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

Protocol Identifying Number: NANOPAC-2017-01

IND Sponsor: NanOlogy, LLC

IND #: 132692

Version Number: 4.0

Dated: 3 September 2019

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASP	Aspartate Aminotransferase
ASP	Alkaline Phosphatase
BUN	Blood Urea Nitrogen
CEA	Carcinoembryonic Antigen
CLIA	Clinical Laboratory Improvement Amendments
CO2	Carbon Dioxide
CRO	Clinical Research Organization
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture System
eCRF	Electronic Case Report Form
EUS-FNA	Endoscopic Ultrasound-Guided Fine Needle Aspiration
EUS-FNI	Endoscopic Ultrasound-Guided Fine Needle Injection
FDA	The U.S. Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
Hct	Hematocrit
Hgb	Hemoglobin
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IP	Intraperitoneal
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate Dehydrogenase
MAC	Monitored Anesthesia Care
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MRCP	Magnetic resonance cholangiopancreatography
NCI	National Cancer Institute
NDA	New Drug Application
OHRP	Office for Human Research Protections
PCA	Precipitation with Compressed Antisolvents
PI	Principal Investigator
PK	Pharmacokinetics
PT	Prothrombin Time
PTT	Activated Partial Thromboplastin Time

RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDLC	Systems Development Life Cycle
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
UP	Unanticipated Problem
USC	University of Southern California
WBC	White Blood Cell

SPONSOR SIGNATURE PAGE

Protocol Title:	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
Version Number:	4.0
Date:	3 September 2019
IND Number:	132692
Investigational Product:	NanoPac® (Sterile Nanoparticulate Paclitaxel) Powder for Suspension
Sponsor:	NanOlogy, LLC. 3909 Hulen St Fort Worth, TX 76107

The Sponsor for IND 132692, NanOlogy, LLC, has transferred responsibility for all obligations set forth in 21 CFR Part 312 to US Biotest, Inc., with regard to the IND; in accordance with 21 CFR Part 312, US Biotest, Inc., shall be considered the sponsor with regard to all activities related to the IND.

SIGNATURE

Sponsor's Representative - Name and Title:
Gere diZerega, MD
President & CEO, US Biotest, Inc.

Gere diZerega
Gere diZerega (Sep 9, 2019)

Signature of Sponsor's Representative

Sep 9, 2019

Date

STATEMENT OF COMPLIANCE

I have read the attached protocol number NANOPAC-2017-01 entitled, *A Trial Evaluating Escalating Doses and the Safety of Intracystic Injection of NanoPac® in Subjects with Mucinous Cystic Pancreatic Neoplasms*, Version 4.0 dated 3 September 2019 and agree to comply with the contents of this document.

I agree to comply with applicable FDA regulations and guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.

This document is a confidential communication of NanOlogy, LLC. The recipient agrees that no unpublished information contained herein will be published or disclosed without prior written permission of NanOlogy. However, this document may be disclosed to appropriate institutional review boards, ethics review committees, or authorized representatives of the Investigator or of boards of health under the condition that they are requested to respect the confidentiality of the document.

The signature of the Principal Investigator below constitutes his/her agreement.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

PROTOCOL SUMMARY

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

Précis: 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).

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.

Plasma samples will be taken on the day(s) of NanoPac injection at 1 and 2 hours after injection, as well as at each of the subsequent study visits, to characterize the pharmacokinetics (PK) of intracystic NanoPac.

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.

Objectives: Primary objective:

- To evaluate the safety and tolerability of NanoPac injected directly into mucinous cystic pancreatic cysts by endoscopic ultrasound-guided injection.

Secondary objectives:

- To describe the pharmacokinetics of NanoPac when administered into the cyst within the pancreas;
- To determine whether any of the NanoPac concentrations (6, 10, or 15 mg/mL) show signs of preliminary efficacy.
- To determine if the selected dose from the escalation phase shows signs of preliminary efficacy when injected on two occasions 12 weeks apart.

Endpoints: Primary endpoint: Safety and tolerability as demonstrated by adverse events (AE), changes in laboratory assessments, physical examination findings and vital signs.

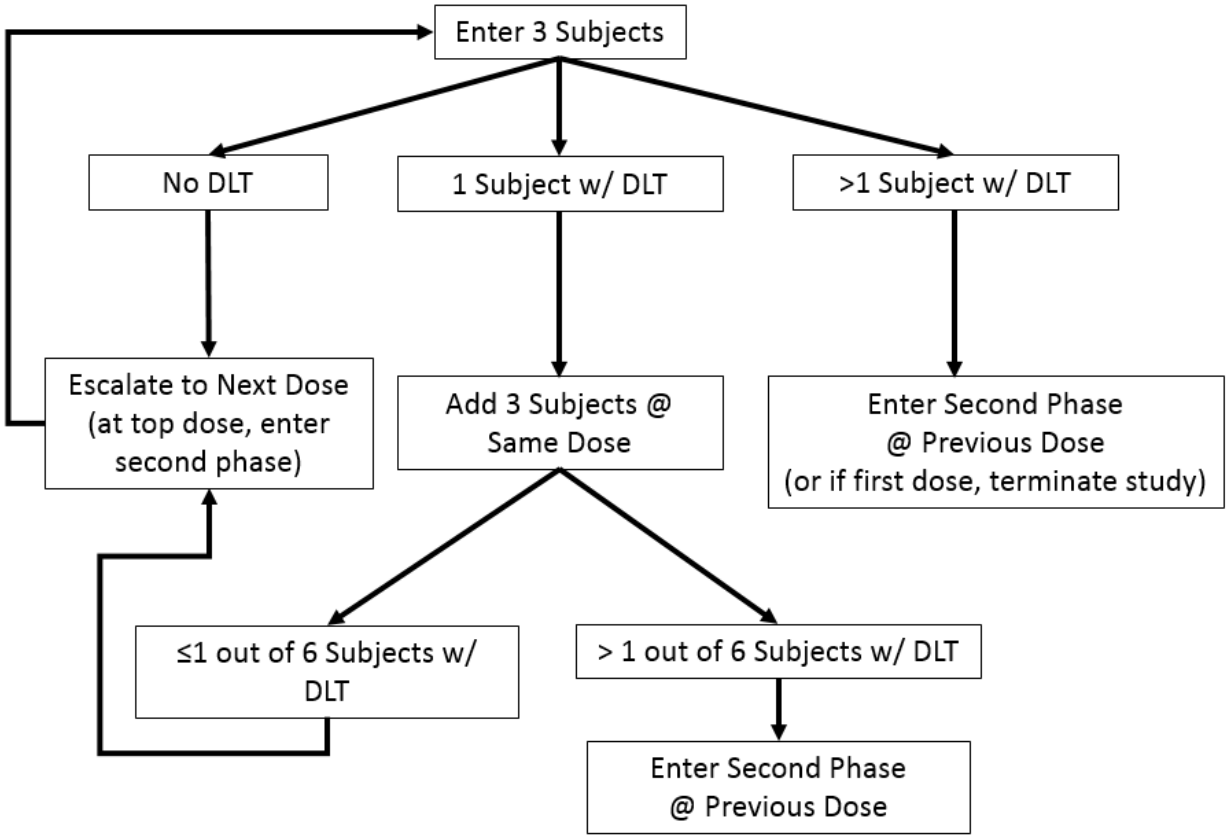
Secondary endpoints:

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

Population: Up to 30 subjects with mucinous cystic pancreatic neoplasms.

Number of Sites enrolling participants:	Five
Description of Study Agent:	NanoPac (Sterile Nanoparticulate Paclitaxel) Powder for Suspension at concentrations of 6, 10, and 15 mg/mL administered into the cyst within the pancreas via EUS-FNI at a volume equal to the volume of cyst fluid aspirated.
Study Duration:	The study duration will be up to 24 months.
Participant Duration:	The participant duration is estimated to be up to six and a half months for each subject

SCHEMATIC OF STUDY DESIGN FOR DOSE ESCALATION



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Laboratory – Routine Hematology and Biochemistry

CLIA Certified laboratory routinely used by the investigators.

Laboratory - Imaging services

Imaging laboratory routinely used by the investigators.

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

The Sponsor for IND 132692, NanOlogy, LLC, has transferred responsibility for all obligations set forth in 21 CFR Part 312 to US Biotest, Inc., with regard to the IND. In accordance with 21 CFR Part 312, US Biotest, Inc., shall be considered the sponsor with regard to all activities related to the IND. Therefore, references to "Sponsor" hereafter in this protocol refer to US Biotest, Inc.

Name and description of study agent:

NanOlogy, LLC (NanOlogy) has produced a formulation of nanoparticulate paclitaxel, identified as NanoPac® (sterile nanoparticulate paclitaxel) Powder for Suspension (NanoPac), which is the subject of this protocol. NanoPac is manufactured using a Precipitation with Compressed Antisolvent (PCA) technique that employs supercritical carbon dioxide and acetone to generate paclitaxel nanoparticles within a well-characterized particle-size distribution. Following PCA, NanoPac is filled into a clear 60mL Type 1, USP, clear-glass vial (306 mg/vial) as a powder fill of nanoparticulate paclitaxel, closed with a bromobutyl rubber stopper and aluminum crimp seal, and sterilized by gamma irradiation. Prior to administration at the hospital/clinic, NanoPac will be reconstituted with 1% Polysorbate 80, *NF* in 0.9% Sodium Chloride for Injection, *USP*, to form a suspension. The suspension will be further diluted with 0.9% Sodium Chloride for Injection, *USP* to achieve the final clinical formulation. This reconstitution and dilution will occur at the clinical site's Pharmacy.

Nonclinical Summary:

Nonclinical studies of NanoPac in animal models of pancreatic neoplasms have not yet been completed. NanoPac demonstrated promising safety and efficacy when injected intratumorally in animals with solid tumors; this data (as well as data from additional animal models) is presented in the NanoPac Investigator's Brochure.

NanOlogy conducted two *in vivo* nonclinical pharmacology studies to determine the effects of nanoparticulate paclitaxel in a PC3 nude mouse tumor xenograft.

In the first PC3 nude mouse xenograft study, mice were administered NanoPac (37.5 mg/kg, qwk x 1), NanoPac (12.5 mg/kg, qwk x 3), NanoPac (37.5 mg/kg, qwk x 3), paclitaxel (30 mg/kg, qwk x 3), or vehicle (0.1% w/v Polysorbate 80 in saline, qwk x 3). Treatments with NanoPac and vehicle were by intratumoral injection. Treatment with three weekly doses of NanoPac at 12.5 or 37.5 mg/kg resulted in significant 92% and 89% TGI tumor growth inhibition, respectively, on Day 32 ($P < 0.01$ for both). Treatment with 12.5 or 37.5 mg/kg paclitaxel resulted in the maximally possible, significant 64% tumor growth delay ($P < 0.001$, logrank) and seven and three partial regressions, respectively. The survival extensions afforded to animals treated with NanoPac therapy are evident.

