STATISTICAL ANALYSIS PLAN (SAP)

A Trial Evaluating Escalating Doses and the Safety of Intracystic Injection of NanoPac® in Subjects with Mucinous Cystic Pancreatic Neoplasms

Protocol Number:	NANOPAC-2017-01	**Study Phase**
Trial Design:	Open-label, Dose Escalation Study including both a Dose-Escalation Phase (Single Dose) and a Second Phase (Two Doses)	
Medication/dosage:	NanoPac® (Sterile Nanoparticulate Paclitaxel) Powder for Suspension at concentrations of 6, 10, and 15 mg/mL administered into the cyst within the pancreas via endoscopic ultrasound-guided fine needle injection (EUS-FNI) at a volume equal to the volume of cyst fluid aspirated	
Population	Up to 30 subjects with mucinous cystic pancreatic neoplasms	
Study/Treatment duration:	Up to 24 months	

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Version: Final

Date: 21-Aug-2020

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Date of Final Protocol (including all amendments)	13-Dec-2018 (Version 3.1) 01-FEB-2018 (Version 2.0) 15-JUN-2017 (Version 1.1) 02-MAY-2017 (Version 1.0)

Date of Final Plan: 21-Aug-2020

I have reviewed the Statistical Analysis Plan. My signature below confirms my agreement with the contents and intent of this document.

Digital Signatures

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Reviewed by:

Shelagh Verco Director Clinical Trials US Biotest	Date (dd-mmm-yyyy)
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LIST OF ABBREVIATIONS

Abbreviations

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse Event
APR	Analysis Programming Requirements - detailed programming specifications required to convert the EDC data into analysis/presentation data sets.
ATC	Anatomical Therapeutic Chemical Classification System
BLQ	Below the Limit of Quantification / Below Limit of Quantitation
BMI	Body Mass Index
CEA	Carcinoembryonic Antigen
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
DLC	Data Logic Check- A combination of programmed and visual checks based on the CRF, protocol, and sponsor input, designed to identify incomplete or illogical data.
DLT	Dose-Limiting Toxicities
DMP	Data Management Plan - details of how data are managed throughout the trial
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form

Abbreviation	**Definition**
EDC	Electronic Data Capture
EUS-FNA	Endoscopic Ultrasound-Guided Fine Needle Aspiration
EUS-FNI	Endoscopic Ultrasound-Guided Fine Needle Injection
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities (coding for AEs)
MRCP	Magnetic resonance cholangiopancreatography
MRI	Magnetic resonance imaging
MSL	McDougall Scientific Ltd - CRO contracted to perform the data management, statistical programming and analysis functions
PK	Pharmacokinetics
PT	Preferred Term (from MedDRA coding dictionary)
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	System Organ Class (from MedDRA coding dictionary)
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary

1 BACKGROUND

In this open-label, dose rising trial of NanoPac (Sterile Nanoparticulate Paclitaxel), subjects with mucinous cystic pancreatic neoplasms will receive intracystic NanoPac via endoscopic ultrasound-guided fine needle injection (EUS-FNI). This study will include a dose escalation phase and a second phase.

In the dose escalation phase, subjects will be enrolled in sequential cohorts of NanoPac at 6, 10, and 15 mg/mL at volumes sufficient to fill the cyst, at least equal to the amount of cyst fluid aspirated. Each cohort will have three subjects, with cohorts enrolled sequentially starting at the lowest concentration. Following Data Safety Monitoring Board (DSMB) review of the cohort data, the next cohort may begin enrolling, an additional three at the current dose may be enrolled, or if the first dose does not provide adequate safety and tolerability the study may be halted. The dose determined to be the most suitable for further evaluation, defined as the highest dose with an acceptable safety and tolerability profile (as determined by the DSMB), will be the dose used in the second phase of the study which will enroll 9 additional subjects. Subjects enrolled in the second phase of the study will also receive a second injection of NanoPac at the same dose 12 weeks after the first NanoPac injection.

