Phase 2 Trial Evaluating the Safety and Tolerability of Intratumoral Injections of NanoPac® with Standard of Care Therapy in Subjects with Lung Cancer

Protocol Identifying Number: NANOPAC-2020-01

IND Sponsor: NanOlogy, LLC

IND #: 147012

Version Number: 4.0

Date: 7 July 2021

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALCOA-C	Attributable, Legible, Contemporaneous, Original, and Accurate - Complete
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ASP	Alkaline Phosphatase
BUN	Blood Urea Nitrogen
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central Nervous System
CO2	Carbon Dioxide
CRO	Clinical Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-Limiting Toxicity
EBUS-TBNI	Endobronchial ultrasound-guided transbronchial needle injection
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture System
eCRF	Electronic Case Report Form
EUS-FNI	Endoscopic ultrasound-guided fine needle injection
FCM	Flow Cytometric
FDA	The U.S. Food and Drug Administration
FNA	Fine Needle Aspiration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyltransferase
Hct	Hematocrit
Hgb	Hemoglobin
CT Scan	Computed Tomography Scan
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions for Use
IHC	Immunohistochemical
IND	Investigational New Drug Application
INR	International Normalized Ratio
IP	Intraperitoneal
IRB	Institutional Review Board
ITP	Intraprostatic
ITU	Intratumoral
IV	Intravenous
LDH	Lactate Dehydrogenase
LN	Lymph Node
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration

MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NDA	New Drug Application (Marketing Application)
PCA	Precipitation with Compressed Antisolvents
PD	Pharmacodynamic
PFS	Progression-free Survival
pH	Hydrogen Ion Concentration
PI	Principal Investigator
PK	Pharmacokinetics
PRO	Patient Reported Outcomes
PT	Prothrombin Time
PTT	Activated Partial Thromboplastin Time
QOL	Quality of Life
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
SRC	Safety Review Committee
TEAE	Treatment-emergent Adverse Event
ULN	Upper Limit of Normal
UP	Unanticipated Problem
VAS	Visual Analog Score
WBC	White Blood Cell

SPONSOR SIGNATURE PAGE

Protocol Title:	Phase 2 Trial Evaluating the Safety and Tolerability of Intratumoral Injections of NanoPac with Standard of Care therapy in Subjects with Lung Cancer.
Protocol Number:	NANOPAC-2020-01
Version Number:	4.0
Date:	7 July 2021
IND Number:	147012
Study Agent:	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 147012, 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 (Jul 7, 2021 10:10 PDT)

Signature of Sponsor's Representative

July 7, 2021
Date

STATEMENT OF COMPLIANCE

I have read the attached protocol number NANOPAC-2020-01 entitled, Phase 2 Trial Evaluating the Safety and Tolerability of Intratumoral Injections of NanoPac with Standard of Care Therapy in Subjects with Lung Cancer, Version 4.0 dated 7 July 2021 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 2 Trial Evaluating the Safety and Tolerability of Intratumoral Injections of NanoPac® with Standard of Care therapy in Subjects with Lung Cancer

Précis: In this open-label trial, 18 subjects with lung cancer will receive intratumoral (ITU) NanoPac® (sterile nanoparticulate paclitaxel) Powder for Suspension via endobronchial ultrasound-guided transbronchial needle injection (EBUS-TBNI).

Eligible subjects include primary or recurrent non-resectable non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC), with primary or recurrent measurable disease limited to the tracheal, hilar, mediastinal, and peribronchial structures (lung tumors and lymph nodes) accessible through EBUS-TBNI, have a life expectancy of at least 6 months, do not have cerebral metastases, ECOG ≤ 2, severe infection and other metabolic disorders, prior sensitivity/anaphylaxis to paclitaxel, or any other clinically significant comorbid disease that may limit the ability of the subject to participate in the study (e.g. significant cardiorespiratory disease that potentially limits the ability to undergo the injection procedure).

Subjects may receive concomitant standard of care intravenous (IV) chemotherapy, radiation therapy, and/or targeted therapy as required for their care.

