STATISTICAL ANALYSIS PLAN

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

Statistical Analysis Plan Status: Final v2
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Study Drugs: Antroquinonol, nab-paclitaxel, and gemcitabine

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Clinical Phase I/II

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

Study Site:
Multiple sites

Sponsor Signatory:
Howard Cheng, Ph.D.
V.P. Clinical Medicine Research Department

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2 ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

ADaM	analysis data model
AE	adverse event
AR	accumulation ratio
$\%AUC_{extrap}$	percentage of the area under the concentration-time curve that is due to extrapolation from the last measurable concentration to infinity
AUC_{inf}	area under the concentration-time curve extrapolated to infinity
$AUC_{SS\tau}$	area under the plasma concentration-time curve over a dosing interval at steady state
AUC_{τ}	area under the concentration-time curve over a dosing interval
AUC_{0-t}	area under the concentration-time curve from time zero to the time of the last measurable concentration
BLQ	below the limit of quantification
BMI	body mass index
CA	cancer antigen
CDISC	Clinical Data Interchange Standards Consortium
CL/F	apparent oral clearance
C_{max}	maximum observed plasma concentration
CR	complete response
CSR	Clinical Study Report
C_{ssave}	average concentration over a dosing interval
CTCAE	Common Terminology Criteria for Adverse Event
C_{trough}	trough plasma concentration
CV%	coefficient of variation
DCR	disease control rate
DDI	drug-drug interaction
DLT	dose limiting toxicity
EC	Early Clinical
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ICH	International Conference on Harmonisation

IMP	Investigational medicinal products
IV	intravenous
LLOQ	lower limit of quantification
λ_z	apparent terminal elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
MFD	maximum feasible dose
MTD	maximum tolerated dose
NCI	National Cancer Institute
NA	not applicable
NC	not calculated
NR	no result
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
RD	recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SD	stable disease
SMC	Safety Monitoring Committee
$t_{1/2}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TID	three times daily
T_{max}	time to maximum observed concentration
V_z/F	apparent volume of distribution

3 INTRODUCTION

This SAP has been developed after review of the clinical study protocol (Final Version dated 16 November 2017).

This SAP describes the planned analysis of the safety, tolerability, PK, PD and efficacy data from this study. A detailed description of the planned TFLs to be presented in the Clinical Study Report (CSR) is provided in the accompanying TFL shell document.

The intent of this document is to provide guidance for the statistical analyses of PK, PD, and efficacy data. In general, the analyses are based on information from the protocol, unless they have been modified by agreement between Golden Biotechnology Corporation and Fortrea Early Clinical (EC) Biometrics. A limited amount of information concerning this study (e.g., objectives, study design) is given to help the reader's interpretation. This SAP must be finalised prior to the lock of the clinical database for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This SAP supersedes the statistical considerations identified in the protocol; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they may be performed and will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Golden Biotechnology Corporation and Fortrea EC Biometrics and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonisation (ICH) E9 guideline entitled, "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH E3 guideline entitled, "Guidance for Industry: Structure and Content of Clinical Study Reports."[1,2]

4 STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objectives

The primary objectives are:

Run-in drug-drug interaction (DDI) and dose escalation:

- To evaluate the effect of antroquinonol 200 mg on the PK of paclitaxel in patients with metastatic pancreatic cancer.

- To determine the MTD or maximum feasible dose (MFD) of antroquinonol in combination with nab-paclitaxel + gemcitabine in patients with metastatic pancreatic cancer.

Cohort expansion:

- A preliminary evaluation of the anti-tumor activity of antroquinonol in combination with nab-paclitaxel + gemcitabine in patients with metastatic pancreatic cancer.

4.2 Secondary Objectives

The secondary objectives are:

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.