In the second PC3 nude mouse xenograft study, mice treated with NanoPac (37.5 mg/kg, qwk x 3) via intratumoral injection demonstrated a median tumor volume of 126 mm^3 on Day 60; whereas in the vehicle group, all but one animal was deceased prior to Day 60 and the only animal remaining on Day 60 had a tumor volume of 1268 mm^3.

Clinical Summary:

NanoPac has not previously been administered to the human pancreas via endoscopic ultrasound-guided fine needle injection (EUS-FNI). The only clinical study of NanoPac to date was Protocol HSC#11140, "A Phase I Study of Intraperitoneal Nanoparticle Paclitaxel in Patients with Peritoneal Malignancies," which was conducted under IND 073529. The results of this study were published by Williamson 2015 in the journal *Cancer Chemotherapy and Pharmacology*.

Protocol HSC#11140 was a dose-escalating study evaluating intraperitoneally (IP)-administered NanoPac (under the name Nanotax®) at doses of 50-275 mg/m^2 given every 28 days until disease progression or unacceptable toxicity occurred. Twenty-two subjects were enrolled in Protocol HSC#11140. IP administration of Nanotax did not lead to increases in systemic toxicity over that typically associated with IV paclitaxel. No Grade 2 or higher neutropenia and/or Grade 3 or higher neurologic toxicities were reported. Grade 3 thrombocytopenia, considered unlikely to be related to study medication, occurred in one subject. The peritoneal concentration-time profile of paclitaxel rose during the two days after dosing to peritoneal fluid concentrations 450-2900 times greater than peak plasma drug concentrations and remained elevated through the entire dose cycle. Best response assessments were made in 16 of the 21 subjects. Four subjects were assessed as stable or had no response and twelve subjects had progressive disease. Five of 21 subjects with advanced cancers survived longer than 400 days after initiation of IP Nanotax treatment. There were no cases of bowel obstruction. Additional data from this clinical trial is presented in the NanoPac Investigator's Brochure.

A Phase 2 study under IND 073529 is ongoing. Protocol NANOPAC-2016-01 is a Phase 2 study of four concentrations of IP NanoPac plus six cycles of IV carboplatin and paclitaxel in subjects with platinum-sensitive stage III epithelial ovarian cancer undergoing cytoreductive surgery.

A Phase 2a study under IND 132694 of NanoPac focal therapy of prostate cancer has completed enrollment and is in the reporting stage. Subjects received intratumoral injection of NanoPac at 6, 10, and 15 mg/mL in an injection volume of 20% of the lobe of the prostate containing the dominant lesion, and were followed for four weeks for safety and tolerability prior to prostatectomy.

A Phase 2a study under IND 132692 of NanoPac therapy for locally advanced pancreatic adenocarcinoma is ongoing. Subjects will receive EUS-administered intratumoral injection of NanoPac at 6, 10, and 15 mg/mL at up to 20% of the calculated tumor volume, and will be followed for up to six months for safety and tolerability.

Relevant Literature:

Multiple studies have confirmed the activity of paclitaxel against pancreatic cysts (Oh 2008; Oh 2009; Oh 2011; Oh 2014; DeWitt 2014). Pancreatic cysts are, in some cases, a precursor to pancreatic cancer and paclitaxel, formulated as Abraxane® (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) ("nab-paclitaxel"), is FDA-approved for IV treatment of metastatic pancreatic cancer.

Importance of the study:

Pancreatic cystic neoplasms are being detected with increasing frequency due to improved cross-sectional imaging and routine examination (Pitman 2010). Mucinous pancreatic neoplasms represent approximately 75% of all pancreatic cystic neoplasms and are divided into two categories: intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs). Both types of mucinous pancreatic neoplasms may present with symptoms such as abdominal pain, pancreatitis, jaundice, weight loss, malabsorption, nausea, vomiting, and palpable abdominal mass (Tanaka 2005; Muthusamy 2016).

Mucinous pancreatic neoplasms have malignant potential, thus each patient diagnosed is at risk for developing pancreatic cancer (Farrell 2015; Sarr 2000). In a study of 401 patients with pancreatic cysts, 11% of resected cysts contained invasive cancer (Ferrone 2009). Patients diagnosed with IPMN have a 40% chance of invasive cancer and 58% have underlying malignant features, while those with MCN have a malignancy risk that varies between 10% and 50% (Greer 2016; Allen 2007). To avoid progression to pancreatic cancer, an aggressive and rapidly fatal disease, all patients with mucinous pancreatic cysts should be carefully evaluated and offered treatment (National Cancer Institute 2016; Fernández-del Castillo 1995). An emerging treatment for mucinous pancreatic cysts is cyst fluid aspiration followed by treatment with ethanol lavage as an ablative agent in order to induce cell death by

membrane lysis, protein denaturation, and vascular occlusion (Jani 2011; DeWitt 2009). However, studies examining cyst volume response to ethanol injection failed to standardize their techniques and ethanol concentration/volume, and a ten-year study conducted by Gómez 2016 demonstrated that only 9% of patients experienced complete cyst resolution (Gomez 2016; Kirtane 2016).

Current methods for determining malignancy within mucinous cysts provide unreliable results. It is difficult to identify cyst histology without resection. Approximately 25% of non-operative histologic diagnoses are inaccurate. Physicians compensate for this deficit by recommending that patients with cysts with features such as symptoms, positive cytology, mural nodules, or greater than 3 cm undergo surgical resection (Pitman 2010). Due to the concerns of mucin leakage, pancreatic fistulae, and recurrence, the standard surgical treatment for invasive and non-invasive MCNs and IPMNs is pancreatectomy with lymph node dissection, rather than focal non-anatomic resections or resections without lymphadenectomy or splenectomy (Tanaka 2012). In a study of 37 high-volume centers (2694 patients), the pancreatectomy mortality rate was reported to be 1.3%, increasing to 3.0% in patients 80 years of age and over, with overall complication rates ranging from 20.0% to 72.2% (Tamirisa 2016). In patients that can be diagnosed with a malignancy rate of less than 3%, the risk of death from pancreatectomy is higher than that of malignancy (Allen 2007). Even after surgery, the recurrence rates of cysts can be as high as 20% (Tanaka 2012). Untreated cysts, however, may progress to malignant disease while under observation (Allen 2007).

2.2 RATIONALE

This study will include subjects with mucinous cystic pancreatic neoplasms. The study design allows for a safety evaluation of EUS-FNI of NanoPac into a cyst within the pancreas.

A first-in-man, Phase I safety and pharmacokinetic (PK) trial in patients with malignancies of the peritoneal cavity (IND 073529, Protocol HSC# 11140; Williamson 2015) found that IP delivery of NanoPac was well tolerated, with no NanoPac-related deaths or dose-limiting toxicities reported. In addition, adverse treatment reactions commonly noted during IV paclitaxel therapy were avoided, as NanoPac does not contain the solvent Cremophor-EL. Peritoneal fluid paclitaxel PK demonstrated a concentration-time profile that increased to a significantly high concentration (mean of all doses = 5,711 ng/mL after 2 hours) and remained elevated over the 2-week sampling period. In contrast, plasma PK data for the study subjects show that peak serum NanoPac concentration was low and near the limit of detection in peripheral blood, and plasma paclitaxel concentrations were well below the threshold plasma concentration of 42.7 mg/mL associated with neutropenia (Gianni 1995).

Multiple studies have confirmed the activity of paclitaxel against pancreatic cysts (Oh 2008; Oh 2009; Oh 2011; DeWitt 2014; Moyer 2016). Pancreatic cysts are, in some cases, a precursor to pancreatic cancer and paclitaxel, formulated as Abraxane, is FDA-approved for IV treatment of metastatic pancreatic cancer. It is hypothesized that the use of NanoPac should result in increased efficacy and decreased toxicity as compared with Taxol® or Abraxane due, at least in part, to the slow release of paclitaxel from the suspended nanoparticle. Instillation of NanoPac directly into the pancreatic cyst should create a depot of paclitaxel which is slowly released from the nanoparticles, resulting in prolonged local paclitaxel exposure. Clearance from the pancreas should be reduced, with lower systemic levels of paclitaxel, further limiting systemic toxicity.

In the proposed trial, NanoPac will be administered via EUS-FNI, a procedure with well-reported safety in treating pancreatic neoplasms (Oh 2008; Oh 2011; Oh 2014; Moyer 2016). In studies of paclitaxel injections of pancreatic cysts, up to 68.74 mL of paclitaxel at concentrations of 2-3 mg/mL was injected into cysts within the pancreas without evidence of systemic hematopoietic toxicity (Oh 2009). The most common adverse events (AE) were

pancreatitis and abdominal discomfort. It has been suggested that pancreatitis after paclitaxel injection is likely due to the Cremophor EL excipient in Taxol, which is not required for the formulation of NanoPac (Mills 2000).

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

NanoPac has not been administered to subjects with pancreatic cysts. However, there have been studies of experimental injections of paclitaxel and ethanol into pancreatic cysts. The most common AE in studies of paclitaxel and ethanol injected into pancreatic cysts were pancreatitis and abdominal discomfort (Oh 2008; Oh 2009; Oh 2011; Oh 2014; DeWitt 2009; DiMaio 2011; DeWitt 2014; Park 2016).

- **Ethanol lavage (without paclitaxel)**: In a double-blind study of subjects with unilocular pancreatic cysts, two of the 17 subjects receiving ethanol lavage administered under EUS guidance experienced abdominal pain, one subject experienced intracystic hemorrhage and one subject experienced acute pancreatitis (DeWitt 2009). A retrospective review of subjects with pancreatic cysts undergoing repeated sessions of EUS-guided ethanol lavage reported that one of the 13 patients had minor abdominal pain; no patients developed pancreatitis. In a recent study of 91 patients with pancreatic cysts not eligible for surgery, Park 2016 found that 18 subjects had mild abdominal pain, eight subjects developed fever without evidence of infection, and three subjects developed mild pancreatitis.
- **Paclitaxel (with ethanol):** A prospective study of fourteen patients receiving EUS-guided ethanol lavage with paclitaxel injection for cystic tumors of the pancreas resulted in six patients with hyperamylasemia (without abdominal pain), one patient with mild pancreatitis and abdominal pain, and one patient with mild, vague abdominal pain lasting one month (Oh 2008). Oh 2009 evaluated the response of 10 subjects with oligolocular pancreatic cysts to EUS-guided ethanol lavage with paclitaxel injection; only one of the patients experienced mild pancreatitis and no other complications were observed. Forty-seven subjects with pancreatic cysts received EUS-guided ethanol lavage with paclitaxel injection and were followed for more than one year after treatment; fever without bacteremia (n=1), vague abdominal discomfort lasting two weeks (n=1), and mild pancreatitis (n=1) were reported (Oh 2011). In a prospective study of EUS-guided pancreatic cyst ablation with ethanol and paclitaxel, DeWitt 2014 report adverse reactions in seven of 22 patients undergoing a total of 31 ablation procedures, including abdominal pain alone in four patients (13%), pancreatitis in three patients (10%), peritonitis in one patient (13%), and gastric wall cyst in one patient (3%). A study by Oh 2014 aimed to evaluate the systemic effect of EUS-guided ablation with ethanol and paclitaxel, finding that five of 10 patients had mild, self-limited abdominal pain, one patient had vomiting soon after the procedure, and one patient had intracystic bleeding during the procedure without sequelae.