Subjects will be administered NanoPac on three occasions, at a 15 mg/mL concentration 4 weeks apart, up to 20% of the total calculated tumor and lymph node volume to allow for up to a maximum volume of 40 mL per bronchoscopic procedure (i.e. the total tumor volume that can be treated is 200 mL). Up to two pulmonary parenchymal lesions will be injected, along with the metastatic lymph nodes selected by the Investigator based on CT findings at baseline and tumor accessibility through EBUS-TBNI. The volume of NanoPac to be delivered at all three injection procedures will be estimated based on the tumor and lymph node volume calculation from CT imaging obtained at baseline. At each injection visit, tumor size/s will also be measured using EBUS, and the tumor/s and node/nodal sizes recorded for comparison only. The volume of NanoPac injected, total and/or lesional, will at no time be increased beyond the maximum as calculated by the baseline CT measurement(s). Delivery of NanoPac to the lesion may be via multiple injections/sticks to maximize the dispersal of NanoPac throughout each individual lesion.

NanoPac injections will be planned according to the following schedule:

- Day 1 – first injection, Week 4 – second injection, Week 8 – third injection.
  - Follow-up visits will occur 1 and 2 weeks following each injection;
  - Additional follow-up visits will occur at Weeks 12, 18, 24, and 38 (9 months following first injection);
  - End of Study visit will occur at Week 52 (12 months following first injection).

All safety parameters will be evaluated alongside the results of the CT scans by the Medical Monitor at regular intervals (monthly) throughout the study period. All imaging will be made available to the Sponsor. Any personal information that could identify the subject will be removed before images are shared with the Sponsor. Data will be reviewed for subjects independently and as a group during this review. Discussion with the Investigator and the Sponsor Medical Director may be required/requested at any time by the Medical Monitor. In addition, the first three subjects will be enrolled singly and sequentially, and a safety review will be performed by the Safety Review Committee (SRC) (by teleconference) after the first subject has undergone the 2-week follow-up visit after their first administration of NanoPac to confirm that the second subject may proceed to injection. This safety review process will be repeated for the second and third subjects in a sequential manner prior to opening general enrollment to the study. The SRC will also perform a safety review after each of the first three subjects has undergone the 2-week follow-up visit after their second administration of NanoPac. The SRC will include the Sponsor Medical Director, the Principal Investigator, Medical Monitor, and an independent therapeutic area specialist.

Blood samples will be obtained from subjects for pharmacokinetic (PK) evaluation of paclitaxel in the systemic circulation and at set time points for flow cytometric (FCM) evaluation of immune markers. Tissue samples (biopsies) may be obtained at each injection prior to the administration of NanoPac to evaluate the presence of paclitaxel in the tissue and for evaluation via immunohistochemical (IHC) staining for immune markers.

All subjects will undergo CT scans within 4 weeks prior to start of treatment, prior to each injection at Weeks 4 and 8, and again at Weeks 12, 18, 24, 38 and 52 (End of Study Visit). CT scans will be used to provide preliminary signs of the effect of NanoPac on the lesion(s) and nodes. The baseline redacted CT scan will be forwarded to the Medical Monitor for review/approval with the completed pre-injection form prior to first injection for all subjects. All imaging will be collected for the subject's record and identifiers removed before images are shared with the Sponsor. At the second and third injections the same volume/dose of NanoPac will be administered to each lesion as was administered at the first bronchoscopic procedure.

Subjects will be followed for a total of a year after the first NanoPac injection; assessments during this time will be primarily for safety (laboratory values, adverse events, concomitant medications, etc.) during the first 6 months of the study, and information will be obtained to evaluate progression-free survival (PFS) using the RECIST 1.1 criteria, and radiological changes using the CT scans. The assessments at Week 38 and Week 52 will provide additional information on PFS and overall survival (OS). Subjects will also complete a quality of life (QOL) questionnaire (EQ-5D) prior to first injection of NanoPac, and throughout the study until the End of the Study at Week 52. Subjects will be grouped for review at study completion based on the number of treatments (bronchoscopic procedures) they received.

Objectives: Primary objective:

- To evaluate the safety and tolerability of NanoPac injected directly into lung cancer lesions and metastatic lymph nodes by endobronchial ultrasound-guided injection on up to three occasions, each occasion 4 weeks apart.

Secondary objectives:

- PK evaluation - paclitaxel in the systemic circulation and in tissue samples;
- To evaluate effect on PFS and OS in this population;
- To assess changes in the treated lesion (and lymph nodes) via CT scan imaging.

Endpoints:

Primary endpoint:

- Safety and tolerability as demonstrated by adverse events (AEs), changes in laboratory assessments, physical examination findings and vital signs.