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

4.3 Endpoints

The primary endpoints for this study are:

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:
    - C_{max}: maximum observed plasma concentration
    - AUC_{0-t}: under the plasma concentration-time curve (AUC) from time zero to the last measurable concentration
    - 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 nabpaclitaxel + gemcitabine combined treatment (Cycle 1). All DLTs and adverse events (AEs) will be described and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) Version 4.03. A DLT is defined as the occurrence of any of the following toxicities:

- 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)
- Grade 4 thrombocytopenia
- Grade 4 neutropenia lasting ≥48 hours or ≥Grade 3 febrile neutropenia
- 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.

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:

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.

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.

5 STUDY DESIGN

This is an open-label, 2-part, multi-center Phase I/II study of antroquinonol in combination with nab-paclitaxel + gemcitabine in first-line treatment naïve patients with Stage IV metastatic pancreatic carcinoma.

5.1 Run-in Drug-drug Interaction and Dose Escalation

The dose escalation part of the study (Phase I) will be conducted to characterize the safety of antroquinonol in combination with the standard of care (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 standard of care) via intravenous (IV) infusion on Days 1, 8, and 15.

- Cycle 1 (28-day cycle): antroquinonol 200 mg administered 3 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 as indicated in Table 8-4 of the protocol. 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 phase 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 (i.e., 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 mg or 300 mg, respectively) 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. .

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. A SMC will be set up for this part of the study to review DLTs, overall safety data, and to judge the relevance of events to the dose escalation scheme (see Section 8.5.4 of the protocol).

After MTD/MFD determination, enrollment will continue in the cohort expansion part of the study at a fixed dose of antroquinonol (MTD or MFD).

DLT definition and evaluation

Dose limiting toxicity is defined as the occurrence of any of the toxicities outlined below occurring during the DLT evaluation period that are determined to be related or possibly related to investigational medicinal products (IMP) combination. The DLT evaluation period will be the first 28-day treatment cycle. Toxicity grading will be determined using NCI CTCAE Version 4.03. Dose limiting toxicities are defined in Section 4.3.

5.2 Cohort Expansion

During the cohort expansion part (Phase II), 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 (i.e., 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.

6 TREATMENTS

The following is a list of the study treatment abbreviations and ordering that will be used in the safety, PK, and PD TFLs.

Study Treatment Name	Abbreviation	Treatment Order on TFLs
125 mg/m^2 nab-paclitaxel and 1000 mg/m^2 gemcitabine (Cohort 1)	Cohort 1 - Cycle 0	1
200 mg antroquinonol, 125 mg/m^2 nab-paclitaxel and 1000 mg/m^2 gemcitabine (Cohort 1)	Cohort 1 - Cycle 1	2
300 mg antroquinonol, 125 mg/m^2 nab-paclitaxel and 1000 mg/m^2 gemcitabine (Cohort 2)	Cohort 2	3
MTD or MFD/RD mg antroquinonol, 125 mg/m^2 nab-paclitaxel and 1000 mg/m^2 gemcitabine	Expansion Cohort and Cohort x	4

The following is a list of the study treatment abbreviations and ordering that will be used in the efficacy TFLs.

Study Treatment Name	Abbreviation	Treatment Order on TFLs
200 mg antroquinonol, 125 mg/m^2 nab-paclitaxel and 1000 mg/m^2 gemcitabine	Cohort 1	1
300 mg antroquinonol, 125 mg/m^2 nab-paclitaxel and 1000 mg/m^2 gemcitabine	Cohort 2	2

MTD or MFD/RD mg antroquinonol, 125 mg/m^2 nab-paclitaxel and 1000 mg/m^2 gemcitabine	Expansion Cohort and Cohort x	3

The actual dosing regimens will be footnoted wherever used in the TFLs. If the second or later cycles have less than 3 patients in them then cycles will be pooled before summarising the data.

Cohort x will be replaced with the actual number of the cohort that matches the dose level of antroquinonol.

7 SAMPLE SIZE JUSTIFICATION

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 an additional 40 patients may be enrolled at the MTD or MFD/RD.

