ Class, Preferred Term (All Causality) , Safety population	14.3.3.1.2
Incidence and Severity of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term (All Causality) , Safety population	14.3.3.1.3
Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term (All Causality) , Safety population	14.3.3.1.6
Laboratory Observed Results and Changes from Baseline – Hematology, Safety population	14.3.4.1.1
Laboratory Observed Results and Changes from Baseline – Biochemistry, Safety population	14.3.4.2.1
ECG Data and Changes from Baseline, Safety Population	14.3.4.3.1
Overall Objective Tumor Assessment	16.2.6.6
Listing of Adverse Events with Toxicity Grade 3/4/5	16.2.7.1.2
Listing of Serious Adverse Events	16.2.7.1.3

	Table Number*
Listing of Deaths	16.2.7.2
12-lead Electrocardiogram Data	16.2.8.4

*Table number can be modified as per the final TFLs mocks for CSR

APPENDIX II: INDEPENDENT REVIEW CHARTER

GHNSCLC2001_IR
C_ Final1p0_20140

APPENDIX III: QOL SCORING CONVENTIONS

All of the scales and single-item measures of the QLQ-C30 and QLQ-LC13 range in score from 0 to 100. A high scale score represents a higher response level. Thus a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.

The principle for scoring these scales is the same in all cases:

1. Estimate the average of the items that contribute to the scale; this is the raw score.
   $RS = (I_1 + I_2 + ... + I_n)/n$

   , where itemts $I_1, I_2, ... I_n$ are included in each scale

2. Use a linear transformation to standardize the raw score, so that scores range from 0 to 100.

   Functional scales: $S = \{1 - [(RS - 1)/range]\}*100$
   Symptom scales/items: $S = \{(RS - 1)/range\}*100$
   Global health status/QoL: $S = \{(RS - 1)/range\}*100$

where range is the difference between the maximum possible value of RS and the minimum possible value.

The QLQ-C30 has been designed so that the items at the beginning (for example, Q1 to Q28), are all scored 1 to 4, and contribute to one set of scales to different sets of scales; for these range = 3. The items Q29, Q30, scoring 1 to 7, contribute to the global health status / QoL which therefore has range = 6. Details on the construction of individual scales are provided in the table below.

Scoring of the EORTC QLQ-C30:

	Abbreviation	Number of items	Items (QLQ question numbers)	Item range
Functional scales				
Physical functioning	PF	5	1 to 5	3
Role functioning	RF	2	6, 7	3
Emotional functioning	EF	4	21 to 24	3
Cognitive functioning	CF	2	20, 25	3
Social functioning	SF	2	26, 27	3
Global health status / QoL				
Global health status/QoL	QL	2	29, 30	6
Symptom scales / items				
Fatigue	FA	3	10, 12, 18	3
Nausea and vomiting	NV	2	14, 15	3

	Abbreviation	Number of items	Items (QLQ question numbers)	Item range
Pain	PA	2	9, 19	3
Dyspnoea	DY	1	8	3
Insomnia	SL	1	11	3
Appetite loss	AP	1	13	3
Constipation	CO	1	16	3
Diarrhoea	DI	1	17	3
Financial difficulties	FI	1	28	3

The QLQ-LC13 module incorporates one multi-item scale to assess dyspnoea, and a series of single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and haemoptysis. The scoring approach for the QLQ-LC13 is identical in principle to that for the symptom scales single items of the QLQ-C30. Details on the construction of individual scales are provided in the table below.

Scoring of the EORTC QLQ-LC13:

	Abbreviation	Number of items	Items (QLQ question numbers)	Item range
Symptom scales / items				
Dyspnoea	LCDY	3	3,4,5	3
Coughing	LCCO	1	1	3
Haemoptysis	LCHA	1	2	3
Sore mouth	LCSM	1	6	3
Dysphagia	LCDS	1	7	3
Peripheral neuropathy	LCPN	1	8	3
Alopecia	LCHR	1	9	3
Pain in chest	LCPC	1	10	3
Pain in arm or shoulder	LCPA	1	11	3
Pain in other parts	LCPO	1	12	3

SAS Commands for scoring the QLQ-C30/LC13 is provided in "Usage of statistical packages" section (page 15) on EORTC QLQ-C30/LC13 Manuals, Reference Values and Bibliography[6].