Subjects will be followed for 6 months after the first NanoPac injection for safety, tolerability, and cyst response to therapy (as shown by imaging). Cyst fluid will also be extracted and analyzed for cyst fluid markers.

2 OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of NanoPac injected directly into mucinous cystic pancreatic cysts by endoscopic ultrasound-guided injection.

2.2 Secondary Objectives

The secondary objectives are: (a) to describe the pharmacokinetics (PK) of NanoPac when administered into the cyst within the pancreas; (b) to determine whether any of the NanoPac concentrations (6, 10, or 15 mg/mL) show signs of preliminary efficacy; and (c) to determine if the selected dose from the escalation phase shows signs of preliminary efficacy when injected on two occasions 12 weeks apart.

3 STUDY DESIGN AND ENDPOINTS

3.1 Study Design

In this open-label trial, up to 30 subjects with mucinous cystic pancreatic neoplasms will have undergone endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) as part of Standard of Care (SOC). Once there is a diagnosis and confirmation of mucinous cystic pancreatic neoplasm, subjects will receive intracystic NanoPac via ultrasound-guided fine needle injection (EUS-FNI). Subjects will be followed for cyst response to therapy (as shown by imaging) and concentration of paclitaxel in the systemic circulation post-injection (as determined by PK analysis).

The study will include a dose escalation phase and a second phase.

In the dose escalation phase, subjects will be enrolled in sequential, escalating cohorts of NanoPac at concentrations of 6, 10, or 15 mg/mL injected directly into the cyst within the pancreas at a volume sufficient to fill the cyst, at least equivalent to the amount of fluid removed from the cyst.

In the second phase, subjects will receive two injections of NanoPac 12 weeks apart at the dose selected in the dose escalation phase.

Cyst Volume Calculations

If more than one cyst is present in the pancreas of a subject, the Investigator will select a single target cyst and will treat only this target cyst. The single target cyst must have a diameter of at least 1.5 cm and no more than 4 cm; the diameter will be measured at the widest point of the cyst. In the dose escalation phase, imaging with magnetic resonance cholangiopancreatography (MRCP), CT scan, or FDG-PET will be used prior to enrollment to visualize and measure the cyst to confirm subject eligibility; the same imaging modality used prior to enrollment will be repeated at the Week 12 and Week 24 time points.

In the second phase of the study, a CT scan will be performed between the Screening visit and Day 1 to obtain a baseline image against which future CT scans (at the Week 12 and Week 24 time points) will be compared. The CT scan at Week 12 will be performed prior to NanoPac injection, however the exact cyst diameter (three dimensional) will be based on measurements performed with endoscopic ultrasound during the NanoPac injection procedure. Injection volume will be at least equal in volume to the amount of fluid removed from the cyst, but may be a larger volume to fill the cyst as determined visually by the Investigator during the endoscopic ultrasound procedure. The exact volume administered to the cyst will be documented in the source.

Dose Escalation of Cohorts

In the dose escalation phase, cohorts will be enrolled sequentially starting at the lowest dose (6 mg/mL). Each cohort will have a planned minimum of three subjects. All data from the first three subjects in a cohort will be reviewed and evaluated by the DSMB to determine whether the dose received is considered safe and tolerable, and to determine if dose escalation may occur. The DSMB will review the data on the three subjects once they have completed the two-week follow-up visit, and will assess safety and tolerability based on the DSMB Charter, which will include reference to dose-limiting toxicities (DLT). Safety and tolerability parameters which will be used to determine whether escalation may proceed are outlined in Section 6.1.7. The DSMB will determine whether to: (a) escalate to the next dose level cohort (no DLT); (b) add three additional subjects to the current cohort (one DLT); or (c) return to the previous (lower) dose cohort and expand by three subjects (more than one DLT).