8 DEFINITION OF ANALYSIS POPULATIONS

The following analysis sets will be used for data analyses according to each population's criteria. Major protocol violations will be identified and reviewed before the database lock. No patients will be excluded from any analysis sets due to protocol violation, if the patient meets the analysis set criteria (no Per Protocol Set will be defined).

The **All Patients Set** will include all the patients who have signed the informed consent for this trial (i.e., screening failures plus patients enrolled) including patients in the dose escalation and cohort expansion parts of this trial.

The **All Patients Set** will be used to describe patient disposition.

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% (at least 76 of the 84 total doses) or more of all planned total doses of antroquinonol during this cycle (Cycle 1).

The **Safety Analysis Set** will include all patients who received at least 1 administration of the trial medication (i.e., 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 (i.e., actual total dose of antroquinonol or nab-paclitaxel + gemcitabine >0).

The **Safety Analysis Set** will be used for all summaries of safety data.

The **Efficacy Analysis Set** will include all patients who received at least 1 administration of planned dose antroquinonol (i.e., 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.

The **Efficacy Analysis Set** will be used for assessment of anti-tumor activity.

The **Full Analysis Set** will include all patients who received at least 1 administration of the planned dose of antroquinonol (i.e., actual total dose of antroquinonol >0) and have any post baseline information on survival status.

The **Full Analysis Set** will be used for assessment of survival analysis.

The **Dose Escalation and Expansion Cohort PK Analysis Set** will include all patients in the dose escalation part who received at least 1 administration of the planned dose of antroquinonol (i.e., actual total dose of antroquinonol >0) in combination with nab-paclitaxel + gemcitabine and who provide sufficient data for a concentration-time profile for antroquinonol.

The **Dose Escalation and Expansion Cohort PK Analysis Set** will be used for PK analysis of antroquinonol and paclitaxel concentrations from the dose escalation part of the study.

The **DDI PK Analysis Set** will include all patients in Cohort 1 who received at least 1 administration of planned dose of nab-paclitaxel (i.e., actual total dose of nab-paclitaxel >0) and who provide sufficient data for a concentration-time profile for paclitaxel.

The **DDI PK Analysis Set** will be used for the PK analysis of paclitaxel concentrations from the DDI part of the study.

9 STATISTICAL METHODOLOGY

9.1 General

Data listings will be provided for the All Patients Population, including screening failures where applicable. Summary statistics and statistical analyses will be performed for patients included in the relevant analysis populations.

For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation, median, minimum, maximum, and number. For log-normal data (eg, the PK parameters: areas under the concentration-time curve [AUCs] and maximum observed concentration [C_{max}]), the geometric mean and geometric coefficient of variation (CV%) will also be presented. For categorical data, frequency counts and percentages will be presented. Data listings will be provided for all patients up to the point of withdrawal, with any patients excluded from the relevant population highlighted. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Missing values will not be imputed.

Data analysis will be performed using SAS® Version 9.4.

Analysis Data Model (ADaM) datasets will be prepared using Clinical Data Interchange Standards Consortium (CDISC) ADaM Version 2.1, and CDISC ADaM Implementation Guide Version 1.1. Pinnacle 21 Community Validator Version 2.2.0 will be utilised to ensure compliance with CDISC standards.

9.1.1 Definition of Baseline and Change from Baseline

Baseline for each parameter is defined as the last value measured prior to first dosing, including unscheduled readings (see Section 9.1.2 for definitions of unscheduled readings). For Cycle 0 the first dose is nab-paclitaxel, for other cycles the first dose is either of antroquinonol or nab-paclitaxel.

If the patients show a significant response in efficacy after Cycle 0 then the baseline for Cycle 1 onwards may be changed to the same as for Cycle 0 for interpreting the efficacy data. This will be decided on review of the efficacy TFLs.

