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This study will be performed in compliance with Good Clinical Practices.

A Phase I/II study to determine the maximum tolerated dose (MTD) and to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of antroquinonol in combination with nab-paclitaxel and gemcitabine in first line metastatic pancreatic cancer

Product: Antroquinonol
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Phase: I/II
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for

Golden Biotechnology Corporation
15 F, No. 27-6, Sec. 2, Zhongzheng E. Rd.
Tamsui District, New Taipei City 251
Taiwan (R.O.C.)

by

Fortrea

SUMMARY OF PROTOCOL CHANGES

Reasons for Changes:

1. A maximum duration of 24 cycles of investigational treatment, in accordance with Investigator's discretion, has been added to the Phase II cohort expansion part of the study to enable the Final Clinical Study Report to be completed within a reasonable time according with pancreatic tumor history. Patients who continue to derive clinical benefit from study treatment in the absence of withdrawal of patient consent, disease progression, unacceptable toxicity, or non-compliance with the protocol will continue in the study at the discretion of the Investigator, even if 24 cycles are completed.
2. A secondary endpoint of median overall survival (OS) and OS rate for 3 months, 6 months, 1 year, and 2 years was added to the Phase II cohort expansion part of the study.
3. A secondary endpoint to perform sub-group analysis based on C-reactive protein levels at baseline (≤ 10 mg/L and > 10 mg/L) has been added to the Phase II cohort expansion part of the study to further evaluate the effect of antroquinonol in combination with nab-paclitaxel + gemcitabine on various efficacy (eg, OS and progression-free survival [PFS]) and safety (eg, neutropenia, leukopenia, liver metastasis) parameters.
4. Given the hypothesis-generating nature of this study, the Sponsor may choose to conduct optional interim analyses.
5. The company Covance Inc is now Fortrea and therefore, changes to the name have been made throughout the protocol.

STUDY IDENTIFICATION

Sponsor's Medical Monitor: Pei-Ni Chen, MD
15 F. No.27-6, Sec.2, Zhongzheng E. Rd.
Tamsui Dist. New Taipei City 251, Taiwan (R.O.C.)
Phone: +886-2-2808-6006
Email address: pnchen79@goldenbiotech.com.tw

Sponsor's Study Contact: Howard Cheng, PhD
15 F. No.27-6, Sec.2, Zhongzheng E. Rd.
Tamsui Dist. New Taipei City 251, Taiwan (R.O.C.)
Phone: +886-2-2808-6006
Email address: howard@goldenbiotech.com.tw

SYNOPSIS

Study Number:	GHPanc-1-001
Title of Study:	A Phase I/II study to determine the maximum tolerated dose (MTD) and to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy, of antroquinonol in combination with nab-paclitaxel and gemcitabine in first line metastatic pancreatic cancer
Indication:	Stage 4 pancreatic cancer
Number of Investigators and Study Centers:	This is a multicenter study with participating sites in the United States, South Korea and Taiwan.
Development Phase:	I/II
Objectives:	**The primary objectives of this study are:** ***Phase I*** **Run-in drug-drug interaction (DDI) and dose escalation:** • To evaluate the effect of antroquinonol 200 mg on the pharmacokinetics (PK) of paclitaxel in patients with metastatic pancreatic cancer. • To determine the maximum tolerated dose (MTD) or maximum feasible dose (MFD) of antroquinonol in combination with nab-paclitaxel + gemcitabine in patients with metastatic pancreatic cancer. ***Phase II*** **Cohort expansion:** A preliminary evaluation of the anti-tumor activity of antroquinonol in combination with nab-paclitaxel + gemcitabine in patients with metastatic pancreatic cancer. **The secondary objectives of this study are:** ***Phase I*** **Run-in DDI and dose escalation:** • To evaluate the safety and tolerability of the combination of antroquinonol and nab-paclitaxel + gemcitabine. • To further characterize the PK of antroquinonol and paclitaxel. • To evaluate the effect of antroquinonol in combination with nab-paclitaxel + gemcitabine on markers of pancreatic cancer. • To obtain preliminary anti-tumor activity of antroquinonol in combination with nab-paclitaxel + gemcitabine in patients with metastatic pancreatic cancer. ***Phase II*** **Cohort expansion:** • To evaluate the safety and tolerability of the MTD/MFD of antroquinonol in combination with nab-paclitaxel + gemcitabine. • To further characterize the PK of antroquinonol.