2.3.2 KNOWN POTENTIAL BENEFITS

There are no known potential benefits of intracystic injection of NanoPac. However, multiple studies have confirmed the activity of paclitaxel injected directly into pancreatic cysts (Oh 2008; Oh 2009; Oh 2011; DeWitt 2014).

3 OBJECTIVES AND PURPOSE

The primary objective of this study is to evaluate the safety and tolerability of NanoPac injected directly into mucinous cystic pancreatic neoplasms by EUS-FNI. Secondary objectives are (a) to describe the PK of NanoPac

when administered into the cyst within the pancreas, (b) to determine whether any of the NanoPac dose 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.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE 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 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).

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 (single injection). 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 timepoints. 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 timepoints) 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 Data Safety Monitoring Board (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.

PK Analysis

Plasma samples will be taken on the day(s) of injection at 1 and 2 hours after NanoPac injection, as well as at all other study visits, to characterize the PK of intracystic NanoPac. Subjects will be followed for six months after the first NanoPac injection for safety and response to therapy (see Section 7.3.4).

4.2 ENDPOINTS

4.2.1 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.

4.2.2 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).

4.2.3 EXPLORATORY ENDPOINTS

Not applicable.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

Patients who meet the following criteria will be considered eligible for participation in the study:

- Signed informed consent;
- Age ≥18 years;

- Recently confirmed mucinous cystic pancreatic neoplasm; may be confirmed by presence of mucin, cyst fluid carcinoembryonic antigen (CEA) above 192 U/L, or other reliable diagnostic means such as endomicroscopy; KRAS analysis may also be performed at the discretion of the Investigator;
- Unilocular cyst with diameter of at least 1.5 cm and no more than 4 cm;
- Subjects of child-bearing potential must follow adequate contraceptive measures. For the purposes of this study, adequate birth control includes at least one medically approved and highly effective method of birth control, defined as those which result in a low failure rate (i.e., < 1% per year) when used consistently and correctly, such as implants, injectables and oral contraceptives combined with the use of condoms. *

** Note: A female patient is considered to be of childbearing potential unless she has had a hysterectomy, is at least one year postmenopausal or has undergone tubal ligation. Only male patients whose vasectomy has been confirmed by semen analysis at least 3 months after the vasectomy are allowed not to use acceptable contraceptive methods.*

5.2 PARTICIPANT EXCLUSION CRITERIA

If a subject meets any of the following criteria, he or she must be excluded from the study:

- Positive cytology indicating malignancy;
- Thrombotic or embolic events;
- Absolute neutrophil count ≤1.5 x 10^9/L and platelets ≤100 x 10^9/L
- Total bilirubin >3x ULN;
- GGT, AST, and ALP >1.5x ULN;
- Creatinine clearance < 60 mL/min/1.73 m^2;
- Elevated serum lipase;
- Hepatobiliary dysfunction within 3 months*;
- Interventions of the upper gastrointestinal tract (i.e. Endoscopic Retrograde Cholangiopancreatography [ERCP] or EUS) within 1 month*;
- Known hypersensitivity to study agent;
- Known drug or alcohol abuse;
- Pregnant or breastfeeding women.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Sufficient subjects will be screened to allow for up to 30 subjects to be enrolled in the trial. Subjects will be recruited at up to five study sites in the US. It is not anticipated that any advertising will be required for recruiting to the study. Subjects will be recruited and screened for eligibility and will proceed to treatment in groups of three during dose escalation. The first three subjects in the second phase will also be reviewed by the DSMB following their second NanoPac injection to confirm safety in this group.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. Their reason for wanting to withdraw will be documented in the source notes and in the Electronic Data Capture system (EDC). The final study visit is planned for six months after the first NanoPac injection.

A subject who is not suitable to be treated will be withdrawn prior to Day 1 (Baseline/Treatment), and therefore in all study documentation this subject would be considered a Screenfail Subject. Reasons for failing the screening will be documented in the source notes and in the EDC.

All subjects should continue to be monitored after initiation of treatment (NanoPac injection) unless they communicate a decision to discontinue protocol follow-up. It is very important that any events occurring be captured and followed for the safety of the subject. If any further treatment is needed, this will be documented and the response imputed as disease progression.

Should the Investigator feel it to be in the best interest of the subject for them to be withdrawn from the study, the Investigator will immediately contact the Medical Monitor to discuss the reasons for withdrawal.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

The sponsor should be notified immediately when a subject is removed or withdrawn from the study after treatment with study agent, as every attempt should be made to capture as much information following treatment as possible.

In the event a subject is withdrawn they would undergo final study visit evaluations (End-of-Study evaluations) which include vital signs, AE collection and concomitant medication updates.

Subjects that refuse or fail to appear for clinic visits following NanoPac injection and fail to respond to or cooperate with reasonable and diligent attempts at contact should not be discontinued from the study, but be considered lost-to-follow-up. Reasonable and diligent attempts such as dates and content of phone calls, emails and registered mail should be recorded in the subject's record.

If a subject repeatedly misses study visits or remains non-compliant following NanoPac injection, and where the majority of data is not available, the option to replace that subject exists, however the data that is collected from the non-compliant subject may still be used in the evaluations in this study.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for the study suspension or termination, will be provided by the suspending or terminating party to sponsor. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform the IRB and will provide the reasons for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants;
    - Routine Medical Monitoring determining a requirement for an ad hoc meeting of the DSMB, and/or routine DSMB reviews, will allow for termination of study based on unacceptable risk, which will consider all safety evaluations and DLT.
    - In the dose escalation phase, the study may be terminated if in the first dose cohort one third of the subjects experience the same DLT (as defined in Section 6.1.7).
    - In the second phase of the study, if one third of the subjects (i.e., 3 subjects) experience the same DLT the study may be stopped or remaining subjects may receive a lower dose of the study drug, or be limited to receive only one injection, as determined by the DSMB.

- Insufficient compliance with protocol requirements;
- Data that are not sufficiently complete and/or evaluable;
- Determination of futility.

Study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the sponsor, IRB, and/or Food and Drug Administration (FDA).

6 STUDY AGENT

6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

NanoPac will be manufactured by CritiTech, Inc. (Lawrence, KS) and provided for use in this study. Study agent will not be shipped to the study site until all Regulatory Documentation has been provided by the site and the site is ready for study Initiation, at which time the study agent will be released for shipment. Shipment will be via courier, temperature controlled 59˚ to 86˚F (15˚ to 30˚C), and will occur prior to the Site Initiation visit. Study Agent will be shipped to the on-site Pharmacy where it will be stored according to the conditions required (see 6.1.3).

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

NanoPac is presented as a white powder, provided in a sealed vial within a study kit.

Study agent for all treatment groups will be supplied to the site in kits with one vial of Sterile Reconstitution Solution (1% Polysorbate 80, *NF* in 0.9% Sodium Chloride for Injection, *USP*), one NanoPac 306 mg powder-filled vial, and one pre-printed Instructions for Use (IFU) insert in a 2ct kit. The site will be responsible for providing 0.9% Sodium Chloride for Injection, *USP* and lactated Ringer's solution.

Kits will be provided for a once-only use and will be assigned to one subject only. Reconstitution will occur at the Pharmacy on-site and the reconstituted study agent will be delivered for use by the Investigator. An IFU insert will be provided in each kit and an instructional video will be provided to each site prior to the Initiation Visit, ahead of the first subject being enrolled. The IFU will contain information on the reconstitution of the drug for all three dose levels, the storage of the drug once reconstituted, the dose withdrawal procedure, and the timeline permitted between reconstitution and use.

The vial will be labelled with at least the following information:

NanoPac (sterile nanoparticulate paclitaxel) Powder for Suspension. 306mg per vial. Lot no.: XXXXXXXXXXX. Caution: New Drug – Limited by federal law to investigational use. For single use only. Manufactured by: CritiTech Inc., 1849 East 1450 Road, Lawrence, KS, 66044.

The carton will be labeled with information indicating the contents as follows:

"Each kit contains: 1 vial of NanoPac (sterile nanoparticulate paclitaxel) Powder for Suspension, 306 mg per vial; 1 vial Sterile Reconstitution Solution for NanoPac Powder for Suspension, 7 ml per vial; 1 instruction sheet for the reconstitution of the NanoPac dosing suspension and the dose withdrawal procedure."

6.1.3 PRODUCT STORAGE AND STABILITY

Prior to administration at the hospital/clinic, the dry, sterilized NanoPac vials will be stored at the Pharmacy, temperature controlled at 59˚ to 86˚F (15˚ to 30˚C).

Once the NanoPac has been reconstituted it must be delivered to the clinic for use. Reconstitution will occur in the Pharmacy at the clinical site, and if the reconstituted agent is not being delivered immediately the storage instructions in the IFU must be followed. Each vial used and each syringe must be labelled with the subject's ID and visit information for accountability purposes.

6.1.4 PREPARATION

Preparation of the study doses will be according to the IFU provided in the study kit.

A prescription will be provided for each subject detailing the subject ID, noting the cohort to which the subject is assigned, and the volume of drug to be prepared, as determined by the Investigator based upon a preliminary estimate of cyst volume. The prescription will also note the date and time required for administration. The prescription will be provided to the Pharmacy at least 24 hours prior to administration time.

Once the drug has been reconstituted to the required dose (6, 10, or 15 mg/mL, according to cohort assignment), a suitable volume for use (as provided on the prescription) will be withdrawn, as described in the IFU, from the vial into a syringe. The syringe for administration will be labeled with the subject ID, the volume contained in the syringe as specified on the prescription, and the date and time of preparation.

6.1.5 DOSING AND ADMINISTRATION

On the day of NanoPac administration, the subject will receive parenteral antibiotic prophylaxis. The subject will be positioned in the left lateral decubitus position and will be sedated by an anesthesiologist or delegate using monitored anesthesia care (MAC) with or without airway intubation. A linear array echoendoscope will be inserted via the mouth and advanced to the stomach or duodenum, whichever provides the best access to the cyst. The cyst will be measured using electronic calipers and the size recorded.

The stylet will be removed from a 22-gauge fine needle aspiration (FNA) needle and the needle will be luer locked into the accessory channel of the echoendoscope. Doppler ultrasound imaging will be used to verify lack of intervening vascular structures in the path to the cyst. The needle tip will be maintained in the cyst for the duration of the procedure. Using a syringe, the Investigator will use their discretion to aspirate the cyst fluid (usually up to 80% of the original volume of the cyst). The volume withdrawn will be documented in the source, and a sample will be sent for analysis. The needle will then be filled with the study treatment, NanoPac, from the syringe provided by the Pharmacy, and NanoPac will be injected at a volume sufficient to fill the cyst, at least equal to the volume of cyst fluid aspirated. The injection volume to fill the cyst will be determined visually by the Investigator during the endoscopic ultrasound procedure, and the exact volume administered to the cyst will be documented in the source and captured in the electronic case report form (eCRF).