Mean change from baseline is the mean of all individual patients' change from baseline values. Each individual change from baseline will be calculated by subtracting the individual patient's baseline value from the value at the timepoint. The individual patient's change from baseline values will be used to calculate the mean change from baseline using a SAS procedure such as Proc Univariate.

Mean percent change from baseline is the mean of all individual patients' percent change from baseline values. Each percent change from baseline will be calculated by subtracting the individual patient's baseline value from the value at the desired timepoint and then dividing this calculated value by the individual patient's baseline value and multiplying by 100. These individual patients' percent changes from baseline values will be used to calculate the mean percent change from baseline using a SAS procedure such as Proc Univariate.

9.1.2 Unscheduled Readings

Unscheduled readings are any readings not taken at a scheduled timepoint and will be labelled as 'Unscheduled' in the listings. Because unscheduled readings are not associated with any scheduled timepoint, they are excluded from all summaries (with the exception that they may be used as baseline, as stated in Section 9.1.1).

9.2 Demographics, Patient Disposition, and Other Baseline Characteristics

The demographic variables age, sex, race, ethnicity, body weight at Screening, height, and body mass index (BMI) will be summarized and listed. Patient disposition data will be summarised and listed. The number of screening failures will also be reported.

The date of the informed consent given by a patient along with details of the inclusion/exclusion criteria will be listed.

Medical history and prior medications will be listed.

The pregnancy test results at screening (if applicable) will be listed.

9.3 Baseline Characteristics Related to the Underlying Disease

The ECOG performance status recorded at Screening will be listed and summarised along with the demography data.

The tumor assessment at Screening will be listed and summarised.

9.4 Compliance

The dose administration details of antroquinonol, nab-pacliataxel, and gemcitabine will be listed.

In addition the total exposure and number of cycles received will be listed and summarised.

9.5 Pharmacokinetic Assessment

9.5.1 Pharmacokinetic Analysis

The plasma concentration data of antroquinonol and paclitaxel will be summarised by treatment and time point. All concentration data will be listed.

Run-in and DDI

PK parameters for paclitaxel only will be calculated from plasma concentration data collected in Cycle 0 of Cohort 1 following administration of nab-paclitaxel + gemcitabine alone.

Run-in, DDI, and Dose Escalation:

PK parameters for antroquinonol and paclitaxel will be calculated from plasma concentration data collected in Cycle 1 for Cohorts 1 & 2 following administration of a combination of antroquinonol and nab-paclitaxel + gemcitabine.

Expansion Cohort:

PK parameters for antroquinonol only will be calculated from plasma concentration data collected in Cycle 1 following administration of a combination of antroquinonol at the MTD/MFD and nab-paclitaxel + gemcitabine.

For each patient from whom evaluable PK blood samples are collected for the determination of antroquinonol and paclitaxel concentrations, where data allow, the following PK parameters will be calculated based on the plasma concentrations of antroquinonol and paclitaxel and according to the model independent approach using Phoenix WinNonlin (Certara USA Inc., Version 6.4 or higher):