The dose most suitable for further evaluation will be the highest dose with an acceptable safety and tolerability profile as determined by the DSMB. If one or fewer subjects in a six-subject cohort, or no subjects in a three-subject cohort at the highest dose, experience a DLT, that cohort may be taken into the second phase. If greater than one subject in a six-subject cohort experience a DLT, the previous dose may be taken into the second phase.

Second Phase

Once the dose deemed appropriate for expansion and further evaluation has been determined by the DSMB, an additional 9 subjects will be enrolled at that dose level. Subjects in the second phase will also receive a second NanoPac injection to their cyst (at the same dose) 12 weeks after the first NanoPac injection. If any subject has a CT Scan following the first NanoPac injection and the cyst cannot be identified/visualized (at Week 12) the subject will not have a second injection and will be followed-up at Week 24 to obtain a CT Scan; visits between Week 12 and Week 24 will not be required for these subjects.

3.2 Primary Endpoint

The primary endpoint will be safety and tolerability, as assessed by AE, changes in vital signs, laboratory results, and physical examination at four weeks following NanoPac injection. Safety and tolerability will continue to be assessed until the end-of-study visit.

3.3 Secondary Endpoints

The secondary endpoints will be:

- Concentration of paclitaxel in the systemic circulation post-injection (as determined by PK analysis);
- Cyst volume response (imaging).

3.4 Study Timeline and Schedule of Events

3.4.1 Schedule of Events Table – Dose Escalation Phase

	Screening[7]	Day 1 (Injection)[8]	Week 1 (±1 day)	Week 2 (±2 days)	Week 4 (±2 days)	Week 8 (±1 week)	Week 12 (±1 week)	24 Weeks/ 6 Months (±2 weeks)
Informed Consent	X							
History[1]	X							
Concomitant therapy	X	X	X	X	X	X	X	X
Physical Exam[2]	F	T	T	T	F	T	T	T
ECOG[3]	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X
Hematology, Biochemistry, and Urinalysis	X	X	X	X	X	X	X	X
Cyst fluid CEA		X						
PK Samples[4]		X	X	X	X	X	X	X
Imaging[5]							X	X
NanoPac[6]		X						
Adverse Events		X	X	X	X	X	X	X

1 History includes all events before initiation of NanoPac treatment.
2 F = Full Physical Exam; T = Targeted Physical Exam
3 ECOG Performance Status Scale attached as Appendix A.
4 PK Samples on Day 1 will be drawn at 1 and 2 hours post-dose, PK samples will also be obtained at each study visit thereafter.
5 Imaging with MRCP, CT scan, or FDG-PET will occur prior to Screening to confirm size of mucinous cystic pancreatic neoplasm. The same imaging modality used to confirm eligibility will be repeated at Week 12 and Week 24. Additional imaging may be performed at the Investigator's discretion as per institutional SOC and all resulting images will be collected for the subject's record. Should the subject withdraw from the study at any time, a scan will be conducted as part of the end-of-study procedures.
6 Prophylactic antibiotics will be administered prior to NanoPac injection; NanoPac will be administered by endoscopic ultrasound-guided fine needle injection.
7 Screening will occur up to four weeks prior to injection.
8 There is a 10-minute window (±10 minutes on either side) around samples taken within the first 2 hours during Day 1 (injection).

3.4.2 Schedule of Events Table – Second Phase

	Screening[7]	Day 1 (Injection)	Week 1 (±1 day)	Week 2 (±2 days)	Week 4 (±2 days)	Week 8 (±1 week)	Week 12 (±1 week)	Week 14[9] (±2 days)	Week 16[9] (±2 days)	Week 24/ 6 Months (±1 week)
Informed Consent	X									
History[1]	X									
Concomitant therapy	X	X	X	X	X	X	X	X	X	X
Physical Exam[2]	F	T	T	T	F	T	T	T	T	T
ECOG[3]	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X
Hematology, Biochemistry, and Urinalysis	X	X	X	X	X	X	X	X	X	X
Cyst fluid CEA		X					X[8]			
PK Samples[4]		X	X	X	X	X	X	X	X	X
Imaging[5]	X						X			X
NanoPac[6]		X					X			
Adverse Events		X	X	X	X	X	X	X	X	X