	• To evaluate the effect of antroquinonol in combination with nab-paclitaxel + gemcitabine on markers of pancreatic cancer.
Endpoints	**The primary endpoints for this study are:** ***Phase I*** **Run-in DDI and dose escalation:** • The following PK parameters, based on paclitaxel concentrations, will be assessed to evaluate the effect of antroquinonol on the PK of paclitaxel: o $C_{max:}$ maximum observed plasma concentration o $AUC_{0-t:}$ under the plasma concentration-time curve (AUC) from time zero to the last measurable concentration o AUC_{inf}: AUC extrapolated to infinity • The MTD is the dose at which <33% of patients experience a dose limiting toxicity (DLT) within the first 28-day cycle of antroquinonol and nab-paclitaxel + gemcitabine combined treatment (Cycle 1). All DLTs and adverse events (AEs) will be described and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (CTCAE) Version 4.03. A DLT is defined as the occurrence of any of the following toxicities: o Non-hematological toxicity of Grade 3 or greater (excluding Grade 3 diarrhea, nausea, or vomiting that resolves to Grade 1 or baseline grade within 3 days of onset with appropriate treatment) o Grade 4 thrombocytopenia o Grade 4 neutropenia lasting ≥48 hours or ≥Grade 3 febrile neutropenia o Persisting toxicity of Grade 2 or greater that causes more than a 14 day delay in dose administration. Adverse events that are considered by the Investigator to be related to the underlying disease condition, concomitant medication, or to new unrelated medical events or treatment will not be defined as a DLT. ***Phase II*** **Cohort expansion:** Anti-tumor activity will be assessed through evaluation of the median progression-free survival (PFS) and PFS rate at 6 months using Investigator assessments according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. **The secondary endpoints for this study are:** ***Phase I*** **Run-in DDI and dose escalation:** • The safety and tolerability of antroquinonol administered in combination with nab-paclitaxel + gemcitabine will be evaluated by the frequency and severity of AEs, the occurrence of DLTs, laboratory evaluations (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure and pulse), Eastern Cooperative Oncology Group (ECOG) status, physical examination findings, and electrocardiograms (ECGs).

	• Plasma concentrations of antroquinonol and paclitaxel will be measured and PK parameters calculated where applicable. • Markers of pancreatic cancer, including CA 19-9 levels, will be measured. Other emerging antroquinonol biomarkers may be evaluated. • Anti-tumor activity will be assessed through the evaluation of the median PFS and PFS rate at 6 months using Investigator assessments according to RECIST 1.1 ***Phase II*** **Cohort expansion:** • The safety and tolerability of antroquinonol administered in combination with nab-paclitaxel + gemcitabine will be evaluated by the frequency and severity of AEs, laboratory evaluations (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure and pulse), ECOG status, physical examination findings, and ECGs. • Plasma concentrations of antroquinonol will be measured and PK parameters will be calculated where applicable. • Markers of pancreatic cancer including CA 19-9 levels will be measured. Other emerging antroquinonol biomarkers may be evaluated. • Median overall survival (OS) and OS rate at 3 months, 6 months, 1 year, and 2 years will be evaluated. • Sub-group analysis based on C-reactive protein levels at baseline (≤ 10 mg/L and > 10 mg/L sub-groups) will be performed to further evaluate the effect of antroquinonol in combination with nab-paclitaxel + gemcitabine on various efficacy (eg, OS and PFS) and safety (eg, neutropenia, leukopenia, liver metastasis) parameters.
Study Population:	Patients with diagnosed Stage 4 pancreatic cancer
Methodology/ Study Design:	***Phase I*** **Run-in DDI and dose escalation:** The dose escalation part of the study will be conducted to characterize the safety of antroquinonol in combination with the standard of care (SOC) (nab-paclitaxel + gemcitabine) and to identify the MTD of antroquinonol in patients with metastatic pancreatic cancer. The MTD is the dose level at which <33% (2/6) of patients experience a DLT. Within the dose escalation part of the study, a total of 6 patients will be enrolled in a run-in DDI portion to assess the effect of antroquinonol (a cytochrome P450 [CYP]3A4/CYP2C8 inhibitor) on the PK of paclitaxel (a CYP3A4/CYP2C8 substrate). Patients within this cohort (Cohort 1) will receive treatment as follows: • Cycle 0 (28-day cycle): nab-paclitaxel 125 mg/m^2 and gemcitabine 1000 mg/m^2 (as per SOC) via intravenous (IV) infusion on Days 1, 8, and 15. • Cycle 1 (28-day cycle): antroquinonol 200 mg administered TID on Days 1 through 28 and nab-paclitaxel 125 mg/m^2 and gemcitabine 1000 mg/m^2 via IV infusion on Days 1, 8, and 15. Intense PK sampling to assess the PK of paclitaxel will be conducted in Cycles 0 and 1. The primary PK endpoints will include C_{max}, AUC_{0-t}, and AUC_{inf}. Available