6.1.6 ROUTE OF ADMINISTRATION

NanoPac will be injected directly into the cyst within the pancreas using endoscopic ultrasound guidance.

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

NanoPac will be administered in concentrations based on cohort assignment. Investigators will administer a volume at least equal to the volume of cyst fluid aspirated. In the dose escalation phase of the study, the first cohort will receive 6 mg/mL NanoPac; the second cohort will receive 10 mg/mL NanoPac; and the third cohort will receive 15 mg/mL NanoPac.

Cohorts will be enrolled sequentially starting at the lowest dose (6 mg/mL). Each cohort will have a planned minimum of three subjects, each receiving a single dose of the study agent. Escalation to the next cohort will proceed following review of data by the DSMB. Data from the three subjects in a cohort, including all DLT described in this section, will be reviewed and evaluated by the DSMB to determine if 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. 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 (greater than one DLT). If one or fewer subjects in a six-subject cohort, or no subjects in a three-subject cohort at the highest dose, experience DLT, that cohort will be taken into the second study phase. If greater than one subject in a six-subject cohort experience DLT, the previous dose will be taken into the second phase of the study.

The highest dose considered to be safe and tolerable in the dose escalation phase will be the dose administered in the second phase of the study. The dose will be administered twice in the second phase, as two single NanoPac injections 12 weeks apart.

Included in the DSMB's review of AE and general study data pertaining to safety (such as laboratory results and questionnaire responses) there will be rules for non-escalation. Any AE that is considered related or possibly related to NanoPac is potentially a DLT. The definition of a DLT will be made by consensus by the Medical Monitor, Sponsor Medical Director, and Principal Investigator for AE. DLT will include the following:

- Any Grade 4 toxicity of any duration;
- Grade 3 and higher pancreatico-biliary events (including but not limited to symptomatic pancreatitis or cholangitis, excluding asymptomatic time-limited pancreatic enzyme elevations);
- Grade 3 and higher febrile neutropenia;
- Grade 3 diarrhea and vomiting lasting more than 72 hours;
- Any life-threatening event (unless there is a clear alternative explanation that the event is not related to the procedure or the investigational product itself).

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

In the dose escalation phase, this study is evaluating one single administration of NanoPac in each subject, therefore there will be no dose adjustment or modification in an individual subject.

In the second phase of the study, where each subject will receive two NanoPac administrations 12 weeks apart, the possibility of adjusting the dose for the second injection based on safety may be discussed and determined between the Investigator and the Medical Monitor on a case-by-case basis. Upon review of the first three subjects in the second phase, the DSMB may also determine that adjustment is required for the remaining subjects in this cohort.

6.1.9 DURATION OF THERAPY

NanoPac will be injected directly into the cyst within the pancreas on either a single occasion or on two occasions 12 weeks apart. Each NanoPac administration/dosing occurs over a period of approximately 5 minutes and does not continue over an extended period.

6.1.10 TRACKING OF DOSE

Not applicable.

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

Not applicable.

6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

The Investigator will maintain adequate records showing the receipt, dispensing, return, or other disposition of the investigational drug, including the date, quantity, batch or code number, and identification of subjects (number, initials) who received study medication.

Accountability will be conducted using the records held by the Pharmacy including details on vial packaging, the individual vials, and the syringes. No used vials or syringes will be kept for accountability purposes, they will be disposed of according to the standard operating procedures at the institutions.

Under no circumstances will the Investigator supply clinical material to other Investigators or clinicians or allow the supplies to be used other than as directed by this protocol without the consent of the sponsor.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

The following procedures and evaluations will be done as part of this study:

- Complete medical history to be completed, documented, and reviewed by the Investigator including review of previous medical records, demographics, and parity;
- Review and documentation of concomitant prescription and non-prescription medications;
- Imaging with EUS-FNA will have occurred prior to consenting to participate in the study as this procedure is required to confirm the diagnosis of mucinous cystic pancreatic neoplasm using cyst fluid markers. Mucinous cystic pancreatic neoplasm may also be confirmed by the presence of mucin, or by endomicroscopy.
- In the dose escalation phase, imaging (MRCP, CT scan, or FDG-PET) results will be used to document the location and size of the cyst to be treated. If multiple cysts are present, the location of each will be documented, and selection of the target cyst to be treated will be at the discretion of the Investigator. Treatment of non-targeted cysts will follow institutional SOC.

- In the second phase of the study, a CT scan will be obtained before the first NanoPac injection to provide baseline data on dimensions and volume of the lesion to be injected;
- A copy of the cytology report and the imaging reports supporting the diagnosis must be filed in the subject's study record;
- Comprehensive physical examination, including ECOG Performance Status assessment (Appendix A), and vital signs (blood pressure, heart rate, temperature, body weight and height);
- PK samples will be taken at 1 and 2 hours post-NanoPac injection, and again at all study visits post injection;
- Samples will be collected and processed for clinical laboratory assessment at Screening, and on the day(s) of NanoPac injection prior to treatment; and at Week 1, Week 2, Week 4, Week 8 (two months), Week 12 (three months), and Week 24 (six months, end of study visit) post-injection for subjects in the dose escalation phase. Subjects in the second phase will have additional samples collected at Week 14 and Week 16. Assessments will include:
    - Sodium, potassium, chloride, carbon dioxide (CO2), calcium, phosphorus, glucose, blood urea nitrogen (BUN), creatinine, serum lipase, serum amylase, alkaline phosphatase (ASP), total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase [GGT], lactate dehydrogenase (LDH), total protein, albumin, triglycerides, cholesterol, uric acid and calculated creatinine clearance;
    - 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, platelet count, and absolute neutrophil count (ANC);
    - Urinalysis including specific gravity, hydrogen ion concentration (pH), RBC, WBC, protein, and glucose;
    - Prothrombin time (PT) and activated partial thromboplastin time (PTT);
- EUS-FNA of the cyst fluid; cyst fluid will be collected after aspiration and analyzed for CEA in the dose escalation phase of the study. In the second phase where subjects will receive two injections of NanoPac, the cyst fluid will be collected and the volume documented, and this will be divided up for CEA analysis and a small amount will be stored for paclitaxel presence/absence evaluation.
- EUS-FNI of the cyst within the pancreas with NanoPac at a volume equal to or greater than the volume of cyst fluid aspirated. Subjects in the dose escalation phase will receive one injection on Day 1. Subjects in the second phase of the study will receive two injections - the first administration will be on Day 1 and the second administration will be at the Week 12 visit.
- Documentation of the volume of cyst fluid aspirated, volume of NanoPac injected, and volume of NanoPac remaining in the syringe (as applicable);
- The same imaging modality performed prior to enrollment and used to confirm eligibility (MRCP, CT scan, or FDG-PET) will occur at three months post-injection and at end-of-study (six months after NanoPac injection) for the subjects in the dose escalation phase of the study. Subjects in the second phase of the study will have a CT scan following consent and prior to first injection, at the Week 12 visit prior to second NanoPac injection, and again at the Week 24 (six month) visit at end of study. Should the subject withdraw from the study at any time, a scan will be conducted as part of the end-of-study procedures. 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. Any data collected from additional procedures conducted while the subject is on study will be available for review and may be provided to US Biotest.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

Following EUS-FNI of NanoPac, the care of the subject will be as dictated by the protocol but will allow for any other standard care the Investigators would routinely provide (such as treatment of multiple cysts, pain relief, additional clinic visits, etc.). Following intracystic injection of NanoPac, EUS-guided aspiration of the NanoPac-treated cyst should not be initiated within six months except as specified by the protocol. However if it is required prior to the end-of-study visit, the Investigator must contact the study Medical Monitor to discuss and document the decision-making process.

Information on standard care and treatment post-injection(s) to the final visit will be captured as appropriate. Any data collected from additional procedures conducted at the final visit will be provided to US Biotest.

7.2 LABORATORY PROCEDURES/EVALUATIONS

7.2.1 CLINICAL LABORATORY EVALUATIONS

Clinical laboratory assessments will be conducted at the local CLIA certified laboratory routinely used by the Investigator.

The following laboratory tests will be performed at Screening, on the day of NanoPac injection, and at Week 1, Week 2, Week 4, Week 8 (two months), Week 12 (three months), and at Week 24 (six months) post-injection for subjects in the dose escalation phase. Subjects in the second phase will have additional samples collected at Week 14 and Week 16:

- Sodium, potassium, chloride, carbon dioxide (CO2), calcium, phosphorus, glucose, blood urea nitrogen (BUN), creatinine, serum lipase, serum amylase, alkaline phosphatase (ASP), total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase [GGT], lactate dehydrogenase (LDH), total protein, albumin, triglycerides, cholesterol, uric acid and calculated creatinine clearance;
- 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, platelet count, and absolute neutrophil count (ANC);
- Urinalysis including specific gravity, hydrogen ion concentration (pH), RBC, WBC, protein, and glucose;
- Prothrombin time (PT) and activated partial thromboplastin time (PTT).

7.2.2 OTHER ASSAYS OR PROCEDURES

PK samples will be taken on day(s) of injection at 1 and 2 hours post-injection. In addition, a PK sample will be obtained at each study visit. PK samples within the first 2 hours after injection will allow for a 10-minute window around the samples, resulting in a total 20-minute window. PK samples for Week 1 will allow for a 1-day window around the samples (±1 day on either side). PK samples for Week 2, Week 4 (one month), Week 14 (if applicable), and Week 16 (if applicable) will allow for a 2-day window around the samples (±2 days on either side), and samples for Week 8 (two month) will allow for a 1-week window (±1 week on either side). In the dose escalation phase of the study there will be a 1-week window (±1 week on either side) for the Week 12 visit, and a 2-week window (±2 weeks on either side) for PK samples collected for the Week 24 (six month) visit. In the second phase where two injections of NanoPac are given, there will be a 1-week window (±1 week on either side) for the Week 12 visit, and

the visits at Week 14 and Week 16 will be conducted with a 2-day window **from the date of second injection**; the Week 24 visit in this group of subjects will allow a 1-week window for PK sample collection.

Imaging with EUS-FNA will have occurred prior to consent, to confirm the diagnosis of mucinous cystic pancreatic neoplasm using cytology and pancreatic cyst fluid markers. Mucinous cystic pancreatic neoplasm may also be confirmed by the presence of mucin, or by endomicroscopy. A copy of the reports supporting the diagnosis must be filed in the subject's study record. The location of the cyst(s) will be documented.

During the dose escalation phase, imaging (MRCP, CT scan, or FDG-PET) will be documented prior to study participation and again at Week 12 and at Week 24. In the second phase of the study, a CT scan will be performed between the Screening visit and the first Day of Injection Visit to obtain a study baseline image against which future CT scans at the Week 12 and Week 24 timepoints will be compared. Should the subject withdraw from the study at any time, a scan will be conducted as part of the end-of-study procedures. The location of the cyst will be documented with imaging. If multiple cysts are present, selection of the cyst to be treated will be at the discretion of the Investigator. Treatment of non-selected cysts will follow institutional SOC.

