Phase IIa Trial Evaluating the Safety of Intratumoral Injection of NanoPac in Subjects with Locally Advanced Pancreatic Adenocarcinoma

Protocol Identifying Number: NANOPAC-2016-05

IND Sponsor: NanOlogy, LLC

IND #: 132692

Version Number: 7.0

25 March 2020

Table of Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ASP	Alkaline Phosphatase
BUN	Blood Urea Nitrogen
CEA	Carcinoembryonic Antigen
CLIA	Clinical Laboratory Improvement Amendments
CO2	Carbon Dioxide
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture System
EUS	Endoscopic Ultrasound
eCRF	Electronic Case Report Form
FDA	The U.S. Food and Drug Administration
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
FNA	Fine Needle Aspiration
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
IFU	Instructions for Use
IND	Investigational New Drug Application
IP	Intraperitoneal
IRB	Institutional Review Board
ITU	Intratumoral
IV	Intravenous
LDH	Lactate Dehydrogenase
MAC	Monitored Anesthesia Care
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
NCI	National Cancer Institute
NDA	New Drug Application (Marketing Application)
OHRP	Office for Human Research Protections
PCA	Precipitation with Compressed Antisolvents
pH	Hydrogen Ion Concentration
PI	Principal Investigator

PK	Pharmacokinetics
PT	Prothrombin Time
PTT	Activated Partial Thromboplastin Time
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDLC	Systems Development Life Cycle
SOC	Standard of Care
TEAE	Treatment-emergent Adverse Event
ULN	Upper Limit of Normal
UP	Unanticipated Problem
USC	University of Southern California
VAS	Visual Analog Score
WBC	White Blood Cell

SPONSOR SIGNATURE PAGE

Protocol Title:	Phase IIa Trial Evaluating the Safety of Intratumoral Injection of NanoPac in Subjects with Locally Advanced Pancreatic Adenocarcinoma
Protocol Number:	NANOPAC-2016-05
Version Number:	7.0
Date:	25 March 2020
IND Number:	132692
Investigational Product:	NanoPac® (sterile nanoparticulate paclitaxel) Powder for Suspension
Sponsor:	NanOlogy, LLC 231 Bonetti Dr., Suite 240 San Luis Obispo, CA 93401-7310 805-595-1300

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 (Mar 31, 2020)

Signature of Sponsor's Representative

Mar 31, 2020

Date

STATEMENT OF COMPLIANCE

I have read the attached protocol number NANOPAC-2016-05 entitled, *Phase IIa Trial Evaluating the Safety of Intratumoral Injection of NanoPac in Subjects with Locally Advanced Pancreatic Adenocarcinoma*, Version 7.0 dated 25 March 2020 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 US Biotest, Inc. The recipient agrees that no unpublished information contained herein will be published or disclosed without prior written permission of US Biotest. 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: Phase IIa Trial Evaluating the Safety of Intratumoral Injection of NanoPac in Subjects with Locally Advanced Pancreatic Adenocarcinoma

Précis: In this open-label, dose rising, Phase IIa trial, subjects with locally advanced pancreatic adenocarcinoma will receive intratumoral (ITU) NanoPac (sterile nanoparticulate paclitaxel) via endoscopic ultrasound (EUS)-guided direct injection. Prior to study entry, subjects in the dose escalation phase of the study will complete at least one course of standard of care (SOC) IV chemotherapy and hematologic recovery will be confirmed before NanoPac is administered; subjects enrolling to the second and third phases will have initiated their SOC IV chemotherapy.

Subjects in the dose escalation phase will be enrolled in sequential cohorts of NanoPac 6, 10, and 15 mg/mL at up to 20% of the calculated tumor volume (with a maximum injection volume of 5 mL per subject). 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 subjects 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 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 22 additional subjects who will receive two injections of NanoPac at the same dose, one month apart. In the third phase of the study, up to 30 subejcts will receive up to four injections of NanoPac at the same dose, one month apart.

Plasma samples will be taken on the day of NanoPac injection pre-injection and at 1, 2, 4, 6, and 24 hours after injection, as well as at each of the study visits in the dose escalation phase of the study, and at 1 and 2 hours after each injection and at all other study visits in the second and third phases of the study, to characterize the pharmacokinetics (PK) of intratumoral NanoPac.

Subjects will be followed for 3 months after NanoPac injection for safety, overall survival (OS), progression-free survival (PFS), CA-19-9 levels, carcinoembryonic antigen (CEA) levels, reduction in pain, and tumor response to therapy (as shown by imaging). A follow-up visit may be conducted at 6 months, as applicable. Subjects in the second phase of the study, following their 1 month follow-up, will receive a second injection, and these subjects will be followed for a further 6 months after this second injection. Subjects in the third phase of the study will receive up to four injections, 1 month apart, and will be followed for 6 months after their last injection.

Objectives: Primary objective:

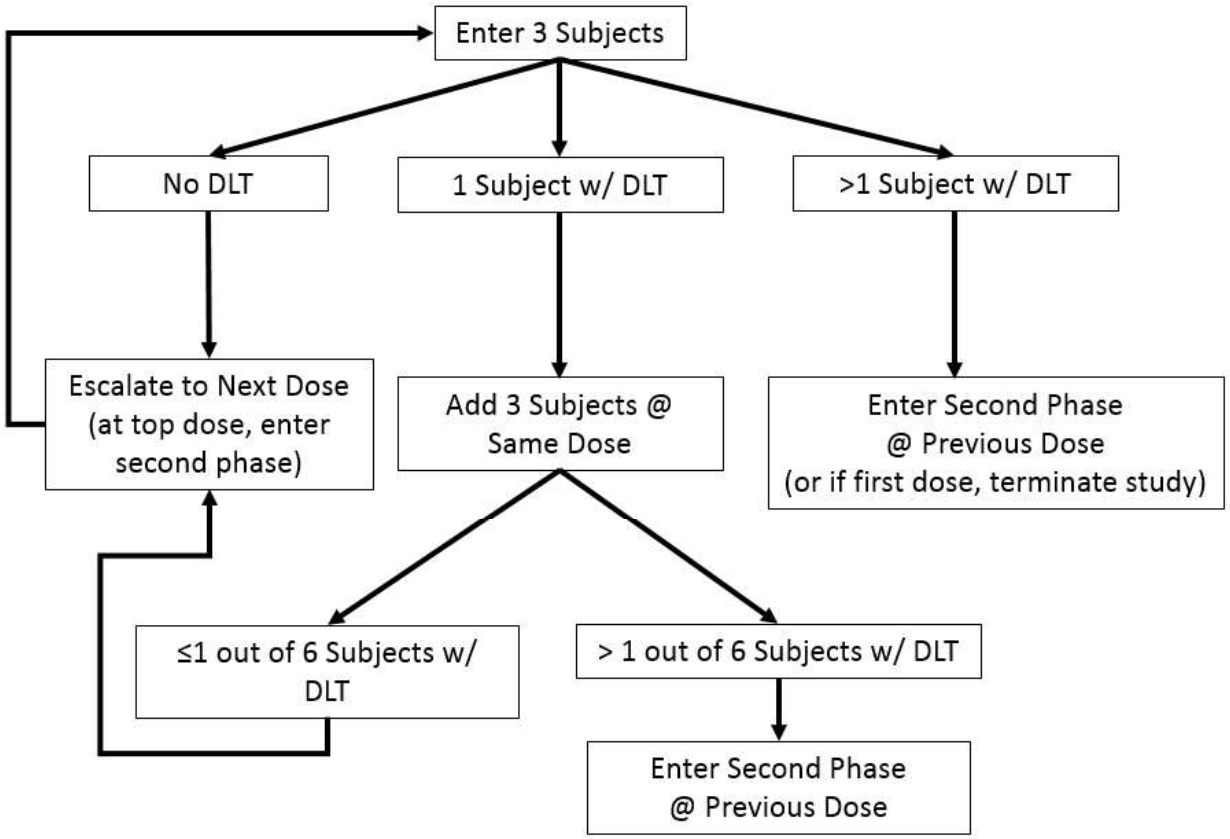
- To evaluate the safety and tolerability of NanoPac injected directly into pancreatic cancer by EUS-guided injection.