	bioanalytical data will be assessed in an ongoing manner to assess the effect of antroquinonol on the systemic exposure (C_{max} and AUCs) of paclitaxel. Data will be reviewed by the Safety Monitoring Committee (SMC) prior to enrollment of additional patients into the dose-escalation part of the study. For Cohort 1, the occurrence of DLTs will be assessed from Day 1 to Day 28 of Cycle 1. If ≤1 patient experiences a DLT, dosing in the dose escalation part will proceed. If ≥2 patients experience a DLT, dosing in the dose escalation part of the study will be discontinued. If ≤1 patient in Cohort 1 experiences a DLT then dosing in Cohort 2 of the dose escalation part will proceed as follows: - All Cycles: antroquinonol 300 mg administered TID on Days 1 through 28 and nab-paclitaxel 125 mg/m^2 and gemcitabine 1000 mg/m^2 via IV infusion on Days 1, 8, and 15 (ie, 1 cycle = weekly for 3 weeks, then 1 week off). Three patients will be enrolled initially into Cohort 2, these patients will be assessed for DLTs within the first 28-day dosing cycle. This cohort will be expanded to 6 total patients if 1 DLT is observed in the first 3 patients within Cohort 2. If ≤1 DLT is observed at the 300 mg dose then the 300 mg dose will be considered the MFD. If >1 DLT is observed at the 300 mg group then 200 mg will be considered the MTD and/or the SMC will review the available data and determine the MTD/recommended dose (RD). Patients enrolled into the dose escalation part of the study (Cohorts 1 and 2) will continue to receive treatment with antroquinonol (200 or 300 mg, respectively) in combination with nab-paclitaxel + gemcitabine in 28-day cycles at the discretion of the Investigator without a maximum duration until unacceptable toxicity or progressive disease (PD). The total number of patients to be entered in the dose escalation part of the study will depend on the emergence of DLTs at each dose level and the total number of dose levels investigated. Up to 12 patients are planned to be treated in the dose-escalation part if no patient needs to be replaced for DLT and safety evaluation. ***Phase II*** **Cohort expansion:** During the cohort expansion part of the study, up to an additional 40 patients will be enrolled at the MTD or MFD/RD. The dose level in the cohort expansion phase will not exceed the MTD, or highest safe dose tested in the dose-escalation phase if MTD is not reached**.** Patients in the cohort expansion will receive treatment as follows: - All Cycles: antroquinonol at the MTD or MFD/RD administered TID on Days 1 through 28 and nab-paclitaxel 125 mg/m^2 and gemcitabine 1000 mg/m^2 via IV infusion on Days 1, 8, and 15 (ie, 1 cycle = weekly for 3 weeks, then 1 week off). Patients enrolled into the cohort expansion part of the study will continue to receive treatment with antroquinonol at the MTD or MFD/RD in combination with nab-paclitaxel + gemcitabine in 28-day cycles at the discretion of the Investigator up to and including 24 cycles or until unacceptable toxicity or PD. Patients who continue to derive clinical benefit from study treatment in the absence of withdrawal of patient consent, disease progression, unacceptable toxicity, or