Secondary endpoints:

- Blood samples will be evaluated for paclitaxel levels at all clinic visits; tissue obtained at the second and third injection timepoints will be compared against baseline paclitaxel levels obtained from a pre-NanoPac sample taken prior to the first injection;
- PFS defined as change in tumor size classified using RECIST 1.1, metastatic disease, and death; OS as determined by survival time following first NanoPac injection;
- Assessment of tumor response (dimensions, volume) as determined by CT scan imaging, measured at baseline and Weeks 12, 24, 38 and 52;
    - Any changes in characteristics of lesion/nodes as determined via CT scan.

Exploratory/Tertiary endpoints:

- Changes in Eastern Cooperative Oncology Group (ECOG) Performance Status;
- Changes in pain (as measured by the visual analog scale [VAS]) in the first 6 months of the study;
- Changes in QOL as measured by the validated EQ-5D QOL instrument;
- Assess immune markers in the blood via FCM, and in the tissues via IHC in the first 6 months of the study.

Population:

Eighteen subjects with primary or recurrent non-resectable NSCLC or SCLC lung cancer, with primary or recurrent measurable disease limited to the tracheal, hilar, mediastinal, and peribronchial structures (lung tumors and lymph nodes) accessible through EBUS-TBNI.

Phase:

Phase 2

Number of Sites enrolling participants:

Up to five (5)

Description of Study Agent:	NanoPac® (sterile nanoparticulate paclitaxel) Powder for Suspension ("NanoPac") at concentration of 15 mg/mL administered into the tumor within the lung via EUS-TBNI.
Study Duration:	The study duration is estimated to be up to 36 months.
Participant Duration:	The study duration is estimated to be up to 13 months for each subject – Screening may occur up to one month prior to first injection.

STUDY SCHEDULE

	Screening[6]	Day 1 NanoPac	Week 1	Week 2	Week 4 NanoPac	Week 5	Week 6	Week 8 NanoPac	Week 9	Week 10	Week 12	Week 18	Week 24 (6 months)	Week 38 (9 months)	Week 52 (12 months)
Informed Consent	X														
History[1]	X														
Physical Exam	X	X			X			X					X		
Pain Assessment[4]	X	X	X	X	X	X	X	X	X	X	X	X	X		
QOL Questionnaire		X			X			X			X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG[2]	X	X			X			X			X	X	X	X	X
Clinical Laboratory Tests[8,9]	X	X		X	X		X	X		X	X	X	X		
PK Samples (blood)[3]		X	X	X	X	X	X	X	X	X	X	X	X		
Blood FCM analysis		X			X			X			X	X	X		
Tissue (biopsy) for IHC and paclitaxel		X			X			X							
Imaging (CT Scans)[5]	X				X			X			X	X	X	X	X
NanoPac Procedure		X			X			X							
Pharmacy		X			X			X							
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X[7]	X[7]
Adverse Events		X	X	X	X	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 PK Samples on Day 1, Week 4, and Week 8 will be drawn prior to injection and at 1, 2, and 4 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.

4 Pain will be assessed with the visual analog scale.

5 Imaging with CT scan will occur during the screening period, prior to each NanoPac administration, and at Weeks 12, 18, 24, 38 and 52. Should the subject withdraw from the study at any time, a CT 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 standard of care and all resulting images will be collected for the subject's record.

6 Screening will occur up to four weeks prior to injection.

7 All concomitant medications will be captured to Week 24. Only SOC lung cancer therapy will be captured at visit Weeks 38 and 52.

8 Urine pregnancy test for women of child-bearing potential at screening, Week 12 and Week 24.

9 Clinical laboratory tests include hematology, chemistry, urinalysis and at screening includes serology (Hepatitis A, Hepatitis, B, HIV).

1 KEY ROLES

Medical Director

Gere diZerega, MD
President & CEO, US Biotest, Inc.
Professor, University of Southern California Keck School of Medicine
231 Bonetti Dr., Suite 240, San Luis Obispo, CA 93401
805-630-2800
gere.dizerega@usbiotest.com

Study Director

Shelagh Verco, PhD
US Biotest, Inc.
231 Bonetti Dr., Suite 240, San Luis Obispo, CA 93401
805-704-1179
shelagh.verco@usbiotest.com

Medical Monitor

Antony Verco, MD
US Biotest, Inc.
231 Bonetti Dr., Suite 240, San Luis Obispo, CA 93401
805-235-9193
tony.verco@usbiotest.com

Laboratory – PK Samples

Covance Madison Laboratories Bioanalytical (BA) Group
3301 Kinsman Blvd, Madison, WI 53704
608-442-8200