Secondary objectives:

- To describe the PK of NanoPac when administered into the tumor within the pancreas.
- To determine whether any of the NanoPac cohorts (6, 10, or 15 mg/mL) show signs of preliminary efficacy.
- To determine if two to four injections of NanoPac (1 month apart at the determined dose for this cohort) shows signs of preliminary efficacy.

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); • Tumor response (RECIST as per Eisenhauer et al. 2009); • Reduction in pain (as measured by the visual analog scale [VAS]); • Change in tumor marker CA19-9; • Change in tumor marker CEA.
Population:	Up to 65 subjects with locally advanced pancreatic adenocarcinoma
Phase:	Phase IIa
Number of Sites enrolling participants:	Up to five
Description of Study Agent:	NanoPac® (sterile nanoparticulate paclitaxel) Powder for Suspension ("NanoPac") at concentrations of 6, 10, and 15 mg/mL administered into the tumor within the pancreas via EUS-guided fine needle injection.
Study Duration:	Up to 48 months.
Participant Duration:	Estimated to be up to 7 months for each subject in the dose escalation phase of the study, up to 8 months for each subject in the second phase of the study, and up to 10 months for subjects in the third phase of the study. Additional follow-up may occur.

SCHEMATIC OF STUDY DESIGN FOR DOSE ESCALATION



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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, previously called Nanotax®, 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 cancer have not yet been completed. NanoPac demonstrated preliminary safety and efficacy when injected intratumorally (ITU) in animals with solid tumors; this data (as well as data from additional animal models) is presented in the NanoPac Investigator's Brochure.

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

In the first 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 ITU 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 tumor xenograft study, mice treated with NanoPac (37.5 mg/kg, qwk x 3) via ITU 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 (EUS)-guided fine needle injection. Two clinical trials with NanoPac have been completed to date.

Clinical trial HSC#11140, "A Phase I Study of Intraperitoneal Nanoparticle Paclitaxel in Patients with Peritoneal Malignancies," was conducted under IND 073529. The results of this study were published by Williamson et al.

(2015) in the journal *Cancer Chemotherapy and Pharmacology*. Clinical trial 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. IP administration of NanoPac 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 NanoPac treatment. There were no cases of bowel obstruction. Additional data from this clinical trial is presented in the NanoPac Investigator's Brochure.

Clinical trial NANOPAC-2016-02, entitled "Phase IIa Dose Escalation Trial of NanoPac Focal Therapy for Prostate Cancer in Subjects Undergoing Radical Prostatectomy," was an open-label, dose-rising study to evaluate the safety and tolerability of NanoPac administered via intraprostatic injection in men with localized adenocarcinoma of the prostate. NanoPac was injected at doses of 6, 10, and 15 mg/mL in a volume equaling ≤ 20% of the lobe of the prostate containing the dominant lesion. Injection was performed under magnetic resonance imaging-transrectal ultrasound fusion (MR-TRUS) guidance directly into the lobe of the prostate containing the dominant lesion. A total of 16 subjects were enrolled to the study, three in the 6 mg/mL dose group, three in the 10 mg/mL dose group, and 10 in the 15 mg/mL dose group. The majority of subjects experienced treatment emergent adverse events (TEAEs) as expected, but with minimal frequency, severity, and relation to NanoPac. The most frequent TEAEs occurred in the system organ class of gastrointestinal disorders, most of which were in the 6mg/mL cohort. There was no obvious dose-response relationship with respect to the frequencies of the TEAEs at the three concentrations of NanoPac. No DLTs or toxicities typically attributable to IV paclitaxel such as neutropenia, thrombocytopenia, peripheral neuropathy, and hypersensitivity reactions such as angioedema and urticaria were reported. There were no SAEs, deaths, or discontinuations from the study due to AEs. The mean total Gleason score remained stable in the 6mg/mL and 10mg/mL cohorts, and improved in the 15mg/mL cohort, implying a possible dose-response relationship. The proportion of the primary lesion considered adenocarcinoma improved in the 6mg/mL and 15mg/mL cohorts but increased in the 10mg/mL cohort. PSA Density decreased (mean change from Baseline) in all three cohorts.

Under IND 073529, protocol NANOPAC-2016-01, a Phase II study of four concentrations of intraperitoneal NanoPac plus six cycles of IV carboplatin and paclitaxel in subjects with platinum-sensitive recurrent stage III epithelial ovarian cancer undergoing second cytoreductive surgery, is completed and in the reporting phase.

Under IND 132692, protocol NANOPAC-2017-01, a trial of intracystic injection of NanoPac in subjects with mucinous cystic pancreatic neoplasms, has recently completed enrollment.

Relevant Literature:

Paclitaxel, formulated as ABRAXANE (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) ("nab-paclitaxel") is FDA-approved as first-line treatment, in combination with gemcitabine, for metastatic adenocarcinoma of the pancreas (ABRAXANE Package Insert). Numerous studies have confirmed that pancreatic cancer is sensitive to paclitaxel when administered as an intravenous infusion (Scheithauer et al. 2016; Ueno et al. 2016; Hosein et al. 2013; Von Hoff et al. 2013; Zhang et al. 2013; Ko et al. 2012). Paclitaxel has been administered via direct injection to the pancreas for the treatment of pancreatic cysts (Oh et al. 2008; Oh et al. 2011; DeWitt et al. 2014).

Importance of the study:

Pancreatic cancer is an aggressive and rapidly fatal malignancy. In 2013, pancreatic cancer was diagnosed in approximately 45,220 Americans and caused 38,460 deaths. It is the ninth most common cancer, yet it is the fourth leading cause of cancer death (Eskander et al. 2016). The incidence of pancreatic cancer is rising and it is expected to be the second leading cause of cancer-related death by 2030 (Matrisian & Berlin 2016). At the time of diagnosis, more than 80% of patients with pancreatic cancer have metastatic or inoperable disease (Chiorean & van Hoff 2016), which is reflected in the five-year overall survival rate of less than 8% (Eskander et al. 2016; Gong et al. 2016).

Pancreatic cancer demonstrates a limited response to the intravenous administration of chemotherapy (Cantore et al. 2000). This is likely due to the desmoplastic, fibrotic microenvironment created by pancreatic cancer, which blocks transport and diffusion of small molecules (Heinemann et al. 2014). Surgery is the only potentially curative treatment for pancreatic cancer (Eskander et al. 2016), yet only 10-20% of patients are candidates for surgery at initial presentation and, even with surgery, up to 92% of patients will experience disease recurrence within two years (Smyth & Cunningham 2015; Gong et al. 2016).

2.2 RATIONALE

This Phase IIa study will include subjects with adenocarcinoma of the pancreas. Only those subjects who are not candidates for surgery will be enrolled in the study. The study design allows for a safety evaluation of EUS-guided fine needle injection of NanoPac into the tumor within the pancreas.

Pancreatic cancer cells are particularly sensitive to paclitaxel, which outperforms gemcitabine in an *in vitro* model of chemoresistant pancreatic cancer (Indolfi et al. 2016). ABRAXANE is FDA-approved as first-line treatment, in combination with gemcitabine, for metastatic adenocarcinoma of the pancreas and has demonstrated significant efficacy in numerous clinical studies (Scheithauer et al. 2016; Ueno et al. 2016; Hosein et al. 2013; Von Hoff et al. 2013; Zhang et al. 2013; Ko et al. 2012). In order to inject pancreatic cancer directly, a minimally invasive procedure known as EUS-guided fine needle injection is proposed for this Phase IIa study. The safety and feasibility of this procedure have been demonstrated in numerous studies (Wang et al. 2011; Kaplan et al. 2015).