1 History includes all events before initiation of NanoPac treatment.
2 F = Full Physical Exam; T = Targeted Physical Exam
3 ECOG Performance Status Scale attached as Appendix A.
4 PK Samples on Day 1 and Week 12 will be drawn at 1 and 2 hours post-dose. PK samples will also be obtained at each study visit thereafter. There is a 10-minute window (±10 minutes on either side) around samples taken within the first 2 hours during Day 1 (injection) and Week 12.
5 Imaging with CT scan will occur during the Screening period (prior to NanoPac administration), and at Week 12 and Week 24. Should the subject withdraw from the study at any time, a scan will be conducted as part of the end-of-study procedures.
6 Prophylactic antibiotics will be administered prior to NanoPac injection; NanoPac will be administered by endoscopic ultrasound-guided fine needle injection.
7 Screening will occur up to four weeks prior to first injection.
8 If sufficient sample is obtained, in addition to CEA analysis the fluid will be evaluated for presence of paclitaxel
9 Week 14 and Week 16 visits should be 2 weeks and 4 weeks after the second injection; all other visits are scheduled from Day 1.

4 DATA MANAGEMENT

4.1 Data Collection and Database Construction

Data will be collected at the sites via an electronic data capture (EDC) system. The study-specific application will be developed based on the protocol requirements and following the full Systems Development Lifecycle (SDLC). The development and management of the trial application, including security and account administration, will adhere to the Standard Operating Procedures (SOPs) at McDougall. All participants will be trained in the use of the application, and the training documented prior to each site being initiated.

The application design will, where appropriate, provide choice fields in the form of checkboxes, buttons and lists to aid in ensuring high quality standardized data collection. In addition, Data Logic Checks (or data Edit Checks) will be built into the application based on variable attributes (e.g. value ranges), system logic (e.g. sequential visit dates) and variable logic (e.g. onset date must be before cessation date). Visual review and data responses will be overseen by a trained data manager.

The database will be locked when all the expected data has been entered into the application, all query responses have been received and validated, the designated data has been noted as monitored in the system and each investigator has signed off the casebook for each of their study subjects. The data coding must be accepted by the Sponsor and any Serious Adverse Events (SAEs) reconciled with the pharmacovigilance data base working with the Medical Monitor.

The data management processes are outlined in the project specific Data Management Plan (DMP). DMP and all related documentations are on file at McDougall and are identified by the project code NA04NAG.

All programming will be performed in SAS version 9.4.

4.2 Coding

Adverse Events and medical history will be coded in MedDRA version 20.0 or the most current version of MedDRA at the beginning of coding process, and signed off by US Biotest, Inc.

All concomitant medications will be coded using WHO Drug Dictionary version March 1, 2017 or the most current version of WHODD at the beginning of coding process.

All coding will be reviewed and signed off by the Medical Monitor or designee prior to data base lock.

4.3 Pharmacokinetics (PK) Data

The PK analysis of plasma paclitaxel concentration will be performed by Covance Inc. The concentration data will be provided to McDougall in Excel data sheets to be read into SAS system for descriptive summaries.

4.4 Adverse Events of Special Interest

Following AEs are of special interest to the sponsor and will be analyzed separately:

> Vomiting, Peritonitis, Retroperitoneal bleeding, Abscess formation, Fistula formation, Gastrointestinal bleed, Neutropenia, Abdominal pain, Pancreatitis, Neutropenic fever, Sepsis, Thrombocytopenia, Anemia.

After all AEs are recorded in EDC, the sponsor will review the AE list and highlight all AEs of Interest.

5 CHANGE TO ANALYSIS AS OUTLINED IN THE PROTOCOL

According to the Protocol, in addition to the summaries of TEAEs for whole study period, where possible and relevant, the TEAEs will also be summarized by different time frames (e.g. first 24 hours, up to Day 7).