Central Laboratory – Immunohistochemistry on Biopsies

NeoGenomics Laboratories, Inc.
Attn: Pharma Services Department
31 Columbia
Aliso Viejo, CA 92656
Phone: 949-445-7300 x7103

Central Laboratory – FCM evaluation on whole blood

NeoGenomics Laboratories, Inc.
Attn: Pharma Services Department
31 Columbia
Aliso Viejo, CA 92656
Phone: 949-445-7300 x7103

2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

The Sponsor for IND 147012, 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 intratumoral (ITU) injection of NanoPac in animal models of lung cancer have not been performed. However, NanoPac has demonstrated preliminary safety and efficacy when injected ITU in animals with solid tumors and when administered as an inhalation therapy in animal models of lung cancer. Preclinical data is presented in the NanoPac Investigator's Brochure.

Two *in vivo* nonclinical pharmacology studies were conducted to determine the effects of ITU delivery of nanoparticulate paclitaxel in a nude mouse xenograft model. Animals treated with NanoPac demonstrated significant reduction in tumor size ($p < 0.01$ for all comparisons) and survival benefit ($p < 0.01$ for all comparisons) compared to vehicle-treated animals. NanoPac reduced mean tumor volume by 74.1% by Day 22 compared to vehicle; body weights for all groups remained stable or increased throughout the treatment phase.

A GLP-compliant study (Study Number P-TR-06-2018) evaluated and characterized the toxicity and toxicokinetics (TK) of NanoPac following a single intraprostatic (ITP) administration into the prostate in rats. There were no test article-related findings in mortality, clinical or ophthalmological observations, organ or body weights, food consumption, hematology, coagulation or clinical chemistry. The death of 1 out of 20 animals/dose group at 0 (control) and 2.9 mg/kg NanoPac were considered procedure-related, were likely due to a combination of local trauma of injection compounded by the local irritation of

paclitaxel in and around the injection site. At the terminal interval on Day 4, findings of necrosis with mixed inflammation and fibrin deposition were noted in the prostate, with mineralization (kidneys), mixed inflammation and fibrin deposition (urinary bladder, seminal vesicles and iliac lymph nodes) noted in the adjacent tissues. At the recovery interval on Day 28 (± 1), similar findings were observed, with partial/ongoing to complete resolution.

The toxicity of NanoPac was evaluated following a single ITP dose in rats. In this non-GLP study (Study Number P-TR-04-2016), there were no NanoPac-related findings in the following parameters evaluated: mortality, clinical observations, body weights, food consumption, coagulation, clinical chemistry, or urinalysis. The death of 1 out of 10 animals/dose group at 8 and 16 mg/kg NanoPac on Day 3 was considered treatment-related but not dose-related. Clinical signs preceding death were limited to decreased activity. Microscopic examination revealed the cause of death was due to urinary obstruction which appeared to have been caused by seminal plugs in the prostatic urethra with secondary backflow in the bladder, ureters, and kidneys. These deaths were considered due to a combination of the local trauma of injection compounded by the local irritation of paclitaxel at and around the injection site.

NanoPac administered by other routes of administration include the intraperitoneal and inhaled routes. Intraperitoneal (IP) administration of NanoPac has demonstrated less toxicity than IP Taxol, and increased survival and tumor load reduction with or without surgical debulking. GLP and non-GLP single and multiple dose toxicity studies in rats and dogs, and an *in vivo* proof-of-concept study of NanoPac in a mouse xenograft study were conducted via the inhaled route of administration. These studies demonstrated preliminary efficacy with toxicity as expected for the route of administration viz. minimal systemic effects due to lack of absorption across the lung parenchyma, and dose-responsive airway epithelial changes secondary to cytotoxicity induced by NanoPac (inflammation, necrosis, fibrosis, pneumonitis).

Clinical Summary:

NanoPac has not previously been administered to the human lung via EBUS-TBNI. Two clinical studies with NanoPac have been completed – one Phase 2a study of ITP injection of NanoPac in locally-advanced prostate cancer and one Phase 1 study of IP NanoPac in patients with peritoneal malignancies. Additional data from these clinical trials is presented in the NanoPac Investigator's Brochure.

Phase 2a Study in Prostate Cancer

In this study of NanoPac focal therapy of prostate cancer (NANOPAC-2016-02; NCT03077659), ITP NanoPac was injected in ascending concentrations of 6, 10, and 15 mg/mL in an injection volume of 20% of the lobe of the prostate containing the dominant lesion. Subjects were followed for 4 weeks for safety and tolerability prior to prostatectomy. The primary objective of the study was to evaluate the safety and tolerability of NanoPac. Sixteen subjects were enrolled and received study agent according to the protocol. 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 6 mg/mL cohort. There was no obvious dose-response relationship with respect to the frequencies of the TEAEs.