In contrast with IV administration, direct injection of paclitaxel should allow for higher concentrations of drug to target local disease with reduced systemic toxicity. ITU NanoPac is expected to be more effective than IV paclitaxel, as the EUS-guided fine needle injection will bypass the fibrotic stroma that acts as a barrier to IV chemotherapy. NanoPac may also allow for prolonged residence and dissolution within the pancreas, resulting in continuous and greater paclitaxel concentrations in the tumor site.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

There are no known potential risks from ITU injection of NanoPac.

2.3.2 KNOWN POTENTIAL BENEFITS

There are no known potential benefits of ITU injection of NanoPac. However, paclitaxel formulated as ABRAXANE is FDA-approved as first-line treatment, in combination with gemcitabine, for metastatic adenocarcinoma of the

pancreas and has demonstrated significant efficacy in numerous clinical studies of pancreatic cancer (Scheithauer et al. 2016; Ueno et al. 2016; Hosein et al. 2013; Von Hoff et al. 2013; Zhang et al. 2013; Ko et al. 2012).

3 OBJECTIVES AND PURPOSE

The primary objective of this study is to evaluate the safety and tolerability of NanoPac injected directly into pancreatic cancer by EUS-guided fine needle injection. Secondary objectives are (a) to describe the pharmacokinetics of NanoPac when administered into the tumor within the pancreas, and (b) to determine whether any of the 6, 10, and 15 mg/mL NanoPac dose cohorts show signs of preliminary efficacy, and (c) to determine if the selected dose from the escalation phase of the study, when injected on up to four occasions 1 month apart, shows signs of preliminary efficacy .

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

In this open-label Phase IIa trial, subjects with locally advanced pancreatic adenocarcinoma will have completed at least one course of chemotherapy as part of Standard of Care (SOC) in the dose escalation phase of the study. Once there is sufficient hematologic recovery (see Section 5.1), subjects will receive ITU NanoPac via EUS-guided direct injection. Subjects will be followed for overall survival (OS), progression-free survival (PFS), CA-19-9 levels, carcinoembryonic antigen (CEA) levels, reduction in pain, and tumor response to therapy (as shown by imaging) while on study. Additional information on PFS and OS may be obtained at 9 and 12 months after the initial NanoPac injection.

Subjects will be enrolled in sequential, escalating cohorts of NanoPac at concentrations of 6, 10, or 15 mg/mL injected directly into the tumor within the pancreas at up to 20% tumor volume (with a maximum of 5 mL volume being administered to any subject). The study will include a dose escalation phase, a second phase which allows for subjects to receive two injections of NanoPac 1 month apart, and a third phase which allows for subjects to receive up to four injections of NanoPac 1 month apart.

For subjects enrolling to the second and third phases, at the dose selected from the dose escalation phase, subjects will have intiated their IV chemotherapy prior to first injection.

Tumor Volume Calculations

If more than one lesion is present in the pancreas of a subject, the Investigator will select a single target lesion and will treat only this target lesion. The single target lesion must have a diameter of at least 1.5 cm but no more than 6 cm as demonstrated via imaging within 6 weeks of study entry. A CT scan will be performed between the Screening visit and the Day of Injection Visit in the second and third phases of the study to obtain a study baseline image against which future imaging will be compared. The tumor volume measurement and injection volume will be determined immediately prior to the NanoPac injection procedure using the ultrasound image. The ultrasound image obtained at the time of the NanoPac injection procedure will provide the lesion measurement at the widest point of the tumor. Tumor volume may be calculated as $\mathbf{V=1/6 \bullet \pi \bullet d^3}$ if not automatically calculated via the imaging software.

Based on these tumor volume calculations at the time of the NanoPac injection procedure, an amount of NanoPac equal to 20% of tumor volume, not to exceed 5 mL in any subject, may be injected into the tumor. The Investigator

may use his discretion, on a subject-by-subject basis, to inject the entire 20% tumor volume or to use a lesser amount as he deems necessary for each individual subject's safety. Examples of tumor volume and injection volume calculations are provided in the table below. Pharmacy will provide the Investigator with 5mLs of reconstituted NanoPac for use in the procedure room, and documentation detailing the volume calculations in the procedure room will be provided in the source.

Examples to Demonstrate Volume Calculations[1]					
Ultrasound Measured Diameter (cm)	**Tumor Volume (mL) $V=1/6 \bullet \pi \bullet d^3$**	**Injection Volume (mL) (20% Tumor Volume)**	**Total (mg) NanoPac Administered at 6 mg/mL**	**Total (mg) NanoPac Administered at 10 mg/mL**	**Total (mg) NanoPac Administered at 15 mg/mL**
1.5	1.8	0.4	2.4	4.0	6.0
2.0	4.2	0.8	**4.8**	**8.0**	**12.0**
2.5	8.2	1.6	**9.6**	**16.0**	**24.0**
3.0	14.1	2.8	**16.8**	**28.0**	**42.0**
3.5	22.4	4.5	**27.0**	**45.0**	**67.5**
4.0	33.5	5.0[2]	30.0[3]	50.0[3]	75.0[3]
4.5	47.7	5.0[2]	30.0[3]	50.0[3]	75.0[3]
5.0	65.4	5.0[2]	30.0[3]	50.0[3]	75.0[3]
5.5	87.1	5.0[2]	30.0[3]	50.0[3]	75.0[3]
6.0	113.0	5.0[2]	30.0[3]	50.0[3]	75.0[3]

[1] All values in table have been rounded to a single decimal. The calculations for total NanoPac administered were performed with the rounded injection volume as this would be the amount administered in a clinical setting.
[2] Twenty percent (20%) of the volume of tumors this size would exceed the 5 mL maximum injection volume and thus could not be administered. In such a situation, where 20% tumor volume exceeds 5.0 mL, the maximum 5 mL of NanoPac would instead be administered as the injection volume.
[3] Based on 5 mL maximum injection volume.

Dose Escalation of Cohorts

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 2-week follow-up visit, and will assess safety and tolerability based on the DSMB Charter, which will include reference to dose-limiting toxicities (DLTs). 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 of Study

Once the dose deemed appropriate for expansion and further evaluation has been determined by the DSMB, an additional 22 subjects will be enrolled to the study and this cohort of subjects will receive two NanoPac injections to their lesion one month apart.

Third Phase of Study

Up to 30 additional subjects will be enrolled to receive up to four NanoPac injections to their lesion, 1 month apart.

PK Analysis

Plasma samples will be taken on the day of injection prior to injection and at 1, 2, 4, 6, and 24 hours after NanoPac injection, as well as at all other study visits in the dose escalation phase of the study, and at 1, and 2 hours after each injection and at all other study visits in the second and third phases of the study, to characterize the pharmacokinetics of ITU NanoPac. Subjects will be followed for 3 months after NanoPac injection for safety and response to therapy. A further follow-up may be conducted at 6 months as appropriate for the subject (see Section 7.3.4). Subjects in the second phase of the study, following their 1 month evaluations, will receive a second injection, and these subjects will be followed for a further 6 months after this second injection (study completion at Month 7). Subjects in the third phase of the study will receive up to four injections 1 month apart, and will be followed for a further 6 months after their last injection (study completion at Month 9 if all injections are received).

4.2 ENDPOINTS

4.2.1 PRIMARY ENDPOINT

The primary endpoint will be safety and tolerability, as assessed by adverse events (AE), changes in vital signs, laboratory results, and physical examination at one month following NanoPac injection.

4.2.2 SECONDARY ENDPOINTS

The secondary endpoints will be:

- Concentration of paclitaxel in the systemic circulation post-injection (as determined by PK analysis);
- Tumor response (RECIST as per Eisenhauer et al. 2009);
- Reduction in pain (as measured by the visual analog scale [VAS]);
- Change in tumor marker CA19-9;
- Change in tumor marker CEA.