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

For all subjects PK samples will be drawn at the specified time/visit, prepared and stored frozen on-site, and samples will be batch-shipped to Covance Laboratories for analysis. Procedures for processing for storage will be provided prior to study initiation.

In the second phase of the study, at the Week 12 visit prior to second dose of NanoPac, any cyst fluid available for paclitaxel presence assessment will be stored frozen on-site, and samples will be batch-shipped to Frontage Laboratories for analysis.

Serum samples for routine laboratory assessments will be obtained at the specified time/visit and will be sent to the local CLIA certified laboratory for analysis. Results will be sent to the Investigator for the source record and for entry to the electronic case report form (eCRF).

7.2.4 SPECIMEN SHIPMENT

PK samples will be drawn at the specified time/visit, prepared and stored frozen on-site until a cohort has completed all draws for analysis, or at another time interval determined by the Sponsor, at which time they will be batch-shipped to Covance Laboratories (Madison, WI) for analysis. Procedures for processing for storage will be provided prior to study initiation. Samples for paclitaxel evaluation will also be stored frozen at the site and batch shipped to Frontage as directed by the Sponsor.

Serum samples for routine laboratory assessments will be obtained at the specified time/visit and will be sent to the local CLIA certified laboratory for analysis. Results will be sent to the Investigator for the source record.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

When subjects have a diagnosis of a mucinous pancreatic cyst, confirmed by analysis of cyst fluid aspirated using EUS-FNA or by endomicroscopy, they will be eligible for consideration to enroll to the study to receive treatment with NanoPac.

The following procedures and assessments must be completed, documented and reviewed by the Investigator (up to and) during the screening period, within 28 days prior to NanoPac injection:

- Written informed consent including comprehensive discussion of the study schedule, procedures and subject protocol requirements;
- Complete medical history, including review of previous medical records, demographics and parity;
- Review and documentation of mucinous cystic pancreatic neoplasm with a diameter of at least 1.5 cm and no more than 4 cm; diagnosis and previous treatments including surgical and chemotherapeutic records. A copy of the reports confirming the diagnosis must be filed in the subject's study record;
- Review and documentation of all concomitant prescription and non-prescription medications;
- Comprehensive physical examination, including ECOG Performance Status assessment (Appendix A), and vital signs (blood pressure, heart rate, temperature, body weight and height);
- Sample collection and processing for clinical laboratory assessments (see section 7.2.1);
- In the second phase of the study, CT scan between screening and Day 1 for detailed baseline measurement. Final injection volume will be determined with ultrasound during the endoscopic-guided procedure.

7.3.2 DAY OF NANOPAC INJECTION

All Screening assessments must have completed prior to this visit, all results confirmed, and inclusion and exclusion criteria confirmed. In the dose escalation phase of the study the following applies to Day 1 (the single day of NanoPac injection) and, in the second phase, applies to both injection days on Day 1 and Week 12.

Prior to the procedure:

- Comprehensive physical examination, including ECOG Performance Status assessment;
- Vital signs will be obtained;
- AE occurring in the period between Screening and this visit must be confirmed as either ongoing or completed. AE occurring prior to the procedure will be considered history, and those occurring after NanoPac administration will be documented separately as treatment emergent adverse events (TEAE), with a start date on or after administration;
- Concomitant medication will be reviewed and updated as necessary;
- Sample collection prior to injection, and processing for clinical laboratory assessments (Section 7.2.1);
- In the second phase of the study, a CT scan will be performed at the Week 12 visit before the second injection;
- EUS-FNI of the cyst within the pancreas with NanoPac at a volume sufficient to fill the cyst that is at least equal to the volume of cyst fluid aspirated;
- Cyst fluid will be extracted and analyzed for carcinoembryonic antigen (CEA), and the aspirated cyst fluid volume will be documented. In the second phase of the study, at the Week 12 visit, prior to the second NanoPac injection, cyst fluid will again be aspirated and analyzed for CEA, and if sufficient sample is available it will also be sent for paclitaxel evaluation (presence or absence).
- Subject will receive NanoPac as described in Sections 4.1 and 6.1.5, according to the cohort allocation, and the injection volume will be documented, as well as the remainder in the syringe;
- PK Samples will be drawn at 1 and 2 hours post-injection.

7.3.3 FOLLOW-UP VISITS

Subjects will return to the clinic one week after the first NanoPac injection for the first study-specific follow-up visit. Subsequent follow-up visits will occur at Week 2, Week 4, and Week 8. Subjects in the dose escalation phase will have a follow-up visit at Week 12. Subjects in the second phase will have additional follow-up visits at Week 14 and Week 16.

The Week 4 (1-month) visit will be the primary endpoint (safety and tolerability) study visit for subjects in the dose escalation phase. The Week 16 (one month following the second NanoPac injection) visit will be the primary endpoint study visit for subjects in the second phase. All further visits will be conducted to assess the ongoing safety and the secondary endpoints.

The following procedures will be performed at the Week 1, Week 2, Week 4, Week 8 (2-month), Week 14 (as applicable), and Week 16 (as applicable) clinic visits. The procedures will also be performed at the Week 12 (3-month) clinic visits for subjects in the dose escalation phase:

- Vital signs obtained; as needed, a directed physical exam may be performed;
    - At Week 4 a comprehensive physical exam, including vital signs will be performed.
- ECOG Assessment;
- Concomitant medications reviewed;
- Sample collection and processing for clinical laboratory assessments (Section 7.2.1);
- PK sample obtained;
- AE collection.
- Imaging will be performed at the Week 12 (3-month) visit for all subjects.

7.3.4 FINAL FOLLOW-UP STUDY VISIT (WEEK 24/6-MONTHS)

The assessments completed at this visit will be used to support the primary (safety) endpoints, and will be used for the secondary (preliminary efficacy) endpoint analysis. The following procedures will be performed:

- Vital signs obtained; as needed, a directed physical exam may be performed;
- Concomitant medications;
- AE collection;
- Sample collection and processing for clinical laboratory assessments (Section 7.2.1);
- PK Sample obtained;
- ECOG Assessment;
- Imaging and disease status assessment.

Any data collected from additional procedures conducted during the study may be provided to US Biotest.

7.3.5 EARLY TERMINATION VISIT

In the event a subject is withdrawn they would, at minimum, undergo End-of-Study evaluations, which include the procedures described in Section 7.3.4 above. If a subject is withdrawn at a routine study visit all evaluations that would have been done at that study visit should be completed, as far as possible, and the least amount of information that must be captured are the vitals, AE, and concomitant medications.

7.3.6 UNSCHEDULED VISITS

Any unscheduled visits will be documented in the source, and any assessments and/or evaluations performed will be noted and reviewed. The subject will undergo any other evaluations determined necessary by the Investigator to ensure the subject's well-being. If the Investigator deems it necessary for blood work to be done this information will be filed in the source and be available if required at a later date, but laboratory results will not be transcribed into the EDC.

7.3.7 SCHEDULE OF EVENTS TABLE – DOSE ESCALATION

	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).

7.3.8 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.

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Sponsor acknowledges that EUS-FNI of NanoPac into the cyst within the pancreas, including the anesthesia necessary for the injection, may qualify as a sensitive procedure and as such should be mentioned in this section.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant prescription medications taken during study participation will be recorded on the eCRF. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications.

Although no interaction studies have been conducted using NanoPac, paclitaxel is metabolized by cytochrome P450 isozymes CYP2C8 and CYP3A4 (Taxol Package Insert). Thus, there is a potential for drug interactions with concomitantly administered substrates (e.g., repaglinide and rosiglitazone), inhibitors (e.g., gemfibrozil), and inducers (e.g., rifampin) of CYP2C8. There is also the potential for paclitaxel to interact pharmacokinetically with CYP3A4 substrates (e.g., midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (e.g., rifampin and carbamazepine).

7.6 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

No precautionary medications, treatments, or procedures are included in this protocol; they may, however, be administered at the discretion of the Investigator, anesthesiologist, or the subject's primary care provider. All medications will be recorded.

7.7 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

Use of concomitant chemotherapy (other than the protocol specified agents), immunotherapy, or radiation therapy, at any time during the study (Screening to the final visit) is to be discussed with the Medical Monitor before any action is taken. The subject may be permitted to remain on study but there is a chance that the subject may be required to be withdrawn at this time. EUS-FNA of the cyst receiving NanoPac subsequent to the injection procedure(s) is also strongly discouraged at any time during the study.

7.8 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Prophylactic antibiotics will be administered on the day of NanoPac injection and any other prophylactic medications will be administered according to the institution's SOC.

7.9 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Rescue medications, treatments, and procedures will be performed according to the institution's standard of care, and will be documented in the source and in the study data as needed.

7.10 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Not applicable.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

Safety assessments being conducted in this study include:

- AE, collected at all study visits from the time of dosing;
- Changes in concomitant medications;
- Findings from physical examinations;
- Changes in vital signs; and
- Changes in laboratory parameters.

Safety will be reviewed by the Medical Monitor in an ongoing manner via the EDC system, and details will be confirmed at routine on-site monitoring visits. Additionally, DSMB assessments will be conducted after every three subjects are dosed and have completed two weeks' follow-up post-NanoPac injection (or more frequently if deemed necessary).

Safety and tolerability will be assessed by the DSMB prior to any dose escalation occurring.

Included in the DSMB's review of the AE and general study data pertaining to safety (such as laboratory results) there will be rules for non-escalation. Any adverse event that is considered related or possibly related to NanoPac is potentially a DLT. The definition of a DLT will be made by consensus by the Medical Monitor, Sponsor Medical Director, and Principal Investigator for AE. DLT will include the following:

- Any Grade 4 toxicity of any duration;
- Grade 3 and higher pancreatico-biliary events (including but not limited to symptomatic pancreatitis or cholangitis, excluding asymptomatic time-limited pancreatic enzyme elevations);
- Grade 3 and higher febrile neutropenia;
- Grade 3 diarrhea and vomiting lasting more than 72 hours;
- Any life-threatening event (unless there is a clear alternative explanation that the event is not related to the procedure or the investigational product itself).

Events of special interest (Section 8.4.4) will be specifically reviewed and will form part of the review between doses, and the DSMB review will provide and document oversight as detailed in the DSMB Charter.

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended change in structure, function, signs, or symptoms temporally associated with the use of a medicinal product, whether or not related to the product. Undesirable changes in laboratory values should not be considered AE unless they are considered symptomatic of a clinical condition or diagnosis, are evaluated as clinically significant or require therapy. Worsening of a pre-existing condition is also considered an AE, as is the discovery of an abnormal finding during physical exam that was not included in the medical history. Clinical conditions attributable to disease progression will be considered AE and reported on the eCRF.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A Serious Adverse Event (SAE) is any AE that meets at least one of following criteria:

1) Is fatal;
2) Is life threatening, meaning the subject was, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form or progressed, might have caused death;
3) Is a persistent or significant disability or incapacity;
4) Requires or prolongs inpatient hospitalization. Inpatient hospitalization will be considered a hospitalization that is longer than 24 hours, or a hospitalization that requires an intervention to treat emergent symptomatology (non-diagnostic);
5) Is a congenital anomaly or birth defect;
6) Other important medical events may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes as listed in #1-5 in this definition.