Compared to Taxol, no dose-limiting toxicities (DLTs) or toxicities typically attributable to paclitaxel such as neutropenia, thrombocytopenia, peripheral neuropathy, and hypersensitivity reactions such as angioedema and urticaria were reported. There were no serious adverse events (SAEs), deaths, or discontinuations from the study due to adverse events (AEs).

Pharmacokinetic (PK)/pharmacodynamic (PD) modeling of Taxol-induced neutropenia suggests toxicity is related to the duration and extent of systemic exposure to paclitaxel which correlates with a threshold plasma paclitaxel concentration of ≥ 42.7 ng/mL. In contrast, plasma paclitaxel concentrations observed after administration of NanoPac in clinical study NANOPAC-2016-02 had C_{max} values of 19 to 20 ng/mL recorded at the earliest sample (the 1-hour timepoint). In addition, and by comparison, a standard intravenous (IV) dose of paclitaxel of 175 mg/m^2 BSA administered over 3 hours resulted in a C_{max} of 3,650 ng/ml (Paclitaxel Drug Label Information – Teva), about 192x higher than the mean NanoPac concentration achieved in the 15 mg/mL cohort at 1 hour after injection. In alignment with this, from a toxicity and safety perspective, ITP injection of NanoPac appears to have a better risk profile compared to IV Taxol administration. The original hypothesis of NANOPAC-2016-02, that direct injection of NanoPac into the prostate would result in limited systemic exposure to paclitaxel and should therefore result in only low-grade and transitory AEs is therefore supported by the safety findings in the study.

Due to the small size of the study and the natural slow rate of progression of prostate cancer, the majority of the individual outcomes showed no changes or variable results across the three concentrations of NanoPac over 4 weeks of exposure to NanoPac. The mean volume of the prostate increased between the time of injection and prostatectomy, likely due to the local inflammatory reaction generated by NanoPac. Reflecting this, the sexual health as measured by the Sexual Health Inventory for Men (SHIM) deteriorated over the course of participation, which can be explained by the increased local pressure effects created by the increased prostate volume. Notably, the mean total Gleason score remained stable in the 6 mg/mL and 10 mg/mL cohorts, and improved in the 15 mg/mL cohort, implying a possible dose-response relationship. Preliminary efficacy was demonstrated by (1) 13 of 16 subjects had stable or improved Gleason scores (all in the 15 mg/mL cohort); (2) 11 of 16 subjects had stable or improved proportions of cancer lesion tissue defined as adenocarcinoma (6 of 11 subjects showed reductions in proportion of tissue identified as adenocarcinoma while 5 showed no change); and (3) 11 of 16 subjects had stable or improved levels of invasion by the cancerous tissue (4 of the 11 subjects showed less invasion into the surrounding tissues, while 7 subjects showed stable disease).

Overall, the primary objective of the study was achieved, i.e. preliminary evidence indicates that direct injection of NanoPac into the prostate appeared safe and tolerable.

Phase 1 Study in Peritoneal Malignancies

A Phase 1 study of intraperitoneal (IP) NanoPac in subjects with peritoneal malignancies, HSC#11140 (NCT00666991) was completed. The results of this study were published by Williamson 2015 in the journal *Cancer Chemotherapy and Pharmacology*.

HSC#11140 was a dose-escalating study evaluating IP administered Nanotax (the same drug as NanoPac, but under a different name) at doses of 50-275 mg/m^2 given every 28 days until disease progression or unacceptable toxicity occurred. Twenty-two patients were enrolled in the study. 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 agent, occurred in one patient. 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 12 subjects had progressive disease. Five of 21 patients with advanced cancers survived longer than 400 days after initiation of IP NanoPac treatment.