Parameter	Definition	Paclitaxel PK	Antroquinonol PK
C_{max}	maximum observed plasma concentration	C0D1, C0D15, C1D1 & C1D15	C1D1 & C1D15
C_{trough}	trough plasma concentration	NA	C1D1, C1D15 and D1 (predose) of each subsequent cycle
T_{max}	time to maximum observed plasma concentration	C0D1, C0D15, C1D1 & C1D15	C1D1 & C1D15
AUC_{0-t}	area under the plasma concentration-time curve (AUC) from time zero to the last measurable concentration, calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations	C0D1, C0D15, C1D1 & C1D15	C1D1 & C1D15
AUC_{inf}	AUC extrapolated to infinity	C0D1, C0D15, C1D1 & C1D15	C1D1
$\%AUC_{extrap}$	percentage of AUC that is due to extrapolation from the last measurable concentration to infinity	C0D1, C0D15, C1D1 & C1D15	C1D1
AUC_{τ}	area under the plasma concentration-time curve over a dosing interval	NA	C1D1
$AUC_{ss\tau}$	area under the plasma concentration-time curve over a dosing interval at steady state	NA	C1D15
Ratio AUC_{inf}	Ratio of effect on AUC_{inf}, calculated by dividing AUC_{inf} on C1D1 against C0D1; and AUC_{inf} on C1D15 compared to C0D15	C1D1 vs C0D1 and C1D15 vs C0D15	NA
Ratio AUC_{0-t}	Ratio of effect on AUC_{0-t}, calculated by dividing AUC_{0-t} on C1D1 against C0D1; and AUC_{0-t} on C1D15 compared to C0D15	C1D1 vs C0D1 and C1D15 vs C0D15	NA
Ratio C_{max}	Ratio of effect on C_{max}, calculated by dividing C_{max} on C1D1 against C0D1; and C_{max} on C1D15 compared to C0D15	C1D1 vs C0D1 and C1D15 vs C0D15	NA
$t_{1/2}$	apparent terminal elimination half-life, computed as $\ln(2)/\lambda z$ (when applicable)	C0D1, C0D15, C1D1 & C1D15	C1D1 & C1D15

Parameter	Definition	Paclitaxel PK	Antroquinonol PK
λz[a]	apparent terminal elimination rate constant, where λ_Z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase	C0D1, C0D15, C1D1 & C1D15	C1D1 & C1D15
V_z/F	apparent volume of distribution	NA	C1D1 & C1D15
CL/F	apparent oral clearance calculated from either dose /AUC_{inf} (C1D1) or dose/$AUC_{ss\tau}$ (C1D15)	NA	C1D1 & C1D15
Css_{ave}	average plasma concentration at steady state, calculated by $AUC_{ss\tau}/\tau$	NA	C1D15
AR	accumulation ratio, calculated by $AUC_{ss\tau}$ (C1D15)/ AUCτ (C1D1)	NA	C1D15

[a] Additionally, the number of points and the upper and lower time intervals used to estimate λz and the adjusted coefficient for determination of the exponential fit will be presented in a listing; C = cycle; D = day; NA = not applicable; τ = dosing interval.

Additional pharmacokinetic parameters may be determined where appropriate.

Pharmacokinetic analysis will, where possible, be carried out using actual postdose times recorded in the raw data. If actual times are missing, nominal times may be used.

Concentrations will be used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters, with amount or concentration in the unit, will be presented as they are received from the analytical laboratory.

$C_{max,}$ C_{trough} and T_{max} will be obtained directly from the plasma concentration-time profiles.

For multiple peaks, the highest postdose concentration will be reported as Cmax. In the case that multiple peaks are of equal magnitude, the earliest Tmax will be reported.

9.5.1.1 Criteria for Handling Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

Concentration values that are below the limit of quantification (BLQ) will be set to zero, with defined exceptions as follows (exceptions will be noted in the appropriate tables):

- Any embedded BLQ value (between 2 quantifiable concentrations) and BLQ values following the last quantifiable concentration in a profile will be set to missing for the purposes of PK analysis.

- If there are late positive concentration values following 2 BLQ concentration values in the apparent terminal phase, these values will be evaluated. If these values are considered to be anomalous, they will be set to missing.

- If an entire concentration-time profile is BLQ, the profile will be excluded from the PK analysis.

- If predose concentrations for antroquinonol are missing in Cycle 1 Day 1, these values may be set to zero.

9.5.1.2 Criteria for the Calculation of Regression Based Parameters

Number of Data Points

At least 3 data points will be included in the regression analysis and preferably should not include C_{max}.

Goodness of Fit

- When assessing terminal elimination phases, the adjusted coefficient for determination of exponential fit (R^2 adjusted) will be used as a measure of the goodness of fit of the data points to the determined line.