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;
- Histologically/cytologically confirmed locally advanced pancreatic adenocarcinoma;
- At least one lesion with a diameter of at least 1.5 cm but no more than 6 cm as documented via imaging (within 6 weeks of Screening);
- Subject is not a candidate for surgery;
- Completion of at least one standard of care IV chemotherapy course for subjects in the dose escalation phase of the study. IV chemotherapy will be initiated prior to first NanoPac injection for subjects in the second and third phase; hematologic recovery with a platelet count ≥ 75 x 10^9/L and ANC ≥ 1.5 x 10^9/L must be confirmed prior to study entry;
- Performance Status (ECOG) 0-1 at study entry;
- Life expectancy of at least 3 months;
- Adequate marrow, liver, and renal function at study entry;
    - ANC ≥ 1.5 x 10^9/L
    - Hemoglobin ≥ 9.5 grams/dL
    - Platelets ≥ 75 x 10^9/L
    - Total bilirubin ≤ 1.5x institutional ULN
    - AST/ ALT ≤ 2.5x institutional ULN
    - Creatinine ≤ 1.5x institutional ULN
- Appropriate steps taken to minimize or avoid the potential for pregnancy for subjects of child-bearing potential.*

** 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. 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.*

5.2 PARTICIPANT EXCLUSION CRITERIA

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

- Thrombotic or embolic events;
- Acute or subacute intestinal occlusion;
- History of inflammatory bowel disease;
- Known hypersensitivity to study drugs;
- Known drug or alcohol abuse;
- Pregnant or breastfeeding women;
- Previous or concurrent history of non-pancreatic malignancy except for non-melanoma skin cancer.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Sufficient subjects will be screened to allow up to 65 subjects to be enrolled in the trial. Subjects will be recruited at up to five study sites. 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 in the dose

escalation phase of the study. The first three subjects in the second phase will also be reviewed by the DSMB following their second injection to confirm safety in this group; the DSMB will be provided information on the first three subjects in the third phase following completion of their injections to confirm safety in this group.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Subjects are free to withdraw from participation in the study at any time upon request. The 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 6 months after the last NanoPac injection. For subjects wishing to pursue other treatment options (such as other clinical trials) sooner than 6 months after NanoPac injection, the final study visit may be conducted sooner.

There is no reason currently anticipated that would cause the Investigator to terminate a subject's participation in the study once the treatment has been administered. It is very important that any events occurring be captured and followed for the safety of the subject.

- Subjects may be non-compliant with the study protocol in a way that much of the data is not captured which would usually require withdrawal for non-compliance; however, any data points missed would be considered "missing data." A subject would not be withdrawn in this situation.
- Clinical AE, laboratory abnormalities, or other medical conditions/situations may occur which would usually require withdrawal from a study. In this instance it is very important that all of these events be captured, followed, and documented, and therefore a subject would not be withdrawn but would continue to completion.

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 terminate 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 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 DLTs.
    - 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, where subjects receive two NanoPac injections one month apart, if one third of the subjects (i.e., 4 subjects) experience the same DLT the study may be stopped, future subjects in the second phase may receive a single NanoPac injection (second injection not administered), or remaining subjects may receive a lower dose of the study drug as determined by the DSMB.
    - In the third phase of the study, where subjects receive up to four NanoPac injections 1 month apart, if one third of the subjects (i.e., 10 subjects) experience the same DLT the study may be stopped or future subjects in the third phase may receive fewer NanoPac injections.
- Insufficient compliance with protocol requirements;
- Data that are not sufficiently complete and/or evaluable;
- Determination of futility.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the Sponsor, IRB, and/or 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 at 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 Section 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 to include details as follows:

"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 clinical site's pharmacy, temperature controlled at 59˚ to 86˚F (15˚ to 30˚C).

Once the NanoPac has been reconstituted, it will 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 syringe may be stored according to the IFU until delivery. Each vial used and each syringe must be labelled with the subject's ID and visit information for accountability purposes.

6.1.4 PREPARATION

A prescription will be provided for each subject detailing the subject ID, the cohort to which the subject is assigned, and the date and time required for administration. This 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 15mg/mL, according to cohort assignment), the maximum injection volume of 5 mL will be withdrawn, as described in the IFU, from the vial into a syringe. The precise volume to be injected will be determined by the physician prior to the injection procedure using EUS. The syringe for administration will be labeled with the subject ID 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 tumor. The tumor 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 filled with the study treatment, NanoPac, from the syringe provided. 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 path to tumor. Using a 22-gauge needle, NanoPac will be injected (according to the cohort, at a concentration of 6, 10, or 15 mg/mL) using multiple passes of the needle in a fan-like pattern of withdrawal and reinsertion, fanning to the periphery of the tumor to ensure that NanoPac is infused evenly throughout the entirety of the tumor. The Investigator will use their discretion to inject NanoPac in a volume up to 20% of the tumor volume (calculated as described in section 4.1), with a maximum injection volume of 5 mL in any subject.

6.1.6 ROUTE OF ADMINISTRATION

NanoPac will be administered directly into the tumor within the pancreas using EUS-guided direct injection.

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

NanoPac will be administered in concentrations based on cohort assignment. Investigators will use their discretion to administer a volume of up to 20% of the tumor volume (as calculated in Section 4.1). Volume administered will not exceed 5 mL in any subject. 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 DLTs 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 2-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 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 dose administered in the second and third phases of the study will be the highest dose considered to be safe and tolerable in the dose escalation pahse.

Included in the DSMB's review of AEs and general study data pertaining to safety (such as laboratory results and questionnaire responses) 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 AEs; DLTs will, in addition, include the following :

- ≥ Grade 3 pancreatico-biliary events (including but not limited to symptomatic pancreatitis or cholangitis, excluding asymptomatic time-limited pancreatic enzyme elevations);
- ≥ Grade 3 febrile neutropenia;

- Grade 3 diarrhea and vomiting lasting more than 72 hours, or Grade 4 diarrhea and vomiting;
- Grade 4 neutropenia lasting 5 days;
- Grade 4 thrombocytopenia;
- Grade 4 biliary toxicity;
- 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

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

In the second and third phases of the study, where more than one NanoPac injection will be given to each participant, there is a possibility that the dose may be adjusted (reduction in number of injections) based on safety, and this will be discussed and determined between the Investigator and the Medical Monitor on a case by case basis. The DSMB may also determine, upon review of the first three subjects in this phase, that adjustment is required for the remaining subjects in this cohort.

It is possible that the full 20% tumor volume for a particular subject will not be able to be administered, and the Principal Investigator will determine this at the time of injection. In the event not all of the calculated volume of NanoPac can be administered, the amount not injected will be measured once the needle is removed and the volume remaining will be noted in the source document.

6.1.9 DURATION OF THERAPY

A single administration of NanoPac is being injected directly into the tumor within the pancreas on either a single occasion (dose escalation phase) or on up to fours occasions 1 month apart (two in the second phase, or up to four in the third phase). Each administration/dose of NanoPac is delivered in 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.

If the investigator determines that the full volume of NanoPac (20% tumor volume as calculated in Section 4.1) cannot be administered, the Investigator will document the amount of NanoPac injected, and the volume remaining, in the source document and in the EDC.

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;
- Review and documentation of diagnosis of adenocarcinoma of the pancreas and previous treatments including surgical and chemotherapeutic records. A copy of the pathology report confirming the diagnosis and the imaging reports must be filed in the subject's study record.
- Confirmation of hematologic recovery (platelets ≥ 75 x 10^9/L and ANC ≥ 1.5 x 10^9/L) must be obtained prior to NanoPac administration and filed in the subject's study record;
- Comprehensive physical examination, including ECOG Performance Status assessment (see Appendix A), and vital signs (blood pressure, heart rate, temperature, body weight and height);
- In the second phase of the study, prior to injection a CT Scan will be obtained to provide baseline data on dimensions and volume of the lesion to be injected;
- Pharmacokinetic (PK) samples will be taken on Day 1 prior to injection, and at 1, 2, 4, 6, and 24 hours post-injection, and again at all study visits post-injection for subjects in the dose escalation phase of the study; for subjects in the second and third phases of the study, PK samples will be obtained prior to each injection and at 1 and 2 hours post injection, and at all other study visits.
- In the third phase of the study, a blood sample will be obtained from subjects for exploratory evaluation of immune markers (using flow cytometry at a central laboratory) prior to injection at each injection visit and also at the 6-month follow-up visit.
- Serum CA-19-9 levels obtained at screening, on the day of NanoPac administration prior to injection (NanoPac Day 1), and at 2 weeks, 4 weeks, 2 months, 3 months, and 6 months post-injection for the subjects in the dose escalation phase of the study; for the subjects in the second and third phases the sample at injection visits will be taken prior to injection, and these subjects will have samples taken at all remaining study visits.
- Serum carcinoembryonic antigen (CEA) levels obtained at screening, on the day of NanoPac administration prior to injection, and at 2 weeks, 4 weeks, 2 months, 3 months, and 6 months post-injection for the subjects in the dose escalation phase of the study; for the subjects in the second and third phases the sample at injection visits will be taken prior to injection, and these subjects will have samples taken at all remaining study visits.
- Samples will be collected and processed for clinical laboratory assessment at screening, and on the day of NanoPac injection prior to treatment; and at 2 weeks, 4 weeks, 2 months, 3 months, and 6 months post-

injection for the subjects in the dose escalation phase of the study; for the subjects in the second and third phases the sample at the injection visit will be taken prior to injection, and these subjects will have samples taken at all remaining study visits.