Phase 2 Study in Ovarian Cancer

Clinical trial NANOPAC-2016-01 entitled, "Phase II Study of Four Dose Levels of Intraperitoneal NanoPac® plus IV Carboplatin and Paclitaxel in Patients with Epithelial Ovarian Cancer Undergoing Cytoreductive Surgery," was a phase 2, open-label, dose-finding trial, designed to evaluate preliminary safety and efficacy of four concentrations of IP NanoPac plus six cycles of IV carboplatin and IV paclitaxel in patients with platinum-sensitive recurrent stage III epithelial ovarian cancer. Subjects had NanoPac instilled directly into the peritoneum just prior to surgical cytoreductive close. A total of 10 subjects were enrolled into the study, seven into the 100 mg/m^2 cohort and three into the 200 mg/m^2 cohort. At least one TEAE was reported in 10 of 10 subjects. A total of 108 TEAEs were reported for both NanoPac concentration cohorts (80 TEAEs in 100 mg/m^2; 28 TEAEs in 200 mg/m^2). Although statistical comparisons were not performed, there was no apparent association of the number of TEAEs with the dose administered. There were no TEAEs which led to subject discontinuation, however one TEAE occurred in each concentration cohort which lead to a fatal outcome; both were attributed to progression of disease. The majority of TEAEs occurred in the gastrointestinal System Organ Class (SOC) in the 100 mg/m^2 and 200 mg/m^2 dose groups and were mostly nausea and vomiting in both groups. Fourteen TEAEs were graded as severe or worse; 10 occurred in the 100 mg/m^2 dose group, and four occurred in the 200 mg/m^2 dose group. Thirty-seven TEAEs were considered possibly related to IP NanoPac, 27 events occurred in five subjects in the 100 mg/m^2 dose group, and 10 events occurred in two subjects in the 200 mg/m^2 dose group. Overall, a 66% progression free survival (PFS) occurred at 12 months post-IP NanoPac, with further improvement noted at 18 months after treatment, supported by sustained reduction in CA-125 and lack of additional cancer-related symptoms six months or more after treatment.

Study in Pancreatic Mucinous Cystic Neoplasms

Completed clinical trial NANOPAC-2017-01 entitled "A Trial Evaluating Escalating Doses and the Safety of Intracystic Injection of NanoPac in Subjects with Mucinous Cystic Pancreatic Neoplasms," was an open-label, dose escalating trial injecting NanoPac into a single mucinous cystic pancreatic neoplasm (diameter ≥ 1.5 cm and ≤ 4 cm) via endoscopic ultrasound-guided fine needle injection (EUS-FNI). Subjects were followed for cyst response to therapy as shown by imaging, and concentration of

paclitaxel in the systemic circulation post-injection. In total, 20 subjects were enrolled into the study; 19 received NanoPac. Overall, 18 of 19 subjects reported at least one TEAE, with a total of 99 TEAEs reported. No deaths or DLT occurred. The majority (91.9%) of TEAEs were of either mild or moderate severity, and 4% were severe (4% of unknown severity). Across all treatment groups, the most frequently reported TEAEs (32.32%) involved the SOC of Gastrointestinal Disorders. Five SAEs were reported in five subjects. Of the five events, three were severe (breast cancer, abdominal pain, organizing pneumonia), and two were of moderate severity (gastric obstruction, hepatic encephalopathy). Only one event of gastric outlet obstruction was considered probably related to study medication. Although statistical comparisons were not performed, there was no apparent association of the number, severity, or relationship of TEAEs with the dose/concentration or number of injections administered. Analysis of the response rate of subjects demonstrated that the majority of subjects demonstrated stabilization or improvement in calculated volume and/or longest diameter of the cyst. Of these subjects, 55.6% showed improvement at Week 12, increasing to 70.6% at Week 24. In addition, 50% of subjects had a reduction in calculated volume of ≥ 30% at both Week 12 and 24. When comparing changes at Week 12 compared to Week 24, 62.5% of subjects showed a further reduction in calculated volume compared to Week 12, occurring after single or double injections. Further, of those subjects who demonstrated increases in calculated volume at Week 12 compared to baseline, 75.0% showed a decrease in calculated volume at Week 24 compared to Week 12, one of which occurred after one injection and five after two injections of the 15 mg/mL concentration of NanoPac.

Ongoing Clinical Studies

Ongoing clinical trials injecting NanoPac directly into lesions include the following:

1) Pancreatic tumors via endoscopic ultrasound guided fine needle injection (EUS-FNI) (NANOPAC-2016-05; NCT03077685).

2.2 RATIONALE

This Phase 2 study will include subjects with lung cancer. Only those subjects who are not candidates for surgery will be enrolled in the study. The study design allows for a safety evaluation of direct ITU injection of NanoPac into lung cancer lesions and associated metastatic lymph nodes.