In consideration of the objective of this analysis, the AE summarized by time frame will be limited to the TEAEs of Second Phase subjects with two injections. For those subjects, two additional TEAE summaries will be provided based on AE onset time: 1) onset before the second injection and, 2) onset on or after the second injection.

6 STATISTICAL METHODS

Descriptive summaries of continuous data will consist of the mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized with frequencies and percentages. All data will be listed by subject and treatment. This study was not powered for inference; therefore, no inferential analysis will be included.

6.1 Sample Size

There is no formal sample size calculation for this safety study. However, to provide a reference for the ongoing safety review of each cohort and the possible expansion of a cohort with safety concerns, nQuery Advisor (version 6) employing the procedure “confidence interval for the probability of observing a rare event” determined that, for an event with an occurrence rate of 0.33, the probability of detecting it with 3 subjects is

69.9% vs 91.0% for 6 subjects and for an event rate of 0.05 the probability of detecting the event was 14.3% and 26.5% for 3 and 6 subjects respectively.

6.2 Missing Data

Data will be presented as observed and no missing data imputation will be performed. All effort will be made to capture sufficient information to allow for medical interpretation of the results.

6.3 Data Conversion for Analysis

In order to summarize quantitative endpoints, e.g. lab test results, some data collected as text values need to be converted to numeric values for analysis. Following conventional rules will be applied for this study.

- All "< xx" lab results will be converted to 0.99 * xx. The adjustment is -1% of xx.
- All "> xx" lab results will be converted to 1.01 * xx. The adjustment is +1% of xx.
- Some PK concentration values may be marked as Below the Limit of Quantification (BLQ) or reported as "< xx". Here xx is the Lower Limit of Quantitation (LLOQ). For the summary of paclitaxel concentration in this study, all BLQ values will be set to 0.

Above data conversions are only applied to data descriptive summaries. In by-subject data listings, original reported data "< xx", "> xx", or "BLQ" will be presented.

For this study's data submission and analysis, all EDC and external data will be converted to SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model) datasets. In the creation of SDTM and ADaM datasets, original lab test results from different sites (laboratories) need to be converted to results in SI units (the International System of Units). For some tests, data rounding may be applied during the conversion. The details will be provided in SDTM and ADaM's define.xml files and their support documents.

6.4 Calculated Outcomes

The following are key endpoints derived from data captured at the sites via the EDC system. Complete documentation of the calculations and data manipulation required to go from the CRF database to the analysis database are contained in the companion document - the study Analysis Programming Requirements (APR).

Outcome	Calculation	Comment
Study Day	= the days from Day 1 (Injection Date) to the event date	
Time in Trial (days)	= Study completion/withdrawal date – date of informed consent date + 1 day	

Outcome	Calculation	Comment
Baseline value	= Value reported prior to treatment injection	If multiple values collected prior to treatment injection, non-missing value closest to the date/time of treatment injection is considered as baseline value
Change from Baseline	= Value collected at time point (Visit) – Baseline value	
BMI	= 10000 * (Weight in kg) / (Height in cm)^2	Value will be rounded to keep one decimal point
Treatment Emergent Adverse Event (TEAE)	= No, if onset date/time AE is before the date/time of NanoPac injection = Yes, otherwise	According to conservative rule, all AEs that cannot be determined as started before NanoPac injection will be considered as TEAE
Tumor Volume	= 1/6 * π * (d_1 * d_2 * d_3), if three tumor diameters d_1, d_2, and d_3 are recorded = 1/6 * π * (d_1^2 * d_2), if only two tumor diameters d_1 and d_2 are recorded, where $d_1 \geq d_2$ = 1/6 * π * (d_1^3) if only one tumor diameter d_1 is recorded.	This calculated tumor volume will be used in efficacy analysis (section 7.3.2). EDC captured tumor volume, if non-missing, will be presented in data listing

6.5 Analysis Population

All enrolled subjects who receive NanoPac injection will be the analysis population for all outcome analyses.