8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

All unanticipated problems in this trial will be captured as either AE or SAE and will be defined and reported accordingly.

8.2 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1 SEVERITY OF EVENT

Signs and symptoms will be graded by the Investigator as mild, moderate, severe, or life threatening according to the following definitions:

- **Mild:** Causing no limitation of usual activity
- **Moderate:** Causing some limitations of usual activities
- **Severe:** Causing inability to carry out usual activities
- **Life-Threatening:** Subject was at immediate risk of death from the event
- **Fatal:** Death related to the event

Toxicities should be evaluated according to the NCI CTCAE, version 4.0; see *https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf*

Toxicity grades should be recorded as: 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life-Threatening, 5 = Fatal.

8.2.2 RELATIONSHIP TO STUDY AGENT

Events will be considered drug-related if classified by the Investigator as possible, probable, or definitely related to the study agent. Association of events to the study agent will be made using the following definitions:

- No relationship to study agent: the event is not associated with study agent.

- Possibly related to study agent: the event follows a reasonable temporal association with the study agent administration, however could have been produced by the subject's clinical condition or other therapy.

- Probably related to study agent: the event follows a) a reasonable temporal association with the study agent administration, but b) abates upon discontinuation of study agent and c) cannot be explained by the subject's clinical condition or other therapy.

- Definitely related to study agent: the event: a) follows a reasonable temporal association with the study agent administration, but b) abates upon discontinuation of study agent, c) cannot be explained by the subject's clinical condition or other therapy, and d) reappears on re-exposure to study agent.

8.2.3 EXPECTEDNESS

The definition of expectedness is related to the study agent specifically. An event may be unexpected in the subject but that in itself does not qualify as unexpected; review against information available and provided for the study agent is what will determine expectedness.

Sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent, in the protocol and within the Investigator's Brochure.

8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

AE will be recorded throughout the study and at early termination, and will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events ongoing at the final study visit must be followed until resolution or until the Investigator determines them to be stable and/or adequately managed.

Subjects will be required to spontaneously report any AE. Study personnel will ask open-ended questions to obtain information about AE at every visit. Date and time of onset and resolution (if applicable) of the AE will be documented.

All SAE must be followed until the event resolves or, in the opinion of the Investigator, becomes stable.

The sponsor will report any serious, unexpected and drug-related AE to applicable regulatory agencies and make these reports available to the investigative sites. The Investigator must promptly inform the IRB of such events and retain a copy of the notification in the site's regulatory binder.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

All AE (whether or not attributable to the study agent) occurring during the study observed by the Investigator or reported by the subject will be recorded on the eCRF. The following information will be recorded for all AE:

- Name of condition/diagnosis/description;
- Onset and resolution dates;
- Severity;
- Relationship to Investigational Agent;

- Action taken;
- Seriousness.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

All SAE, including death, due to any cause which occurs during this study, whether or not expected and regardless of relationship to study agent, must be reported to the Medical Monitor immediately upon discovery of the event, using the SAE reporting form, by email or fax and, if necessary, by phone to:

Antony Verco, MD
Medical Monitor
Email: tony.verco@usbiotest.com
Phone: 805-235-9193
Fax: 805-980-4897

24-hour Emergency Contacts:	Gere diZerega, MD Medical Director 805-630-2800	or	Antony Verco, MD Medical Monitor 805-235-9193

The Study Manager, Dr. Shelagh Verco, should be copied on all correspondence via email at shelagh.verco@usbiotest.com, and can be reached by phone at 805-704-1179.

The sponsor will advise the Investigator regarding the nature of any further information or documentation that is required. The Investigator should provide the following documentation at the time of notification if available:

- SAE Report Form;
- Concomitant and support medication pages;
- Relevant diagnostic reports;
- Relevant laboratory reports;
- Admission Notes;
- Hospital discharge summary (when available).

8.4.3 UNANTICIPATED PROBLEM REPORTING

Unanticipated incidents or events that occur during the conduct of the study, meeting the criteria for an AE or SAE, will be captured in the source documents and in the EDC, and in the case of an SAE also on the formal reporting form designed to capture the required information. Reporting of these events will be in accordance with the rules around AE and SAE reporting described in the protocol, including notification of the IRB and/or FDA as required.

8.4.4 EVENTS OF SPECIAL INTEREST

Of particular interest will be signs of systemic toxicity due to paclitaxel exposure; this is not expected and is considered unlikely given the mode of administration and dose levels. Pancreatitis has occurred after injection of the pancreas; subjects will be monitored for pancreatitis, in particular during the first 36 hours after the procedure, and will be encouraged to report symptoms such as abdominal pain with or without nausea/vomiting. Pain is an adverse event also associated with pancreatic injection, in particular pain in the mid-epigastrium and/or the back. Additional events sometimes associated with pancreatic injection include vomiting, peritonitis, retroperitoneal bleeding, abscess formation, and fistula formation.

8.4.5 REPORTING OF PREGNANCY

Female subjects must take a pregnancy test before receiving any treatment. A female patient is considered to be of childbearing potential unless she has had a hysterectomy, is at least one year postmenopausal or has undergone tubal ligation. For the purposes of this study, adequate birth control includes at least one medically approved and highly effective method of birth control, defined as those which result in a low failure rate (i.e. < 1% per year) when used consistently and correctly, such as implants, injectables and oral contraceptives combined with the use of double condoms. Only male patients whose vasectomy has been confirmed by semen analysis at least 3 months after the vasectomy are allowed not to use acceptable contraceptive methods.

Any pregnancy occurring in a subject or a subject's sexual partner during the study or within 6 months after injection of NanoPac must be reported to US Biotest as soon as the Investigator is aware of it. The pregnancy will not be considered an SAE; however, information on these pregnancies will be collected and followed for the outcome of the pregnancy and the health of the newborn.

Any pregnancy complication or premature terminations including miscarriage, spontaneous abortion, or elective termination of a pregnancy for medical reasons will be reported as an SAE, as described in Section 8.4.2. Should the pregnancy result in a congenital anomaly or birth defect, a separate SAE report must be submitted. Furthermore, all neonatal deaths that occur within 30 days of the birth should be reported as SAE, without regard to causality. In addition, any infant death that occurs after the 30-day reporting period that the Investigator suspects is related to the in utero exposure to the study treatment should also be reported.

8.5 STUDY HALTING RULES

This study is a dose escalation study, and dose escalation will be determined following review of the safety and tolerability data in a cohort by the DSMB. Following review, at any timepoint, the study may be terminated. Should this occur, all subjects who have received treatment will be followed to the completion of their end-of-study visit to ensure all safety data is collected on all treated subjects.

The DSMB will review data from the first three subjects in each cohort once they complete the two-week follow-up visit after NanoPac injection. The DSMB may determine that a further three subjects should be treated at the same dose as a current cohort to provide additional safety and/or tolerability information needed in order to determine if dose escalation should proceed; they may also determine that it is acceptable to proceed with an increased dose in the next cohort; or they may determine that the safety and tolerability profiles are not acceptable and may stop the study.

The sponsor is responsible for notifying FDA of any temporary halts to the study or when a study is terminated; the Investigator will be required to notify the IRB accordingly.

8.6 SAFETY OVERSIGHT

Safety will be overseen by the Medical Monitor and the DSMB.

The DSMB, comprising the Medical Director and at least two independent key opinion leaders in the field of study, will review all safety and tolerability parameters at regular intervals throughout the study.

All subject study data will be captured in an EDC system, allowing real-time access to ongoing safety and tolerability data. The Medical Monitor will review the data for each subject entered to the database on a regular

basis. In the event the Medical Monitor has any concerns or sees any safety trends emerging during his ongoing reviews, he will bring it to the immediate attention of the Medical Director (and the Principal Investigators, as appropriate).

Upon completion of a cohort and prior to dose escalation proceeding the DSMB will convene to review the cohort data, and a report will be generated outlining any safety concerns from the data available for review in the EDC. This review will take place prior to proceeding with either addition of more subjects to a current cohort or proceeding to dose escalate in a new cohort.

The DSMB will convene once the first three subjects in the second phase of the study have completed their Week 14 visit (two weeks after their second injection) to review safety data. Subject recruitment to this cohort of subjects will continue during the review. If the DSMB have concerns regarding future subjects receiving a second injection then they may propose alternative actions, which may include reducing the dose of the injections or limiting future subjects to a single injection.

During the DSMB review, members will review all safety data as available in the EDC provided as reports generated directly from the EDC system and provided by the Data Management group. Particular emphasis will be placed on the events of special interest as outlined in Section 8.4.4 and on events which may constitute dose limiting toxicities as outlined in Sections 6.1.7 and 8.1.

9 CLINICAL MONITORING

US Biotest monitors, or monitors designated by US Biotest, will conduct scheduled site visits to the investigational centers for the purposes of monitoring the study. The Investigator agrees to allow these monitors, and other authorized sponsor personnel or designees, access to the subject's medical records, regulatory binder, study binder, eCRF, and source documents as needed to assure the conduct of the study was within compliance. In addition, the FDA or other government agencies may request an inspection following notification to the site. In such an event, the Investigator agrees to notify the sponsor immediately of the request, and will allow sponsor and inspectors to review records.

US Biotest will conduct a Site Initiation Visit to provide the Investigator and their staff with a comprehensive overview of the protocol and study procedures and to review mutual obligations and requirements of regulatory authorities. A regulatory file or binder containing required documentation will be kept at the site for reference and inspection.

Routine monitoring visits will be made to assure compliance with the study protocol and regulatory requirements, to review and verify the subject's eCRF by comparing with source documents, to ensure adequate records of clinical supplies are maintained, and to assess the continued suitability of the investigational site. On completion of the study, the monitor will make a final assessment of the conduct of the study and inventory all clinical supplies to be returned to US Biotest.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL AND ANALYTICAL PLANS

A formal Statistical Analysis Plan (SAP) will be prepared for this trial, and the SAP will be signed off prior to study database lock.

10.2 STATISTICAL HYPOTHESES

No inferential analyses are proposed, thus no hypotheses are stated.

10.3 ANALYSIS DATASETS

All subjects who receive treatment will be included in the outcome presentations.

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

In this dose escalation trial, the focus will be on providing descriptive statistical summaries including tables and graphs for each of the dose groups. The clinical/medical review of these data will determine if there are any issues with toxicity that could be associated with dose and if there is any effect of the treatments on the mucinous cystic pancreatic neoplasm.

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary objective of this study is to evaluate the safety and tolerability of three doses of NanoPac (concentrations of 6, 10, and 15 mg/mL) injected directly into mucinous cystic pancreatic neoplasms.