Lung cancer cells are particularly sensitive to paclitaxel. Paclitaxel is approved as first-line treatment of NSCLC in combination with cisplatin in patients who are not candidates for potentially curative surgery and/or radiotherapy. Similarly, both Taxol and ABRAXANE are FDA-approved first-line treatments of locally advanced or metastatic NSCLC, in combination with carboplatin, in patients who are not candidates for potentially curative surgery and/or radiotherapy.

In order to inject lung cancer directly, a minimally invasive procedure known as EBUS-TBNI is proposed for this Phase 2 study. The safety and feasibility of this procedure have been demonstrated in numerous studies (Lu 2015, Mehta 2015, Mehta 2017).

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 EBUS-TBNI may bypass the fibrotic stroma that acts as a barrier to IV chemotherapy. NanoPac may also allow for prolonged residence and dissolution within the tumor tissue, resulting in continuous and greater paclitaxel concentrations in the tumor site.

Multiple clinical studies have been published demonstrating the use, efficacy, and safety of ITU injection of cytotoxic compounds. Cisplatin has demonstrated safety and efficacy when administered repeatedly on a weekly basis for 4 weeks at concentrations of 4 mg/mL and up to 40 mL per injection session for Malignant Airway Obstruction (MAO) (Çelikoğu 2006, Mehta 2015). The same dose regimen of cisplatin was used in patients with recurrent lung cancer (≥ 1 site; tumor and/or nodal) in patients who had received prior radiotherapy, with good efficacy and safety (Mehta 2017).

ITU liposomal paclitaxel (1 – 3 mg/mL concentrations) has been administered twice, one week apart, in combination with IV carboplatin and gemcitabine to 48 patients with unresectable stage III NSCLC with good efficacy and safety outcomes (Lu 2015).

An ITU cocktail of drugs was administered to 93 patients with non-resectable MAO with primary or recurrent malignancy (Çelikoğu 1997). The cocktail comprised 5-FU (50 mg/mL), mitomycin (1 mg/mL), methotrexate (5 mg/mL), bleomycin (10 mg/mL), and mitoxantrone (2 mg/mL). Volumes of 1 -3 mL were injected every 1 -3 days until patency of the airways was restored; the average number of treatment sessions was 4 (range 1 – 6) over a 2 week period. In those with recurrent malignancy, ITU injections were performed weekly for 6 – 10 weeks, and then every 1 – 3 months if patency was maintained. Dosing was stopped if patency not maintained or established after 6 successive ITU injections. Eight of 93 patients were slightly febrile on day of injection. There were no episodes of pneumonitis, marrow suppression, inflammation, nausea, depilation, or clinically important AEs.

The PK of FDA approved Taxol shows a standard IV dose of paclitaxel of 175mg/m^2 BSA administered over 3 hours results in a C_{max} of 3,650 ng/mL (Paclitaxel Package Insert). In the completed prostate cancer study, ITU injection of a mean dose of 53.6 mg NanoPac in a 15 mg/mL concentration resulted in C_{max} of 19 – 20 ng/mL at the earliest recorded timepoint i.e. 1 hour post-injection. By day 28, levels were still measurable at a mean 0.057 ng/mL. (LLOQ = 0.025 ng/ml). Studies in ITU injection of NanoPac in pancreatic cancer and intralesional injection in pancreatic cyst are ongoing. However, in the pancreatic cyst study, preliminary information shows an average dose of 84.37 mg NanoPac in a 15 mg/mL concentration results in a plasma C_{max} of 0.24 ng/mL two hours after injection. In the pancreatic cancer study preliminary information indicates an average dose of 53.375 mg NanoPac in a 15 mg/mL concentration results in a C_{max} of 3.19 ng/mL one hour after injection.

In this study, NanoPac will be administered at a concentration of 15 mg/mL directly into the tumor at a volume up to 20% of the total tumor and lymph node volume(s), up to a maximum of 40 mL. Subjects will therefore be enrolled with maximum tumor volumes 200 mL i.e. a maximum dose of 600 mg or 10 mg/kg in a 60 kg subject. Injection volumes up to 20% of tumor volume has been demonstrated to be safe in completed and ongoing studies with ITU injections of NanoPac into prostate and pancreatic

cancer, as well as pancreatic cyst. The maximum tumor (and node) volume for injection is therefore 200 ml, which includes the combined volume of up to 2 lung tumor lesions (1 primary and 1 secondary) and metastatic lesions to local/regional lymph nodes.