- Regression-based parameters (AUC_{inf}, $t_{1/2}$, λz, CL/F [C1D1] and V_z/F) will only be calculated if the R^2 adjusted value of the regression line is greater than or equal to 0.7.

Period of Estimation

- Where an elimination half-life is estimated over a time period of less than two times the subsequently estimated half-life, it will be flagged in the data listings at the discretion of the Pharmacokineticist, and the robustness of the value discussed in the CSR.

Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification (LLOQ), with at least 1 of these concentrations following C_{max}.

- AUC_{inf} values where the percentage extrapolation is less than 20% will be reported. AUC_{inf} values where the percentage extrapolation is between 20 to 30% will be reported, flagged, and included in the descriptive statistics. AUC_{inf} values where the percentage extrapolation is greater than 30% will be reported and flagged but excluded from descriptive statistics. Parameters affected by $AUC_{inf,}$ such as CL/F and V_z,/F, will be handled the same way as AUC_{inf}.

Anomalous Values

- If a value is considered anomalous because it is inconsistent with the expected PK profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and CSR.
- Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

9.5.2 Presentation of Pharmacokinetic Data

9.5.2.1 Presentation of Pharmacokinetic Plasma Drug Concentration Data

The following rules will be applied if there are values that are BLQ or if there are missing values (eg, no result [NR]) in a plasma concentration data series to be summarized.

- For the calculation of descriptive statistics, BLQ values will be set to zero.
- If an embedded BLQ value is considered anomalous within the concentration-time profile, this value will be excluded from the descriptive statistics.
- Where there is NR, these will be set to missing.
- If there are less than 3 values in the data series, only the minimum, maximum, and N will be presented. The other descriptive statistics will be denoted as not calculated (NC). BLQ is considered a value.
- If all the values are BLQ, then the arithmetic mean, arithmetic standard deviation, median, minimum and maximum will be presented as zero, and the geometric mean, geometric CV%, and arithmetic CV% will be denoted as NC.
- If the value of the arithmetic mean or median is BLQ, it will be presented as zero, and the geometric mean, geometric CV%, and arithmetic CV% will be denoted as NC.

9.5.2.2 Presentation of Pharmacokinetic Parameters

- For the calculation of descriptive statistics of PK parameters, all NR and NC values in a data series will be set to missing.
- The AUC values will be set to NC if they have been calculated using fewer than 3 concentrations, and/or 3 concentrations if the last value is C_{max}.

9.6 Pharmacodynamic Assessment

9.6.1 Pharmacodynamic Analysis

Cancer antigen (CA) 19-9 levels will be assessed.

9.6.2 Pharmacodynamic Statistical Methodology

The CA19-9 data will be summarised by treatment and time point, together with changes from the Cycle 1 assessment.

All CA19-9 data will be listed.

9.7 Safety and Tolerability Assessments

9.7.1 Dose Limiting Toxicity

The number and proportion of patients experiencing DLTs during Cycle 1 for Cohorts 1 and 2 will be assessed on the DLT Analysis Set.

9.7.2 Adverse Events

A baseline sign and symptom is defined as an AE that starts after the patient has provided written informed consent and that resolves prior to the first dosing occasion of any study medication, or an AE that starts prior to the first dosing occasion and does not increase in severity after dosing. A treatment-emergent AE (TEAE) is defined as an AE that occurs postdose or that is present predose and becomes more severe postdose.

All AEs will be listed.

The AEs occurring in the baseline period will be summarised by the treatment the patient will receive on the study, Common Terminology Criteria for Adverse Events (CTCAE) version 4 grade, and relationship to the product(s). An overall summary will also be produced for the AEs occurring in the baseline period.

The frequency (the number of AEs, the number of patients experiencing an AE, and the percentage of patients experiencing an AE) of AEs will be summarised by treatment and by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. The summary and frequency AE tables will be presented for all causalities and for those AEs considered related to the product (those that have a relationship of possibly related or probably related). Any serious AEs will be tabulated as will any AEs leading to withdrawal. For any AEs that change CTCAE grades the AE will be included only once under the maximum severity rating in the summaries.