	non-compliance with the protocol will continue in the study at the discretion of the Investigator, even if 24 cycles are completed.
Number of Patients:	***Phase I*** **Run-in DDI and dose escalation:** Six patients will be enrolled in the run-in DDI cohort of the dose-escalation part of the study (ie, Cohort 1) and 3 to 6 patients may be enrolled in Cohort 2. The total number of patients to be entered in the dose-escalation part of this study will depend on the emergence of DLTs at each dose level, but will be up to 12 if no replacement occurs at the 2 predefined dose levels. ***Phase II*** **Cohort expansion:** Up to an additional 40 patients may be enrolled at the MTD or MFD/RD. A power calculation was not employed to determine the sample size of the study, as this is a proof of concept study with a preliminary assessment of anti-tumor activity of antroquinonol in combination with nab-paclitaxel + gemcitabine in metastatic pancreatic cancer patients.
Diagnosis and Main Criteria for Inclusion:	To be eligible to participate in the study, patients must meet the following criteria: 1. Male and female patients ≥18 years of age. 2. Histologically or cytologically confirmed metastatic adenocarcinoma of the pancreas, including variants as per WHO Classification (ductal adenocarcinoma, including adenosquamous carcinoma, mucinous adenocarcinoma, hepatoid carcinoma, medullary carcinoma, signet ring cell carcinoma, undifferentiated carcinoma, undifferentiated carcinoma with osteoclast-like cells). 2.1 Measurable disease according to the RECIST 1.1. Computerized tomography scans (with oral and IV contrast) of the chest, abdomen, and pelvis. In the case of CT contrast agent allergy, magnetic resonance imaging of the abdomen and pelvis (with IV contrast) along with CT scan of the chest is acceptable. 3. Diagnosed with metastatic disease within 6 weeks before enrollment. 4. Treatment-naïve patients with metastatic pancreatic adenocarcinoma who have received no previous systemic therapy (except adjuvant or neoadjuvant therapy if progression occurred >6 months from last treatment or surgery, respectively, and no prior nab-paclitaxel). 5. Adequate hematologic, hepatic, and renal function, including: - Hemoglobin ≥9 g/dL - Absolute neutrophil count ≥1500/mm^3 - Platelet count ≥100 000/mm^3 - Total bilirubin ≤1.25 × upper limit of normal (ULN) - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN; for patients with hepatic metastases, ALT and AST ≤5 × ULN - Albumin ≥3 mg/dL - Serum creatinine ≤1.5 mg/dL or calculated creatinine clearance ≥50 mL/min as determined by the Cockcroft-Gault equation.

	6. ECOG performance status of 0 or 1. 7. For women of childbearing potential, a negative serum pregnancy test result at Screening. 8. Willing to use 2 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 postvasectomy 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). 9. Patient must be able to provide written informed consent for participation in the study. 10. Life expectancy ≥12 weeks as assessed by the Investigator.
Exclusion Criteria:	Patients who meet any of the following criteria will not be eligible to participate in the study: 1. Islet-cell neoplasms or locally advanced disease. 2. Chemo-, hormone-, or immunotherapy or investigational drug at Screening or prior to enrollment. 3. 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 and during study treatment. 4. Other malignancies diagnosed within the past 5 years (other than curatively treated cervical cancer in situ, nonmelanoma skin cancer, superficial bladder tumors Ta [noninvasive tumor] and TIS [carcinoma in situ], or nonmetastatic 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]). 5. Patients with any serious active infection (ie, requiring an IV antibiotic, antifungal, or antiviral agent). 6. Patients with known human immunodeficiency virus, active hepatitis B, or active hepatitis C. 7. 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. 8. Known or suspected substance abuse or alcohol abuse; or regular use of alcohol beyond moderate drinking (moderate drinking defined as alcohol consumption of > 14 units per week for males [> 2 drinks per day] and