- Assessments will include:
  - Sodium, potassium, chloride, carbon dioxide (CO2), calcium, phosphorus, glucose, blood urea nitrogen (BUN), creatinine, serum lipase, serum amylase, alkaline phosphatase, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total protein, albumin, triglycerides, cholesterol, 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);
- Pain will be assessed with the visual analog scale (VAS) at screening, on the day of NanoPac administration (pre- and post-injection), and at 2 and 4 weeks, 2 months, 3 months, and 6 months post-injection for the subjects in the dose escalation phase of the study; for the subjects in the second and third phases the assessments at injection visits will be conducted pre- and post-injection and at all other study visits..
- Imaging with CT scan will have occurred prior to injection (within 6 weeks in order to estimate tumor volume), at 3 months post-injection, and at end-of-study (6 months after NanoPac injection) for the subjects in the dose escalation phase of the study; for the subjects in the second phase of the study a CT Scan will be obtained following consent and prior to first injection, 3 months past first injection (at the Week 12 visit), and at the 6 month visit; for the subjects in the third phase of the study a CT Scan will be obtained following consent and prior to first injection, 3 months after the first injection (at the Week 12 visit) which will be their fourth injection visit (if they have all four injections), at the 6 month visit, and at the 9 month visit. 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.
- EUS-guided fine needle injection of the tumor within the pancreas with 6, 10, or 15 mg/mL NanoPac at a volume up to 20% of tumor volume (as calculated in Section 4.1), depending on study cohort assignment. Subjects in the dose escalation phase of the study will receive one injection on Day 1. In the second phase of the study, once the selected dose for expansion is confirmed, subjects will receive NanoPac on two occasions, at Day 1 and again at the Week 4 visit. In the third phase of the study subjects will receive NanoPac on up to four occasions, at Day 1, Week 4, Week 8, and Week 12.
- Subjects will be "admitted" to the hospital during the post-injection period for up to 23 hours, for observation and capture of AEs, and to permit the acquisition of the 6-hour and 24-hour PK samples for subjects in the dose escalation phase of the study.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

The subjects being enrolled to the dose escalation phase of this study will have received at least one course of standard neoadjuvant IV chemotherapy, and their platelet and neutrophil recovery will meet inclusion criteria for

participation. Subjects in the second and third phases of the study will have IV chemotherapy initiated prior to first injection.

Following EUS-guided fine needle injection 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 pain relief, additional clinic visits, etc.). Following ITU injection of NanoPac, IV chemotherapy should not be initiated within one month if at all possible for subjects in the dose escalation phase of the study. Following the 4-week follow-up visit, at which point the primary endpoint for safety and tolerability has been reached, further chemotherapy will be permitted as per institutional standard of care. If chemotherapy is required prior to the 4-week visit, the Investigator must contact the study Medical Monitor to discuss and document the decision-making process. For subjects in the second and third phases of the study SOC IV chemotherapy will have been initiated prior to first injection and chemotherapy administered while on study will be recorded in the concomitant medication forms.

Information on standard care and treatment post-injection(s) to the 3-month visit, 6-month follow-up visit, and 9-month follow-up visit for subjects in the third phase of the study, will be captured as appropriate.

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 2 weeks, 4 weeks, 2 months, 3 months, and 6 months post-injection for the subjects in the dose escalation phase of the study; for the subjects in the second and third phases the sample at injection visits will be taken prior to injection, and these subjects will have samples taken at all remaining study visits:

- Sodium, potassium, chloride, carbon dioxide (CO2), calcium, phosphorus, glucose, blood urea nitrogen (BUN), creatinine, serum lipase, serum amylase, alkaline phosphatase, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total protein, albumin, triglycerides, cholesterol, 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); and
- Tumor markers CA-19-9 and CEA (to evaluate tumor response to therapy).

7.2.2 OTHER ASSAYS OR PROCEDURES

For subjects in the dose escalation phase of the study pharmacokinetic (PK) samples will be taken on Day 1 prior to NanoPac injection, and at 1, 2, 4, 6, and 24 hours post-injection. Subjects will be in hospital overnight in order to obtain the 6- and 24-hour PK samples. In addition, a PK sample will be obtained at each study visit. Subjects in the

second and third phases of the study will provide PK samples pre-injection and 1 and 2 hours post injection at injection visits, and at all other study visits.

PK samples within the first 4 hours on the day of injection will allow for a 10-minute window around the samples. The remaining samples within the first 24 hours in the dose escalation pahse of the study will allow for a 30-minute window.

In the third phase of the study a blood sample will be obtained at each injection visit, prior to injection and at the 6-month follow-up visit. Samples will be processed and sent to a central laboratory (NeoGenomics; Alisa Viejo, CA) for immune marker assessment via flow cytometry.

Imaging with CT scan will occur within 6 weeks prior to NanoPac injection for study eligibility in the dose escalation group, at three months post-injection, and at end-of-study (six months after NanoPac injection). Subjects in the second phase of the study will have a CT Scan following consent and prior to first injection, and at the 3 and 6 month follow-up visits. Subjects in the third phase will have CT Scans following consent and prior to first injection, and at 3, 6, and 9 month follow-up visits.

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 and all resulting images will be collected for the subject's record.

Pain assessment will be conducted with the visual analog scale at all study visits. On the day(s) of NanoPac administration the pain assessment will be conducted prior to and following the procedure.

7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

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, 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.

Blood samples for flow cytometry will be drawn at the specified time/visit, prepared and shipped on the same day to the central laboratory for this evaluation, NeoGenomics. A kit for sample preparation and instructions will be provided.

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.

7.2.4 SPECIMEN SHIPMENT

Routine laboratory samples will be sent to the local laboratory upon collection.

Shipment process for the PK samples will be provided once established with the laboratory, prior to study initiation, and details will be provided to the site in their Regulatory Binder.

Shipment of the sample for flow cytometry will occur on the same day as the blood draw. A manual describing details for (preparation and) shipping will be provided to the sites.

7.3 STUDY SCHEDULE

7.3.1 SCREENING

Assessments, visits, and other assays performed in the interval between the end of IV chemotherapy and before consent to the study for NanoPac injection in the dose escalation cohorts will be performed according to the institution's standard of care and are not considered part of this study. When platelets ≥ 75 x 10^9/L and ANC ≥ 1.5 x 10^9/L, subjects will be eligible to enroll to the dose escalation phase of the study to receive treatment with NanoPac. Subjects in the second and third phases of the study will have initiated IV chemotherapy prior to first NanoPac injection.

The following procedures and assessments must be completed, documented and reviewed by the Investigator 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 pancreatic adenocarcinoma with a diameter of at least 1.5 cm but not more than 6 cm as determined by imaging; diagnosis and previous treatments including surgical and chemotherapeutic records. A copy of the pathology report 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);
- Visual analog scale for pain assessment;
- Sample collection and processing for clinical laboratory assessments (see Section 7.2.1);
- Imaging with CT scan will have occurred recently to confirm and document tumor volume and estimate the injection volume required on day of NanoPac administration. For the subjects in the second and third phases of the study a CT Scan will be required between Screening and prior to injection for detailed baseline assessment and comparison purposes. Final injection volume will be determined with ultrasound during the EUS-guided injection procedure.