Summaries of AEs will also be produced for NCI CTCAE Grade ≥3 TEAEs, NCI CTCAE Grade ≥3 TEAEs related to the study treatment, AEs leading to withdrawal, AEs requiring dose modifications, and AEs requiring interruption of the study treatment or discontinuation of the study treatment.

Onset times postdose are calculated from the time of the previous dose of antroquinonol for all subjects apart from those in Cohort 1 at Cycle 0. For this cohort and cycle onset times postdose are calculated from the time of the start of the previous infusion.

The TEAE summary tables will include counts of patients. Therefore, if a patient experiences more than one episode of a particular AE, the patient will be counted only once for that event. If a patient has more than one AE that is coded to the same preferred term, the patient will be counted only once for that preferred term. Similarly, if a patient has more than one AE within a system organ class, the patient will be counted only once in that system organ class. In addition

if an AE changes in CTCAE grade then the AE will only be summarised under the highest CTCAE grade.

9.7.3 Concomitant Medications

All concomitant medication will be listed.

9.7.4 Clinical Laboratory Parameters

Laboratory test variables will be summarized by treatment and visit (if applicable) using descriptive statistics (number of patients, mean, standard deviation, minimum, maximum, as well as mean change from baseline, standard deviation for mean and standard error for mean change, minimum, median, maximum, and number and percent of patients within specified categories). Shift tables (ie, cross-tabulations of below the lower limit of the normal range, within the limits of the normal range and above the upper limit of the normal range at baseline versus scheduled visits) will be presented by laboratory test (if applicable). Laboratory tests with categorical results that cannot be analyzed by change from baseline or shift table analysis will not be included in these summaries, but will be listed. Data obtained from laboratory tests not required by the protocol will not be summarized, but will be listed.

Any laboratory values reported as AEs will be summarised within the AE tables.

Values for any serum biochemistry, haematology, and urinalysis values considered clinically significant will be flagged on the individual patient data listings.

9.7.5 Vital Signs

The vital signs data will be summarised by treatment and time point.

All vital signs data will be listed.

9.7.6 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the, the QT interval calculated using the Fridericia correction (QTcF), the PR, RR, and QT intervals, the QRS duration, and heart rate.

For the triplicate ECGs taken at screening the mean value will be calculated prior to summarising the data.

The ECG data will be listed and summarised by treatment and time point.

9.7.7 Physical Examination

The physical examination data will be listed.

9.7.8 ECOG Performance Scale

The ECOG performance scale collected after screening will be listed and summarised.

9.7.9 Other Assessments

All other safety assessments not detailed in this section will be listed but not summarised or statistically analysed.

9.7.10 Safety and Tolerability Statistical Methodology

No inferential statistical analyses are planned on the safety data.

9.8 Efficacy Assessment

The RECIST 1.1 criteria will be used to assess patient response to treatment by determining objective response rate (ORR), duration of response (DoR), disease control rate (DCR), PFS, PFS 3 months, and PFS 6 months. The RECIST 1.1 guidelines for measurable, non-measurable, target, and non-target lesions and the objective tumor response criteria (complete response [CR], partial response [PR], stable disease [SD], or PD) are presented in Appendix C, Section 12.3 of the protocol. The overall survival (OS), OS 3 months to OS 24 months will also be evaluated.

The baseline tumor assessments should be performed no more than 28 days before start of study treatment and ideally should be performed as close as possible to the start of study treatment. Efficacy for all patients will be assessed by objective tumor assessments at Screening, every 8 weeks for the first 48 weeks relative to the first antroquinonol dose, and every 12 weeks thereafter up to and including 24 cycles until unacceptable toxicity or disease progression. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at his or her scheduled visits.