The adverse events reported will be coded in MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT) for each of the dose groups. Where possible and relevant, these will also be subset temporally by date and time of onset (e.g. first 24 hours, up to Day 7); the details of the timeframes will be established medically and presented in the SAP. Events reported as DLT and those that lead to trial discontinuation will be noted. Any serious AE and any deaths will be summarized separately.

The vital signs raw data, collected at each visit, and changes from Day 1 will be tabulated and listed.

The laboratory analyses will be presented in summary tables with changes from Day 1 to Days 14 and 28. By applying the normal ranges (high, normal and low) shift tables will be generated. Values which are noted by the investigator to be abnormal and clinically relevant will be summarized separately as will any analytes where the shift in category is greater than two (e.g. high to low or low to high). The SAP may capture medically relevant changes (e.g. 3 x the normal range), and analytes which meet this criterion will also be presented separately.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

To address the secondary objective of the concentration of paclitaxel in the systemic circulation post-injection, the PK samples taken on Day 1 at 1 and 2 hours post-injection, and again at all study visits post injection (Weeks 1, 2, 4, 8, 12 and 24) will be presented (at a minimum) by individual listings. If some concentration data is above the detectable limit and can be reported numerically, this data will be tabulated and graphed for individuals and by dose group.

To determine if there are any indications of efficacy, the cyst volume at screening will be compared with the volume calculated for the images at Weeks 12 and 24 (or early termination). Although the number of subjects within each dose group is low (3 to 6 subjects), if there is some evidence that the change from baseline is greater with the higher dose(s) as seen in scatterplots and mean value summary tables, then this would be suggestive of a

possible treatment effect (i.e. increased dose = increased effect). The by-subject listings will also include possible predictor factors (e.g. gender, CEA at baseline) which will be specified in the SAP by the medical/clinical input. If helpful some of the factors may also be included in the summary displays (i.e. graphs and tables) to aid in interpretation.

10.4.4 SAFETY ANALYSES

All safety analyses will be presented as part of the primary endpoint analysis.

10.4.5 ADHERENCE AND RETENTION ANALYSES

All subjects who are enrolled and treated in the trial will be accounted for. Subjects terminating early will be noted and the reasons provided.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Complete demographic, medical history (coded in MedDRA) and disease history will be summarized for each of the dose groups.

10.4.7 PLANNED INTERIM ANALYSES

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.

10.4.7.1 SAFETY REVIEW

The safety review will be ongoing for this dose-escalation trial, as outlined in sections 6.1.7 and 8.1

10.4.7.2 EFFICACY REVIEW

There is no formal plan to review the imaging data results on an ongoing basis. However given the early phase of development, if there is an increase in the number of early terminations due to disease progression, a formal safety review may be instigated.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

Not applicable.

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

Not applicable.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

All data collected in the trial and any calculated outcomes derived from this data will, at a minimum, be listed with the dose group, subject identifier and a timepoint, if relevant. The organization of the listings will support the writing of the Clinical Study Report (CSR) as outlined in the ICH E3 guidelines.

10.4.11 EXPLORATORY ANALYSES

Not applicable.

10.4.12 CONCOMITANT MEDICATION

All medication taken during the trial will be, at a minimum, listed with the start and stop dates. For this small clinical trial, the medications will not be coded using the WHO Drug Dictionary.

10.5 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.

10.6 MEASURES TO MINIMIZE BIAS

10.6.1 ENROLLMENT/ RANDOMIZATION/ MASKING PROCEDURES

Not applicable.

10.6.2 EVALUATION OF SUCCESS OF BLINDING

Not applicable.

10.6.3 BREAKING THE STUDY BLIND/PARTICIPANT CODE

Not applicable.

11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

An eCRF is required and must be completed for each consenting and enrolled subject by qualified and authorized personnel. Subjects who fail the Screening assessments will not have an eCRF. All data in the eCRF must reflect the corresponding source document. Any corrections to entries made on the eCRF must be documented in a valid audit trail. Only data required by the protocol for the purposes of the study should be collected within the EDC.

The Investigator must maintain adequate and accurate source documents on which the eCRF for each subject are based. They will be separate and distinct from the eCRF. These records should include detailed notes on:

- The medical history prior to the subject's involvement in the study;
- Date of informed consent;
- The basic identifying information that links the subject's medical record with the eCRF;
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject;
- The medical condition during the subject's involvement in the study;

- All AE;
- The subject's exposure to the study medication;
- The subject's exposure to any concomitant therapy;
- All relevant observations and data on the condition of the subject throughout the trial;
- Justification for all entries in the subject's eCRF.

12 QUALITY ASSURANCE AND QUALITY CONTROL

Data required by the protocol will be collected and entered into a validated data management system that is compliant with all regulatory requirements. The eCRF is an electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each study subject.

Data recording must follow the instructions described in the CRF Completion Guidelines. The PI has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The PI or designee, as identified on Form FDA 1572, must electronically sign the completed eCRF for each participating subject to attest to their accuracy, authenticity, and completeness.

The EDC application being used in this study is TrialMaster® version 4.2.1 from OmniComm Systems. TrialMaster studies are hosted from a state-of-the-art data center with rigorous physical and electronic security. All data is backed up daily to Iron Mountain, in Ohio and is also backed up to a hurricane-proof bunker in Fort Lauderdale, Florida. OmniComm has achieved certification with European "Safe Harbor" regulations, meaning that all necessary measures are in place to protect patient confidentiality even with the data being stored in a US data center. The data management and statistical CRO, McDougall Scientific Ltd., ensures that the development of the eCRF follows their SOPs which are based on the Systems Development Life Cycle (SDLC) methodology. Access to the system is restricted by username and password; these are controlled by the Data Management CRO. All personnel using the system will be trained and the training documented. All changes to the database are recorded in an audit trail. The database will be locked when all outstanding queries have been addressed, all agreed-to data is marked as source-verified, and the PI has signed off on the eCRF contents.

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements.

13 ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1 ETHICAL STANDARD

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki. Sponsor and Investigator will comply with their responsibilities as defined in 21 CFR 312.50-312.70.

13.2 INSTITUTIONAL REVIEW BOARD

Before the start of the study, the study protocol, informed consent form and/or other appropriate documents will be submitted to the IRB and/or the authorities, in accordance with local legal requirements. It is the responsibility of the Investigator to assure that all aspects of the IRB review are conducted in accordance with current regulations. US Biotest and the Investigator must inform each other in writing that all ethical and legal requirements have been met before the first subject is enrolled in the study.

Amendments to the protocol will be subject to the same requirements as the original protocol. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

13.3 INFORMED CONSENT PROCESS

13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Subjects being considered for participation in this study will be provided an Informed Consent Form (ICF) to read and sign before being permitted to participate. The ICF will describe the study agent and any prior findings from previous studies; study procedures including the timing of study clinic visits and their responsibilities to adhere to those timelines; any risks which may be associated with the study agent or the procedures being carried out in the study; and all other items required under 21 CFR Part 50.25.

Subjects will be required to provide signed consent prior to any study-related procedures are carried out. The Investigator is required to document the process for obtaining informed consent in the source notes.

Subjects in the second phase of the study will have a different informed consent form than those in the dose escalation phase of the study due to variation in study schedules.

13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

The Investigator will obtain informed consent from each subject enrolled in the study, in accordance with the U.S. FDA regulations 21 CFR 50.20 - 50.27 and the laws and regulations of the state in which the investigation is being conducted. The IRB must approve ICF to be used by the Investigator. The Investigator will provide the sponsor with a copy of the written approval generated by the IRB or Ethics Committee before the Investigator will be permitted to enroll subjects into the study.

It is the responsibility of the Investigator to ensure that informed consent is obtained from the subject or his/her guardian or legal representative before any activity or treatment is undertaken which is not part of routine care. This includes, but is not limited to, the performance of diagnostic or therapeutic procedures and the administration of study agent. The draft version of the informed consent document will be modified by each site and reviewed and approved in writing by US Biotest prior to submission to the IRB.

Should a protocol amendment be made, the subject consent form may be revised to reflect the changes of the protocol. If the consent form is revised, it is the responsibility of the Investigator to ensure that an amended consent is approved by the IRB and signed by all subjects currently on study as well as those subsequently entered in the study.

The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the eCRF. The original, signed informed consent document must be maintained on file at the study site and be made available for review during monitoring visits and site audits.

13.4 PARTICIPANT AND DATA CONFIDENTIALITY

All local legal requirements regarding data protection will be enforced. All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from US Biotest.

The anonymity of participating subjects must be maintained to the extent required by law. Throughout documentation and evaluation, the subjects will be identified on eCRF and other documents submitted to US Biotest by their initials, birth date, and their subject number. The subjects will be told that all study findings will be stored and handled in strictest confidence, according to legal requirements, and that authorized research Investigators and agents of the FDA, the NCI, and authorized personnel of US Biotest have the right to inspect their medical records.

13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS OR DATA

Samples and data collected under this protocol are specifically for use in the evaluation and analyses being conducted in the study. Samples will not be available for purposes other than indicated within this protocol, and no genetic testing will be performed.

Access to stored samples will be limited to personnel authorized to have access at the site prior to shipping to the laboratories for analysis/assessment. Samples will be stored using codes assigned by the Sponsor or as required by the clinical laboratories.

Samples will only be retained until analysis is complete, following which samples will be disposed of according to the laboratory SOP. No samples will be retained for any future use.

Data will be kept in password-protected computers. Only Investigators and those delegated responsibility on the Delegation of Authority Log will have access to the samples and data.

13.5 FUTURE USE OF STORED SPECIMENS

Not applicable.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Black ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

For electronic source, the institution must provide a secure, validated electronic medical record (EMR) data management system that is 21 CFR Part 11 compliant and meets all regulatory requirements, regulations and quality standards.

Source documents will be maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents. Any discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

The EDC application being used in this study is TrialMaster version 4.2.1 from OmniComm Systems. TrialMaster studies are hosted from a state-of-the-art data center with rigorous physical and electronic security. All data is backed up daily to Iron Mountain, in Ohio and is also backed up to a hurricane-proof bunker in Fort Lauderdale, Florida. OmniComm has achieved certification with European "Safe Harbor" regulations, meaning that all necessary measures are in place to protect patient confidentiality even with the data being stored in a US data center. The data management and statistical CRO, McDougall Scientific Ltd., ensures that the development of the eCRF follows their SOP which are based on the Systems Development Life Cycle (SDLC) methodology. Access to the system is restricted by username and password; these are controlled by the Data Management CRO. All personnel using the system will be trained and the training documented. All changes to the database are recorded in an audit trail. The database will be locked when all outstanding queries have been addressed, all agreed-to data is marked as source-verified, and the PI has signed off on the eCRF contents.

Data recording must follow the instructions described in the eCRF Completion Guidelines. The PI has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The PI or designee, as identified on the Delegation of Responsibilities Log (and included on Form FDA 1572), must electronically sign the completed eCRF to attest to the accuracy, authenticity, and completeness of the data.

The database will be locked when all outstanding queries have been addressed, all agreed to data is marked as source verified, and the PI has signed off on the eCRF contents.