7.3.2 DAY OF NANOPAC INJECTION

All screening assessments must have completed prior to the first injection visit, and all results and inclusion/exclusion criteria must have been confirmed.

Prior to the procedure:

- Comprehensive physical examination, including ECOG Performance Status assessment;
- Vital signs will be obtained and a visual analog scale for pain assessment will be completed pre- and post-injection.
- Adverse events occurring in the period between screening and this visit must be confirmed as either ongoing or completed. Adverse events occurring prior to the procedure will be considered history, and

those occurring after NanoPac administration will be documented separately as 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):
- Subjects will receive NanoPac as described in Sections 4.1 and 6.1.5, according to the cohort allocation;

In the dose escalation cohorts:

- PK Samples will be drawn prior to NanoPac injection, and then 1, 2, 4, 6, and 24 hours post-injection.
- Subjects will be admitted to the hospital for an overnight stay in order to assess adverse events in the immediate post-injection period, and to obtain the 6- and 24-hour PK samples.

In the subjects enrolling in the second and third phases of the study:

- PK samples will be drawn prior to NanoPac injection, and then 1 and 2 hours post-injection. No overnight hospitalization is required.
- Only subjects in the third phase of the study will have a blood sample drawn for immune marker assessment prior to injection at each of the injection visits occurring.

7.3.3 FOLLOW-UP VISITS

After NanoPac injection on Day 1 (and the overnight hospital stay for subjects in the dose escalation cohorts), subjects will return to the clinic in 2 weeks for the first study-specific follow-up visit. Subsequent follow-up visits will occur at 4 weeks post-injection, two months post-injection, and three months post-injection, and where possible a further visit will be conducted six months post-injection.

Subjects in the second phase of the study will follow the above schedule to Week 4 at which time they will have a second NanoPac injection. They will return to the clinic 2 weeks after the second injection and then at the scheduled visits from Week 8 through to Month 6; one further follow-up visit – which may be by phone call - at month 7 (6 months following last injection) is possible.

Subjects in the third phase of the study will receive up to four NanoPac injections. Assuming all injections are given, the subject will have a follow-up visit 2 weeks after each injection visit attending the site on Days 1, Week 4, Week 8, and Week 12 for injections and on Weeks 2, 6, 10, and 14 for follow-up visits. Additional follow-up visits will occur on Weeks 16, 20, and 24.

The Week 4 (1-month) visit will be the primary endpoint study visit for all subjects in the dose escalation phase of the study, the Week 8 (2-month) visit will be the primary endpoint study visit in the second phase of the study (which is one month following the second injection), and the Week 16 visit will be the primary endpoint visit in the third phase of the study (1 month after last injection). All further visits will be conducted to assess the secondary endpoints and to document any progression of disease during this time period.

Dose escalation phase:
The following procedures will be performed at the Week 2, Week 4, Week 8 (2-month) and Week 12 (3-month) clinic visits:

- Vital signs obtained; as needed, a directed physical exam may be performed;

    - At Week 4 a comprehensive physical exam, including vital signs and ECOG Performance Status assessment, will be performed.
- Visual analog scale for pain assessment;
- ECOG Assessment;
- Concomitant medications reviewed;
- Sample collection and processing for clinical laboratory assessments (Section 7.2.1);
- PK sample obtained;
- AE collection;
- Imaging with CT scan will be performed at the Week 12 (3-month) visit.

Second phase of study; two injections:

- The same procedures as above will be carried out to the Week 4 (1-month) visit.
- At the Week 4 visit the subject will have a second NanoPac injection via EUS and in addition to the visits noted above, the same follow-up procedures will be carried out at Week 6 (2 weeks after the second injection).

Third phase of study; up to four injections:

- The same procedures as above will be carried out to the Week 4 (1-month) visit.
- At the Week 4 visit the subject will have a second NanoPac injection via EUS and in addition to the visits noted above, the same follow-up procedures will be carried out at Week 6 (2 weeks after the second injection). This will be repeated for the third and fourth injections, having two week follow-up visits conducted at Weeks 10, 14, 16, 20, and 24.
- For subjects in the third phase of the study, a blood sample will be drawn for immune marker assessment at the 6-month follow-up visit.

7.3.4 FINAL FOLLOW-UP STUDY VISIT

This final visit will be conducted at a time point after the 3-month visit, as close to six months as possible, in the dose escalation phase. Subjects in the second phase will complete a final clinic visit as close to six months as possible, with a follow-up phonecall to occur one month later. Subejcts in the third phase of the study will complete their final study visit as close to nine months as possible.

Subjects may decide to withdraw participation prior to this point and at that time this visit should be conducted if possible.

At the final study visit, the following procedures will be performed:

- Vital signs obtained;
- Concomitant medications;
- AE collection;
- Sample collection and processing for clinical laboratory assessments (Section 7.2.1);
- PK Sample obtained;
- Visual analog score to record pain symptoms;
- ECOG Assessment;
- Imaging with CT scan and disease status assessment.

No further follow-up will be required or requested of subjects after this visit in the dose escalation cohorts. In the second phase of the study where subjects receive a second injection at the Week 4 visit, one further follow-up will be conducted at 7 months by phone.

Sites will be requested to provide information on progression and progression free survival (PFS) and overall survival (OS) on all study participants in the second and third phases at the 9 and 12 months time point following first NanoPac injection. This information will be provided for information only, and will not be used to support a study endpoint.

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, AEs, and concomitant medications.

7.3.6 UNSCHEDULED VISITS

Any unscheduled visits will be documented in the source documents, 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 transcribed into the EDC, and any imaging assessments which may be performed will also be noted in the EDC. If during the period the subject is on study they undergo additional EUS procedures these will be documented in the EDC and reports on findings provided for information, as appropriate.

7.3.7 SCHEDULE OF EVENTS TABLE – DOSE ESCALATION SUBJECTS

	Screening[3, 8]	Day 1 (Injection)	24 Hours Post-Injection	Week 2	Week 4 (1 Month)	Week 8 (2 Months)	Week 12 (3 Months)	6 Months (Final Study Visit)
Informed Consent	X							
History[1]	X							
Concomitant therapy	X	X		X	X	X	X	X
Physical Exam	X	X		X	X	X	X	X
ECOG[2]	X	X		X	X	X	X	X
Pain Assessment[6]	X	X		X	X	X	X	X
Vital Signs	X	X		X	X	X	X	X
Clinical Laboratory Tests (section 7.2.1)	X	X		X	X	X	X	X
PK Samples[5]		X	X	X	X	X	X	X
Imaging[7]	X						X	X
NanoPac[4]		X						
Adverse Events		X	X	X	X	X	X	X

1 History includes all events before initiation of NanoPac treatment.
2 ECOG Performance Status Scale attached as Appendix A
3 During the interval after the conclusion of intravenous chemotherapy but prior to injection with NanoPac, subjects will visit the clinic for evaluation and hematologic assessment according to their institution's standard of care. NanoPac injection may be performed when platelets ≥ 75 x 10^9/L and absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.
4 Prophylactic antibiotics will be administered prior to NanoPac injection; NanoPac will be administered by EUS-guided fine needle injection; subjects will be admitted to the hospital for overnight observation.
5 PK Samples on Day 1 will be drawn prior to injection and at 1, 2, 4, 6, and 24 hours post-dose, PK samples will also be obtained at each study visit thereafter. PK samples within the first 4 hours on Day 1 will allow for a 10-minute window around the samples. The remaining samples within the first 24 hours will allow for a 30-minute window.
6 Pain will be assessed with the visual analog scale
7 Imaging with CT scan will occur within 6 weeks of NanoPac administration, at three months post-injection, and at end-of-study (six months after NanoPac injection). 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.
8 Screening will occur up to 4 weeks prior to injection