	> 7 units for females [> 1 drink per day]. One unit of alcohol equals 12 oz [360 mL] beer, 1½ oz [45 mL] liquor, or 5 oz [150 mL] wine). 9. Uncontrolled current illness, including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from study treatment, or compromise the ability of the patient to give written informed consent. 10. Inability to swallow oral medications or a recent acute gastrointestinal disorder with diarrhea (eg, Crohn's disease), malabsorption, or CTCAE Grade >2 diarrhea of any etiology at baseline. 11. Female patients who are pregnant or breastfeeding, or male or female patients of reproductive potential who are not employing an effective method of contraception. 12. Any known hypersensitivity to any component of nab-paclitaxel, gemcitabine, or antroquinonol. 13. Use of Antrodia camphorata-containing products within 2 weeks prior to the date of first administration of study drug and/or during study participation. 14. Use of tobacco- or nicotine-containing products within 3 months prior to the date of first administration of study drug. 15. Evidence of pancreatic cancer metastases to the brain.
Study Medications:	Antroquinonol: 100 mg and corn oil 100 mg encapsulated in a gelatin capsule (volume capsulated = 212 microliter), administered orally. Reference therapy: not applicable.
Dose and Regimen:	200 or 300 mg antroquinonol TID
Study Medications:	Nab-paclitaxel (see product insert)
Dose and Regimen:	125 mg/m^2 nab-paclitaxel (as per SOC) via a 30 minute IV infusion on Days 1, 8, and 15
Study Medications:	Gemcitabine (see product insert)
Dose and Regimen:	1000 mg/m^2 gemcitabine (as per SOC) via a 30 minute IV infusion on Days 1, 8, and 15
Duration of Treatment:	Phase I, run-in DDI and dose escalation: No maximum duration of treatment. Patients may continue to receive study treatment until unacceptable toxicity or RECIST 1.1-defined disease progression. Phase II, cohort expansion: The maximum duration of treatment is 24 cycles of investigational treatment or until unacceptable toxicity or PD, at the discretion of the Investigator.
Duration of Patient Participation in Study:	Patients who continue to derive clinical benefit from study treatment in the absence of withdrawal of patient consent, disease progression, unacceptable toxicity, or non-compliance with the protocol will continue in the study at the discretion of the Investigator, even if 24 cycles are completed.
Study Populations:	**All Patients Set** The All Patients Set will include all patients who have signed the informed consent

	for this trial (ie, screening failures plus patients enrolled) including patients in the dose escalation and cohort expansion parts of this trial. **DLT Analysis Set** The DLT Analysis Set is only applied to the dose-escalation part of the study. The DLT Analysis Set will include all of the following patients: Patients who experienced a DLT or patients who did not experience a DLT, and completed the first cycle of antroquinonol dosing in combination with nab-paclitaxel + gemcitabine (Cycle 1) and who received 90% or more of all planned total doses of antroquinonol during this cycle (Cycle 1). **Safety Analysis Set** The Safety Analysis Set will include all patients who received at least 1 administration of the trial medication (ie, actual total dose of antroquinonol or nab-paclitaxel + gemcitabine >0). Patients who were replaced for evaluation of DLT will still be included in the Safety Analysis Set if they received at least 1 administration of the trial medication (ie, actual total dose of antroquinonol or nab-paclitaxel + gemcitabine >0). **Efficacy Analysis Set** The Efficacy Analysis Set will include all patients who received at least 1 administration of planned dose antroquinonol (ie, actual total dose of antroquinonol >0) and who had a baseline tumor assessment and at least 1 tumor assessment according to RECIST 1.1 after the first dose of trial medication. Patients who experienced early discontinuation due to disease progression will also be included in the Efficacy Analysis Set and will be classified with PD in the best response. **Full Analysis Set** The Full Analysis Set will include all patients who received at least 1 administration of the planned dose of antroquinonol (ie, actual total dose of antroquinonol >0) and have any post baseline information on survival status. **Dose Escalation PK Analysis Set** The PK Analysis Set will include all patients in the dose escalation part who received at least 1 administration of the planned dose of antroquinonol (ie, actual total dose of antroquinonol >0) and who provide sufficient data for a concentration-time profile for antroquinonol. **DDI PK Analysis Set** The DDI PK Analysis Set will include all patients in Cohort 1 who received at least 1 administration of planned dose of nab-paclitaxel (ie, actual total dose of nab-paclitaxel >0) and who provide sufficient data for a concentration-time profile for paclitaxel.
Evaluation Criteria: Efficacy	Objective response rate (ORR), duration of response, disease control rate (DCR), and PFS using Investigator assessments according to RECIST 1.1 (assessments every 8 weeks), OS.
Evaluation Criteria: Safety	Adverse event collection, physical examinations, laboratory findings (including clinical chemistry, hematology, and urinalysis), vital signs (including blood pressure and pulse), ECOG performance status, physical examination findings, ECGs, and DLTs.
Evaluation Criteria: Pharmacokinetics	Pharmacokinetic endpoints will be derived for intensively sampled PK profiles by noncompartmental analysis (NCA) and will include:

	Phase I **Run-in DDI and dose escalation:** • Paclitaxel PK: o C_{max} o AUC_{0-t} o AUC_{inf} • Antroquinonol PK: o C_{max} o C_{trough}: trough plasma concentration o T_{max}: time to maximum observed plasma concentration o AUC_{0-t} o AUCssτ: AUC over a dosing interval at steady state o $t_{1/2}$: apparent terminal half-life, computed as ln(2)/λz o V_z/F: apparent volume of distribution o CL/F: apparent oral clearance o C_{ssave}: average plasma concentration at steady state o AR: accumulation ratio The NCA will be performed for the PK Population. Descriptive statistics will be presented for all PK parameters. If possible, antroquinonol PK data will be analyzed using population-based PK (PopPK) methods as well. The PopPK methods will be used to estimate exposure metrics for patients with at least 2 plasma concentrations and with accurate records of dosing histories. The potential response-exposure/concentration relationships could be evaluated based on the post hoc estimates of antroquinonol exposure (ie, model predicted C_{max}, C_{trough}, and $AUC_{0-t)}$ from the above PopPK model or the concentration observations.
Evaluation Criteria: Pharmacodynamics	CA19-9 levels will be measured as a routine pancreatic cancer marker
Statistical Methods:	**Sample size calculation:** The sample size is not based on any statistical assumptions. A total of 6 patients will be enrolled in the run-in DDI portion of the study. The total number of patients in the dose escalation part will depend on the number of dose levels investigated and DLTs observed. A total of 12 patients has been estimated based on 2 dose levels investigated. In the cohort expansion phase, up to 40 patients may be enrolled at the MTD of MFD/RD. **Analysis of endpoints:** **Preliminary efficacy:** Descriptive summary of patients with best overall response in each category (complete response [CR], partial response [PR], stable disease [SD] and PD); the ORR (CR + PR); the DCR (CR + PR + SD [SD of ≥16 weeks]) according to RECIST 1.1 will be performed. Median OS time and PFS time with 95% confidence interval will be evaluated. **Safety and tolerability:** The number and proportion of patients experiencing treatment-emergent AEs, clinically significant changes in laboratory parameters, vital signs, physical

	examinations, weight, ECOG performance status, and ECGs; judged to be related to the trial medication; and number and reasons of deaths will be summarized. **Pharmacokinetics:** The effect of antroquinonol on the PK of paclitaxel will be assessed on the DDI PK Analysis Set. Antroquinonol and paclitaxel PK will be assessed on the Dose Escalation PK Analysis Set. **Pharmacodynamics:** Descriptive statistics will be performed; no formal statistical methods will be applied. Data will be summarized and plotted appropriately according to data type.