6.6 Interim Analysis/ Data Monitoring

A formal interim analysis is not planned. However, there will be ongoing data review and report preparation for the DSMB as outlined in the DSMB Charter.

6.7 Analysis Methods

All calculations and analyses will be performed using SAS version 9.4 under the Windows Server 2012R2 operating system at McDougall Scientific Ltd. in Toronto, Canada.

Continuous data will be summarized via PROC MEANS - mean, standard deviation, median, and range, while categorical data will be presented as counts and percentages (or proportions) via PROC FREQ for the descriptive displays.

All outcomes will be summarized by cohort (dose level), and visit, if applicable. Outcomes of two study phases will be summarized separately because of the differences of treatment and visit schedules.

No statistical inference will be made for all outcomes.

7 RESULTS

All enrolled and treated subjects will be the analysis population for all analyses. All data collected in EDC will be at a minimum listed.

All summaries will be presented by cohort, i.e., NanoPac concentration level.

Because of the extra NanoPac injection and the different visit structures, all safety and efficacy outcomes of the second phase subjects will be summarized separately.

The eligibility data of screen failures will be presented in a separate listing.

7.1 Study Subjects

7.1.1 Patient Disposition

All enrolled and treated subjects will be accounted for. All early discontinuations will be summarized by primary reason of discontinuation.

Time in trial will also be summarized.

7.1.2 Demographics and Baseline Characteristics

Demographic (age, sex, ethnicity, and race), baseline body measurements (height, weight, and calculated BMI), and baseline vital signs (systolic and diastolic blood pressures, heart rate, and temperature) will be summarized.

7.1.3 Medical History

Medical history will be coded in MedDRA and presented in by-cohort tables by System Organ Class (SOC) and Preferred Term (PT).

7.1.4 Pregnancy Test

Pregnancy test will be conducted at Screening Visit. For female subjects, the childbearing potential (yes/no), the date of pregnancy test and test result will be listed.

7.1.5 NanoPac Administration

NanoPac administration data at study Day 1 and Week 12 (second phase subjects only), including administration date, time, dose level, will be listed. Cyst diameters measured by ultrasound, cyst volume, volume of cyst fluid aspirated, and volume of NanoPac administrated will be summarized by cohort.

7.1.6 Cyst Fluid CEA

According to inclusion criteria, pre-screening cyst fluid CEA analysis should be performed for all enrolled subjects. Prior to NanoPac injection(s) on Day 1 and Week 12 (second phase subjects only), cyst fluid is aspirated and analyzed for CEA.

All CEA results will be summarized by visit and cohort.

7.2 Primary Outcomes

The primary endpoint will be safety and tolerability, as assessed by AE, changes in vital signs, laboratory results, and physical examination at one month following the completion of NanoPac administration, i.e., at Week 4 for dose escalation phase subjects and at Week 16 for the second phase subjects. Safety and tolerability will continue to be assessed until the six month end-of-study visit.

All primary outcomes will be descriptively summarized. No statistical inference will be made for primary endpoint.

7.2.1 Adverse Events

Only treatment emergent adverse events (TEAEs) will be summarized. Summaries will be provided by dose level cohort, and include:

- Summary of TEAEs - include the total number of TEAEs, serious TEAEs, DLT, and death
- TEAEs by MedDRA System Organ Class (SOC) and Preferred Term (PT)
- TEAEs by MedDRA SOC, PT, and severity
- TEAEs by MedDRA SOC, PT, and relationship to NanoPac treatment
- TEAEs by MedDRA SOC, PT, and outcome
- Serious TEAES by MedDRA SOC, and PT
- Unexpected TEAEs by MedDRA SOC and PT, if enough data available

Adverse events of special interest will be presented, separately, by dose level cohort, SOC and PT.