14.2 STUDY RECORDS RETENTION

The Investigator must retain a copy of all study documents in accordance with the FDA or local regulations, whichever are the more stringent.

The Investigator must maintain study documents:

- For a minimum of two years following the date the marketing application (NDA) is approved for the indication for which the drug was investigated for;
- For a minimum of two years following the release date of the final report, if no marketing application is to be filed, or if the marketing application is not approved for the indication of which the drug was investigated or is discontinued and the FDA has been notified; or,
- For a minimum of 15 years after the completion or discontinuation of the study to be filed in support of the registration in the European Union.

If the Investigator relocates, retires or withdraws from the study for any reason, the study records may be transferred to an acceptable designee, such as another Investigator, another institution, or the sponsor. The Investigator must obtain the sponsor's written permission before transferring or disposing of any records.

14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, Good Clinical Practice (GCP), FDA or IRB requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations as soon as possible after occurrence and identification of the protocol deviation. All deviations must be addressed in study source documents, reported to the Sponsor and to the data Management group.

The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

Serious non-compliance on the part of the site, and an inability of the Sponsor to bring the site back into compliance, will be reported to the FDA in accordance with their requirements.

14.4 PUBLICATION AND DATA SHARING POLICY

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. The sponsor will prepare an integrated clinical/statistical report. Publication/presentation of data is not allowed without explicit permission from US Biotest. Submission of data for publication/presentation will be coordinated and approved by US Biotest in collaboration with the Investigators.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in subjects or participants, including pharmacokinetic measures and AE. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Data entered to the ClinicalTrials.gov website will be in accordance with the FDA requirements for this registration and for publication of study results on that site.

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The study will be overseen by the Study Manager who will be responsible, together with the Investigators, for tracking enrolment, timelines, and deliverables, and other study-related performance.

All questions regarding the enrollment of subjects, regulatory requirements for the conduct of the study, safety reporting, or study conduct should be addressed to the Study Manager or Site Monitor designated by the sponsor. Contact information for the sponsor is provided near the beginning of this protocol and will be provided to the Investigator in separate study documents.

16 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical and therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. As required by the FDA, a Financial Disclosure Form will be completed by each person noted on the FDA Form 1572 for this study at the site, the original will be filed in the TMF and a copy will remain in the site's regulatory binder.

17 LIABILITY AND INSURANCE

The sponsor will take out reasonable third-party liability insurance coverage in accordance with all local legal requirements. This insurance will cover all parties involved in the trial including, but not necessarily limited to, the principal Investigator, clinical trial site, and subjects.

18 LITERATURE REFERENCES

Abraxane Package Insert. Celgene Company. Rev July 2015.

Allen, P. J., & Brennan, M. F. The management of cystic lesions of the pancreas. Adv Surg. 2007;41:211-228.

DeWitt, J., McGreevy, K., Schmidt, C. M., & Brugge, W. R. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. Gastrointest Endosc. 2009;70(4):710-723.

DeWitt, J. M., Al-Haddad, M., Sherman, S., LeBlanc, J., Schmidt, C. M., Sandrasegaran, K., et al. Alterations in cyst fluid genetics following endoscopic ultrasound-guided pancreatic cyst ablation with ethanol and paclitaxel. Endosc. 2014;46(06):457-464.

DiMaio, C.J., DeWitt, J.M. and Brugge, W.R. Ablation of pancreatic cystic lesions: the use of multiple endoscopic ultrasound-guided ethanol lavage sessions. Pancreas. 2011;40(5):664-668.

Farrell, J. J. Prevalence, diagnosis and management of pancreatic cystic neoplasms: current status and future directions. Gut Liver. 2015;9(5):571-589.

Fernández-del Castillo, C., & Warshaw, A. L. Cystic tumors of the pancreas. Surg Clin N Am. 1995;75(5):1001.

Ferrone, C. R., Correa-Gallego, C., Warshaw, A. L., Brugge, W. R., Forcione, D. G., Thayer, S. P., et al. Current trends in pancreatic cystic neoplasms. Arch Surg. 2009;144(5):448-454.

Gaujoux, S., Brennan, M. F., Gonen, M., D'Angelica, M. I., DeMatteo, R., Fong, Y., et al. Cystic lesions of the pancreas: changes in the presentation and management of 1,424 patients at a single institution over a 15-year time period. J Am College Surgeons. 2011;212(4):590-600.

Gómez, V., Takahashi, N., Levy, M. J., McGee, K. P., Jones, A., Huang, Y., et al. EUS-guided ethanol lavage does not reliably ablate pancreatic cystic neoplasms (with video). Gastrointest endosc. 2016;83(5):914-920.

Gianni, L., Kearns, C. M., Giani, A., Capri, G., Vigano, L., Lacatelli, A., et al. Nonlinear pharmacokinetics and metabolism of paclitaxel and its pharmacokinetic/pharmacodynamic relationships in humans. J Clin Oncol. 1995;13(1):180-190.

Greer, J. B., & Ferrone, C. R. Spectrum and classification of cystic neoplasms of the pancreas. Surg Oncol Clin N Am. 2016;25(2):339-350.

Hosein PJ, de Lima Lopes Jr G, Pastorini VH, Gomez C, Macintyre J, Zayas G, et al. A phase II trial of nab-Paclitaxel as second-line therapy in patients with advanced pancreatic cancer. Am J Clin Oncol. 2013 Apr 1; 36(2):151-6.

Jani, N., Bani Hani, M., Schulick, R. D., Hruban, R. H., & Cunningham, S. C. Diagnosis and management of cystic lesions of the pancreas. Diagn Ther Endosc. 2011:1-10.

Kirtane, T., & Bhutani, M. S. EUS for pancreatic cystic neoplasms: The roadmap to the future is much more than just a few shades of gray. Asian Pac J Trop Med. 2016;9(12):1218-1221.

Ko AH, Truong TG, Kantoff E, Jones KA, Dito E, Ong A, Tempero MA. A phase I trial of nab-paclitaxel, gemcitabine, and capecitabine for metastatic pancreatic cancer. Cancer Chemother Pharmacol. 2012 Dec;70(6):875.

Mills, K. M., Johnson, D. M., Middlebrooks, M., & Burton, G. V. Possible Drug‐Associated Pancreatitis after Paclitaxel‐Cremophor Administration. Pharmacother: J Human Pharmacol Drug Ther. 2000;20(1):95-97.

Moyer, M. T., Dye, C. E., Sharzehi, S., Ancrile, B., Mathew, A., McGarrity, T. J., et al. Is alcohol required for effective pancreatic cyst ablation? The prospective randomized CHARM trial pilot study. Endosc Int Open, 2016;4(05):E603-E607.

Muthusamy, V. R., Chandrasekhara, V., Acosta, R. D., Bruining, D. H., Chathadi, K. V., Eloubeidi, M. A., et al. The role of endoscopy in the diagnosis and treatment of cystic pancreatic neoplasms. Gastrointest Endosc, 2016;83(3):481-488.

National Cancer Institute (2016). SEER Stat Fact Sheets: Pancreas Cancer http://seer.cancer.gov/statfacts/html/pancreas.html Accessed September 13, 2016.

Oh, H. C., Seo, D. W., Lee, T. Y., Kim, J. Y., Lee, S. S., Lee, S. K., et al. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. Gastrointest Endosc. 2008;67(4):636-642.

Oh, H. C., Seo, D. W., Kim, S. C., Yu, E., Kim, K., Moon, S. H., et al. Septated cystic tumors of the pancreas: is it possible to treat them by endoscopic ultrasonography-guided intervention? Scand J Gastroenterol. 2009;44(2):242-247.

Oh, H. C., Seo, D. W., Song, T. J., Moon, S. H., Park, D. H., Lee, S. S., et al. Endoscopic ultrasonography-guided ethanol lavage with paclitaxel injection treats patients with pancreatic cysts. Gastroenterol. 2011;140(1):172-179.

Oh, H. C., Seo, D. W., Kim, S. H., Min, B., & Kim, J. Systemic effect of endoscopic ultrasonography-guided pancreatic cyst ablation with ethanol and paclitaxel. Dig Dis Sci. 2014;59(7):1573-1577.

Park, W. G., & Pasricha, P. J. The conundrum of pancreatic cysts: are we finally moving the (EUS) needle? Gastroenterol. 2011;140(1):28-31.

Park, J.K., Song, B.J., Ryu, J.K., Paik, W.H., Park, J.M., Kim, J., et al. Clinical outcomes of endoscopic ultrasonography–guided pancreatic cyst ablation. Pancreas. 2016;45(6);889-894.

Pitman, M. B., Lewandrowski, K., Shen, J., Sahani, D., Brugge, W., & Fernandez‐del Castillo, C. Pancreatic cysts. Cancer Cytopath. 2010;118(1):1-13.

Sarr, M. G., Carpenter, H. A., Prabhakar, L. P., Orchard, T. F., Hughes, S., van Heerden, J. A., et al. Clinical and Pathologic Correlation of 84 Mucinous Cystic Neoplasms of the Pancreas: Can One Reliably Differentiate Benign From Malignant (or Premalignant) Neoplasms?. Ann Surg. 2000;231(2):205–212.

Scheithauer W, Kornek G, Prager G, Stranzl N, Laengle F, Schindl M, et al. Phase II trial of capecitabine plus nab-paclitaxel in patients with metastatic pancreatic adenocarcinoma. J Gastrointest Oncol. 2016 Apr 7; 2:234.

Tamirisa, N. P., Parmar, A. D., Vargas, G. M., Mehta, H. B., Kilbane, E. M., Hall, B. L., et al. Relative contributions of complications and failure to rescue on mortality in older patients undergoing pancreatectomy. *Ann Surg*. 2016;*263*(2):385-391.

Tanaka, M., Chari, S., Adsay, V., Fernandez-del Castillo, C., Falconi, M., Shimizu, M., et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatol. 2006;6(1-2):17-32.

Taxol Package Insert. Bristol-Myers Squibb Company. Rev April 2011.

Ueno H, Ikeda M, Ueno M, Mizuno N, Ioka T, Omuro Y, et al. Phase I/II study of nab-paclitaxel plus gemcitabine for chemotherapy-naive Japanese patients with metastatic pancreatic cancer. Cancer Chemother Pharmacol. 2016; 3(77):595-603.

Von Hoff DD, Ervin T, Arena FP, Chiorean EG, Infante J, Moore M, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013 Oct 31; 369(18):1691-703.

Williamson, S. K., Johnson, G. A., Maulhardt, H. A., Moore, K. M., McMeekin, D. S., Schulz, T. K., et al. A phase I study of intraperitoneal nanoparticulate paclitaxel (Nanotax®) in patients with peritoneal malignancies. Cancer chemother pharmacol. 2015;75(5):1075-1087.

Zhang DS, Wang DS, Wang ZQ, Wang FH, Luo HY, Qiu MZ, et al. Phase I/II study of albumin-bound nab-paclitaxel plus gemcitabine administered to Chinese patients with advanced pancreatic cancer. Cancer Chemother Pharmacol. 2013 Apr 1; 71(4):1065-72.

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.