A confirmatory scan is required following the initial demonstration of PD. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment will continue between the initial assessment of progression and confirmation for progression. If a patient discontinues treatment (and/or receives a subsequent anti-cancer therapy) prior to progression, then the patient should still continue to be followed until confirmed objective disease progression.

Objective tumor response (CR or PR) should be confirmed preferably at the next scheduled visit and not less than 4 weeks after the visit when the response was first observed. Following confirmed progression, patients should continue to be followed up for survival every 8 weeks as outlined in the follow-up schedules of assessments (see Table 8-3 of the protocol). In addition, all patients will be contacted in the week following data cutoff to confirm survival status.

9.8.1 Statistical Analysis of Efficacy Assessments

Descriptive summaries of patients with best overall response in each category (CR, PR, SD, and PD); the ORR (CR+PR); the DCR (CR+PR+SD [SD of ≥16 weeks]) with 95% CIs according to RECIST 1.1 will be provided for Efficacy Analysis Set.

RECIST 1.1 will be performed for median OS time and PFS time with 95% CI will be evaluated using Kaplan-Meier[3] methods on Full Analysis Set. The OS is defined as the time from first dose of study drug to patient death. The PFS is defined as the time from first dose of study drug to the start of disease progression or patient death, whichever occurred first. The overall response rate and the DCR by dose level will be estimated along with 95% CIs calculated using the method of Clopper and Pearson[4].

The longest diameter from the tumor assessments post-treatment and changes from baseline (Screening) will be listed and summarised.

9.8.2 Subgroup Analysis

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, sub-group analysis based on C-reactive protein levels (≤ 10 mg/L and > 10 mg/L) at baseline will be performed.

10 INTERIM ANALYSES

11 GIVEN THE HYPOTHESIS-GENERATING NATURE OF THIS STUDY, THE SPONSOR MAY CHOOSE TO CONDUCT OPTIONAL INTERIM ANALYSES.CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol-specified statistical analyses.

12 DATA PRESENTATION

13.1 Insufficient Data for Presentation

Some of the TFLs may not have sufficient numbers of patients or data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, “No serious adverse events occurred for this study.”

13 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

3. Kaplan, E. L.; Meier, P. (1958). Nonparametric estimation from incomplete observations. J. Amer. Statist. Assn. 53 (282): 457–481.

4. Clopper, C.; Pearson, E. S. (1934). The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 26: 404–413.

Type of Approval (select one) : ☒ **SAP** ☐ **Initiation of Programming SAP** ☐ **SAP Addendum**

Sponsor Name:	**Golden Biotechnology Corporation**		
Sponsor Protocol/ CIP ID:	**GHPanc-1-001**	**Fortrea Study ID:**	**COV000000155726**
SAP text filename:	**GHPanc-1-001_SAP_Final 2.0**		
TFL shells filename:	**GHPanc-1-001_TFL_shells_Final 2.0**		
Version:	**Fianl v2**	**Date:**	**20SEP2023**

Fortrea Approval(s):

Lead Statistician

Approval Signature **Print Name** **Date**	DocuSigned by Tao Bian Tao Bian I am the author of this document 25 Sep 2023 | 5:48:29 PM EDT C76A2810AE064F1D92B26802B9464EE3

<Amend accordingly if required>

Approval Signature **Print Name** **Date**	

Sponsor Approval(s):

By signing below when the statistical analysis plan (SAP) is considered final, the signatories agree to the analyses to be performed for this study and to the format of the associated tables, figures, and listings (TFLs). Once the SAP has been signed, programming of the Analysis Dataset Model (ADaM) datasets and TFLs based on these documents can proceed. Any modifications to the SAP text and TFL shells made after signing may result in a work-scope change.

Approval Signature **Print Name** **Date**	 Howard Cheung 16 Sep 2025

<Amend accordingly if required>

Approval Signature **Print Name** **Date**	