All these summaries will include the counts and frequencies of events, and of subjects who had events.

For second phase subjects with two injections, additional TEAE summaries will be presented for two time-frames: onset prior and post the 2nd injection.

All TEAEs will be listed by subject. Death and other serious TEAEs will be listed separately.

7.2.2 Vital Signs

Vital Signs (weight, BMI, systolic and diastolic blood pressure, heart rate, and temperature) will be summarized by dose level cohort and visit.

Change of vital signs (weight, BMI, systolic and diastolic blood pressure, heart rate, and temperature) from baseline values will be summarized for all post-injection visits.

Unscheduled vital signs will only be presented in by-subject listing.

7.2.3 Laboratory Assessments

Laboratory assessments with quantitative results, including raw assessments at each visit and change from baseline at post-baseline visits, will be summarized by dose level cohort, and visit for each test.

Each no-missing lab result's normal/abnormal status (e.g. normal/low/high for quantitative results, and normal/abnormal for qualitative results) will be calculated based on the normal reference ranges provided by the lab. The status will be summarized using shift tables from baseline to each post-baseline time point.

All lab data will be presented in by-subject data listing.

Following lab tests are required for the study:

Chemistry: Sodium, potassium, chloride, carbon dioxide (CO2), calcium, phosphorus, glucose, blood urea nitrogen (BUN), creatinine, serum lipase, serum amylase, alkaline phosphatase, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total protein, albumin, triglycerides, cholesterol, and uric acid;

Hematology: Red blood cell count (RBC), hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell count (WBC) including differential, reticulocyte count, and platelet count;

Urinalysis: Specific gravity, hydrogen ion concentration (pH), RBC, WBC, protein, and glucose;

Coagulation: Prothrombin time (PT) and activated partial thromboplastin time (PTT).

7.2.4 Physical Examination

All abnormal findings from the physical examination after study treatment will be recorded as AEs. The analysis of physical examination will be included in AE summaries.

7.3 Secondary Outcomes

7.3.1 Plasma Paclitaxel Concentration

Two PK samples for paclitaxel concentration are collected on each injection day, i.e. Day 1 for dose escalation subjects and Day 1/Week 12 for second phase subjects, at 1 and 2 hours post-injection. One PK sample is collected at each post-baseline visit. All concentration data will be descriptively summarized.

All BLQ values will be set as 0 in doing the summaries. Original value “BLQ” will be used in data listings.

If applicable, paclitaxel concentration data will be graphed for individuals and by dose group. BLQ values will be displayed as 0 in the graphs.

7.3.2 Cyst Responses

Cyst diameter and volume are measured by imaging (Magnetic resonance cholangiopancreatography (MRCP), CT scan, Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET), MRI, Ultrasound, or other imaging methods) at Screening Visit, Week 12 Visit and Week 24 Visit. The size and calculated volume of target cyst and changes of from baseline will be tabulated by dose level cohort.

Spaghetti plots of visit vs. target cyst volume will be provided. If applicable, different dose levels, and gender will be indicated on the plots.

All cyst data will be presented in the by-subject data listings. Gender and baseline CEA will be included in the listings.

7.4 Other Outcomes

7.4.1 Eastern Cooperative Oncology Group (ECOG)

Eastern cooperative oncology group (ECOG) performance status scale will be obtained at all study visits.

ECOG scale will summarized as frequencies by treatment group and visit.

7.4.2 Prior and Concomitant Medications

A summary of all concomitant medications taken during the course of the study will be presented in tabular form by therapeutic drug class (ATC Level 2 code) and generic drug name (ATC Level 4 code) using the World Health Organization (WHO) Drug Dictionary

(WHODD). The summaries will be provided for medications prior to and following the injection separately.

7.4.3 Concomitant Procedures

All concomitant procedures performed during the study will be listed.

Appendix A: ECOG Performance Scale

Patient performance status will be graded according to the Eastern Cooperative Oncology Group (ECOG) scale* as described below.

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

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