7.3.8 SCHEDULE OF EVENTS TABLE – SECOND PHASE SUBJECTS

	Screening[3, 8]	Day 1 (Injection)	Week 2	Week 4 (1 Month)	Week 6	Week 8 (2 Months)	Week 12 (3 Months)	Week 24 (6 Months)	Week 28-30 (phone call)
Informed Consent	X								
History[1]	X								
Concomitant therapy	X	X	X	X	X	X	X	X	
Physical Exam	X	X	X	X	X	X	X	X	
ECOG[2]	X	X	X	X	X	X	X	X	
Pain Assessment[6]	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	
Clinical Laboratory Tests (section 7.2.1)	X	X	X	X	X	X	X	X	
PK Samples[5]		X	X	X	X	X	X	X	
Imaging[7]	X						X	X	
NanoPac[4]		X		X					
Adverse Events		X	X	X	X	X	X	X	X

1 History includes all events before initiation of NanoPac treatment.
2 ECOG Performance Status Scale attached as Appendix A
3 NanoPac injection may be performed when platelets ≥ 75 x 10^9/L and absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.
4 Prophylactic antibiotics will be administered prior to NanoPac injection; NanoPac will be administered by EUS-guided fine needle injection
5 PK Samples will be drawn prior to injection and at 1 and 2 hours post-dose, and at all other study visits. PK samples on the injection days will allow for a 10-minute window.
6 Pain will be assessed with the visual analog scale
7 Imaging with CT scan will occur during the Screening period (prior to NanoPac administration), and at three and six months post-first-injection. 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.
8 Screening may occur up to four weeks prior to injection

7.3.9 SCHEDULE OF EVENTS TABLE – THIRD PHASE SUBJECTS

	Screening[3, 8]	Day 1, Weeks 4 and 8 (Injection)	Weeks 2, 6, 10	Week 12 (Injection)	Weeks 14, 16, 20	Week 24 (6 Months)	9 Months (Final Study Visit)
Informed Consent	X						
History[1]	X						
Concomitant therapy	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X
ECOG[2]	X	X	X	X	X	X	X
Pain Assessment[6]	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X
Clinical Laboratory Tests (section 7.2.1)	X	X	X	X	X	X	X
PK Samples[5]		X	X	X	X	X	X
Blood for FCM[9]		X		X		X	
Imaging[7]	X			X		X	X
NanoPac[4]		X		X			
Adverse Events		X	X	X	X	X	X

1 History includes all events before initiation of NanoPac treatment.
2 ECOG Performance Status Scale attached as Appendix A
3 NanoPac injection may be performed when platelets ≥ 75 x 10^9/L and absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L.
4 Prophylactic antibiotics will be administered prior to NanoPac injection; NanoPac will be administered by EUS-guided fine needle injection
5 PK Samples on injection days will be drawn prior to injection and at 1 and 2 hours post-dose; PK samples will also be obtained at all other study visits. PK samples on injection days post-injection will allow for a 10-minute window around the samples.
6 Pain will be assessed with the visual analog scale pre-and post-injection on injection days.
7 Imaging with CT scan will occur at the time of Screening, prior to NanoPac administration, at three months post-first-injection but prior to final injection, at three months following final injection (at Week 24), and at end-of-study (9 months after first NanoPac injection). 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.
8 Screening may occur up to 4 weeks prior to injection
9 Blood sample for flow cytometric analysis will be taken prior to each injection and again at the Week 24 visit.

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Sponsor acknowledges that EUS-guided fine needle injection of NanoPac into the tumor 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 case report forms (eCRFs). 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 or oncologist. 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 during the 4 weeks following NanoPac injection is prohibited in the dose escalation cohorts of the study.

If chemotherapy is to be initiated the PI must contact the study Medical Monitor to discuss the assessments made to determine the need to initiate therapy, and document date to start and medications prescribed. This will all be entered to the EDC at the next study visit, but the Medical Monitor must be made aware of this as soon as possible.

In the second and third phases of the study subjects may be receiving concurrent IV chemotherapy, however immunotherapy and radiation therapy is prohibited during the 4 weeks following NanoPac injections.

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 standard of care.

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 documents 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 to be conducted in this study include:

- Adverse events, 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 2 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 AEs and general study data pertaining to safety (such as laboratory results and questionnaire responses) 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 AEs; DLTs will, in addition, include the following:

- ≥ Grade 3 pancreatico-biliary events (including but not limited to symptomatic pancreatitis or cholangitis, excluding asymptomatic time-limited pancreatic enzyme elevations);
- ≥ Grade 3 febrile neutropenia;
- Grade 3 diarrhea and vomiting lasting more than 72 hours, or Grade 4 diarrhea and vomiting;
- Grade 4 neutropenia lasting 5 days;
- Grade 4 thrombocytopenia;
- Grade 4 biliary toxicity;
- Any life-threatening event (unless there is a clear alternative explanation that the event is not related with 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 AEs 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 AEs and reported on the eCRF.

8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A Serious Adverse Event (SAE) is any adverse event 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)

As this is a Phase IIa study, all unanticipated problems will be captured as either AEs or SAEs 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, life-threatening, or fatal 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 possibly, probably, 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 drug 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

Adverse events 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 AEs. Study personnel will ask open-ended questions to obtain information about AEs at every visit. Date and time of onset and resolution (if applicable) of the AE will be documented.

All SAEs 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 AEs (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 AEs:

- Name of condition/diagnosis/description;
- Onset and resolution dates;
- Severity;
- Relationship to study agent;
- Action taken;
- Seriousness.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

All SAEs, 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:

Dr. Antony Verco
Medical Monitor
E-mail: *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 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 and meet 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 SAEs, 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 Phase IIa 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 time point, the study may be terminated. Should this occur, all subjects who have received treatment will be followed to the completion of their 3-month follow-up/primary 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 2-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 Data Safety Monitoring Board (DSMB).

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 escalation in a new cohort.

DSMB will again convene following the first three subjects in the second phase of the study completing a 2 week follow-up after their second NanoPac injection to review safety data. Subject recruitment to this cohort of subjects will continue and if during the review the DSMB have concerns regarding future subjects receiving a second injection they may propose alternative actions (which may include reducing the dose of the injections or not permitting two injections in future patients, reverting to a single injection).

DSMB will also convene following the first three subjects in the third phase of the study completing a 2 week follow-up after their fourth NanoPac injection to review safety data. Subject recruitment to this cohort of subjects will continue and if, during the review, the DSMB have concerns regarding future subjects receiving additional injections they may propose alternative actions (which may include reducing the dose of the injections or not permitting third and fourth injections in future patients, reverting to only two injections).

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, eCRFs, and source documents as needed to assure that the conduct of the study is within compliance. In

addition, 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 after a final review of the data by the medical monitor and prior to study database lock. The focus of the SAP will be to present the accumulated safety information from the three phases (dose escalation and one dose, two monthly doses and four monthly doses) that will provide insight into and dose-response relationship that may exisit for the safety and preliminary efficacy (e.g. changes in Ca19-9, CEA, plasma levels of paclitaxel) outcomes.

AEs of special interest will be summarized and the MedDRA terms provided; these will be tabulated separately with groupings as described in section 10.4.4.1 below.

10.2 STATISTICAL HYPOTHESES

No formal statistical inference (i.e., "p-values") will be applied. The results of this trial will be based on descriptive statistics only.

10.3 ANALYSIS DATASETS

In this safety and tolerability trial, all subjects who are enrolled and receive a minimum of one dose of study agent will be included in the descriptive analysis.

10.3.1 MISSING DATA

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

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

The focus of the trial will be on the safety and tolerability of the dose-escalated treatments. The general approach will be to highlight any trends that cause concern for the reviewing medical monitoring team (i.e., dose-limiting toxicities (DLTs)).

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

Not applicable. The primary objective is to evaluate the safety and tolerability as demonstrated by AE, changes in laboratory assessments, physical examination findings and vital signs.

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints will be summarized descriptively. These will include supportive information to provide context for the dose(s) chosen to move forward for a future study, as follows:

- Concentration of paclitaxel in the systemic circulation post-injection (as determined by PK analysis);
- Tumor response (including RECIST 1.1 as per Eisenhauer et al. 2009);
- Reduction in pain (as measured by the visual analog scale [VAS]);
- Change in tumor marker CA19-9;
- Change in tumor marker CEA.

See also Section 10.4.11, Exploratory Analyses, for further details.

10.4.4 SAFETY ANALYSES

10.4.4.1 ADVERSE EVENTS

Adverse events (AE) recorded during the trial will capture medically relevant changes found during the physical exam, and medically relevant changes in vital signs and laboratory analytes found during the course of the trial. In addition, spontaneously reported or observed events will be recoded

Events reported at or after the application of NanoPac will be considered TEAE. All reported events will be listed by subject number and assigned treatment, investigator term, MedDRA coded term, total NanoPac injections administered to date, date/study day (from initial treatment) and number of days post the most recent injection for onset and cessation, severity (using the NCIC severity grading), and relationship to study medication. Only the TEAE will be tabulated.

The dose escalation of phase 1, will be presented separately to provide insights into the increasing dose per injection. Here the primary safety analysis will focus on the data at the 3-month follow-up period. Additional tabulations including safety data up to and including the 6-month follow-up visit will also be presented.

The dose confirmation part of Phase 1 (i.e. one dose of 15 mg), Phase 2 (2 doses one month apart) and Phase 3 (4 doses one month apart) will be the second comparative focus. Tables and listings will be formatted to allow for comparisons of frequency, adjust for number of subjects in the cohort, for AEs.

Adverse event reports will be coded using the most recent version of MedDRA, signed off by the Medical Monitor, and presented by system organ class and preferred term. All AE and abnormal laboratory variables will be assessed according to the NCI-CTCAE v4.0 grading system. The number of subjects reporting and number of events reported will be presented in frequency tables (overall, by intensity, by relationship and by outcome) for each dose cohort.

Adverse events of special interest will be presented separately. The criteria for the most frequently reported events will be determined in the SAP after reviewing the data.

10.4.4.2 LABORATORY ANALYTES

Quantitative laboratory data will be summarized as mean values and change from screening scores (i.e., change = time point-screening) presented by dose level for each sampling time point. For tests with normal range provided, the clinical status and its change from screening (Normal/High Abnormal/Low Abnormal) will be summarized using shift tables for each dose group. Analytes of particular interest (e.g., hematological tests) may be graphed by subject with the dose indicated; these special analytes will be confirmed in the SAP.

10.4.4.3 VITAL SIGNS

Vital signs (systolic and diastolic blood pressure, heart rate, temperature and body weight) will be tabulated and mean raw values and changes from baseline scores (change = baseline-visit) where baseline is the last measurement prior to the study agent application, for each treatment group.

10.4.4.4 ECOG

The ECOG scale will be tabulated by treatment dose using shift tables to summarize and highlight and changes in category across the visits.

10.4.5 ADHERENCE AND RETENTION ANALYSES

All subjects who enter the trial will be accounted for and any reasons for early termination noted – including disease progression.

10.4.6 BASELINE DESCRIPTIVE STATISTICS

Complete demographic and baseline data will be tabulated. The medical history, which will be coded in MedDRA, will be presented. The disease history data, with a focus on the previous treatment and current staging, and the information collected on the procedure to apply the treatment will also be summarized.

10.4.7 PLANNED INTERIM ANALYSES

There are no formal interim analyses planned. There will be an ongoing safety and tolerability review by the Medical Monitor and regular DSMB meetings between cohorts.

10.4.7.1 SAFETY REVIEW

Safety Review is described in Section 8.1.

10.4.7.2 EFFICACY REVIEW

Imaging with CT scan will occur within six weeks prior to the injection procedure, every-three-months intervals for the time the subject remains in the study or if the subject's condition deteriorates. Tumor markers and pain assessments will be performed at each visit to guide the clinical oversight.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

Subjects who perform particularly well (i.e., experience minimal AEs) may be compared to those who perform more poorly. This topic, and the criteria for defining each group, will be detailed in the SAP.

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

Not applicable, as no inferential analyses will be employed.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

All data collected in the eCRF will at a minimum be listed; listings will support the tabulated data/outcomes.

10.4.11 EXPLORATORY ANALYSES

Pharmacokinetic (PK) parameters (i.e., AUC, C_{max}, T_{max}) will be calculated based on the plasma concentration data for the first 24 hours. Concentration data collected at subsequent visits will be summarized separately. The method of summary will include tabulations by dose group and individual subject plots of concentration across time, if the data is amenable to these concepts. The final decision will be made after a review of the data and recorded in the SAP.

Tumor markers (CA-19-9 and CEA) will be summarized as mean values by dose group across time as well as mean changes from baseline. The SAP will clarify if doubling of marker concentration is considered a notable event. Any notable events will be highlighted.

Pain assessment scores will be summarized as mean values by dose group across time as well as mean changes from baseline scores.

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

As there are no formal inferential statistical analyses planned, the sample size estimates below are provided for informational purposes only to help with decision-making around the cohort size and the rarity of events that could be detected.

Defining the primary endpoint explicitly requires understanding the primary purpose of the study. If, in this case, the primary purpose of the study is dose-finding, then the incidence of DLTs would be an appropriate endpoint. When choosing events that will qualify as DLTs, it's important to consider the rarity of events given the small number of subjects. For example, if a particular adverse event is known to occur in only 5% of subjects, there is a 26.5% chance it will appear in a particular cohort of 6 subjects, and a 60.3% chance it will occur during the study of 18 subjects. If the event only occurs in 1% of patients, there is only a 6% chance it will appear in a given 6-subject cohort, and a 16.5% chance it will be observed in the entire study. So rarity is a factor that should be considered when deciding which adverse reactions to include as part of the endpoint. Estimates were obtained using the "confidence interval for probability of observing a rare event" calculation in nQuery 6.01.

The rationale to expand the second phase to 22 subjects, from either 3 or 6 subjects, was based on the "reasonable gain" in detection rate that each additional subject would provide in this early phase exploratory trial. The calculations were performed using nQuery Advisor 6.01 "confidence interval for probability of observing a rare event". With 22 subjects the probability of detecting the 0.1 event rate is 90.2% as well as some probability of detecting much rarer events (19.8% probability of detecting an event with a base rate of 0.01, and 67.6% probability of detecting an event with a 0.05 base rate).

The additional 30 subjects in the third phase and the total number of subjects (i.e. 65) across all three phases increases the probability of detection proportionally as can be seen in the table below. Calculations were perfomed in nQuery version 8.5.1.0 , procedure POC2-1 "confidence interval for probability of observing a rare event".

Probability of Observing a Rare Event

	Rare Event Frequency		
Sample Size	0.1	0.05	0.01
12	71.8%	46.0%	11.4%
22	90.2%	67.6%	19.8%
30	95.8%	78.5%	26.0%
65	99.9%	96.4%	48.0%

The table assumes that each subject has an equal probability of having the adverse event, and so could be conservative, if there is any dose related effect; the actual dose given increases across the phases.

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. 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 eCRFs for each subject are based. They will be separate and distinct from the eCRFs. 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 eCRFs;
- 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 AEs;
- 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 its 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 the conduct of any study-related procedures. The Investigator is required to document the process for obtaining informed consent in the source notes.

Subjects in the second and third phases of the study will have a different ICFs to those in the dose escalation phase of the study, due to the different study schedules being followed.

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. Food and Drug Administration (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 the 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 eCRFs and other documents submitted to US Biotest by their initials, birth date, and 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. 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, after which they will be disposed of according to the laboratory SOPs. 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.

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 subject'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 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.

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 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 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 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), or 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, and reported to the Sponsor and the Data Management group.

Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to 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 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, Inc. Submission of data for publication/presentation will be coordinated and approved by US Biotest in collaboration with the Investigator.

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 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 enrollment, 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 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

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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.