Since systemic absorption from ITU injections of NanoPac has been confirmed to be significantly low compared to IV infusions, a patient in this study administered a maximum single ITU treatment of 600 mg NanoPac is expected to achieve a C_{max} of at least 9 times less paclitaxel than a breast or ovarian cancer patient treated with a single IV infusion of 175 mg/m^2 Taxol (assuming 100 % bioavailability for an ITU dose and linear PK).

Overall, the ITP injection studies provide the most relevant indirect evidence of expected toxicity when injecting NanoPac directly into lung tumors. The observed effects were typically minimal to mild in severity, and likely secondary to leakage of paclitaxel. Systemic exposure at the highest dose of 28.8 mg/kg is orders of magnitude below that achieved after conventional IV doses of paclitaxel. Local toxicity and systemic exposure after injection of lung tumors is expected to be similar to ITP injections.

Given the systemic exposure after ITU injection of prostate and pancreatic cancer, and pancreatic cyst, systemic exposure after 40 mL of ITU NanoPac is expected to remain well below levels seen from IV chemotherapy.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

There are no known potential systemic risks from the ITU injection of NanoPac into lung tumors. The injection procedure itself includes risks related to the sedation and/or anesthesia required for the procedure, bronchospasm, hemorrhage from the injection, and possible leakage of NanoPac from the injection site into the conducting airways.

2.3.2 KNOWN POTENTIAL BENEFITS

There are no known potential benefits of ITU injection of NanoPac. However, paclitaxel formulated as Taxol and Abraxane are both FDA-approved as first-line treatment of locally advanced or metastatic NSCLC, in combination with carboplatin, in patients who are not candidates for potentially curative surgery and/or radiotherapy.

3 OBJECTIVES AND PURPOSE

The primary objective of this study is to evaluate the safety and tolerability of NanoPac injected into lung cancer lesions by EBUS-TBNI on multiple (up to three) occasions, each injection procedure administered 4 weeks apart. Safety and tolerability will be assessed for 24 weeks following first NanoPac injection; with additional follow-up at weeks 38 and 52.

Secondary objectives are:

a) To describe the PK of NanoPac when administered into the tumor(s) within the lung;
b) To evaluate effect on progression free survival (PFS) and overall survival (OS) in this population; and
c) to assess changes in the treated lesion (and lymph nodes) via CT scan imaging, histology, and immunochemistry (IHC).

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

In this open-label Phase 2 trial, subjects with lung cancer will be receiving standard of care (SOC) treatment, and will be enrolled after confirmation of adequate hematologic function (see Section 5.1). Subjects will receive NanoPac via EBUS-TBNI to up to two lung lesions and their associated nodes (at the Investigator's discretion).

Subjects will be followed for safety during the 24 weeks following first NanoPac injection.

Subjects will be followed for signs of preliminary efficacy by assessment of tumor response classified according to RECIST 1.1 criteria, with tumor size assessed by CT imaging at baseline (Screening), prior to each injection, and at Weeks 12, 18, 24, 38, and 52. Subjects will also be assessed for quality of life (QOL) changes using the EQ-5D QOL questionnaire and PFS.

The lesion(s) to be treated must have been captured via imaging within 4 weeks of study entry. Follow-up scans will be performed at Weeks 12, 18, 24, 38, and 52 to provide information on tumor response to the injections. The CT scan must provide a demonstrated measurement (3-dimension) for volume calculation. The volume calculation will be made using the ellipsoid formula: **$V = 1/6 \times \pi \times l \times w \times d$.**

The tumor diameter and volume measurement(s) will be determined from this imaging and recorded in the source and in the electronic data capture system (EDC). The CT imaging at Weeks 12, 24, 38, and 52 will be used for RECIST purposes, for the secondary endpoint assessment of tumor response and PFS.

Subjects will be enrolled to receive up to three injection procedures with 15 mg/mL NanoPac, each injection 4 weeks apart, in up to two parenchymal lung lesions and associated local/regional lymph nodes, up to a maximum of 20% of the tumor and lymph node volume, individually and/or in total. A maximum of 40 mL of NanoPac will be injected in one procedure. If more than one lesion is present in the lung and more than one lesion is planned to be treated, the Investigator will select a primary or target lesion. Depending on the amount of NanoPac used for injection of the primary/target lesion, the remaining NanoPac may be administered into a second lung tumor lesion and/or metastatic lymph nodes up to a maximum volume of 40 mL of NanoPac.

For example, the sum of the volumes of lesions to be injected at baseline is 200 mL, from which the maximum volume allowed to be injected during any single bronchoscopic procedure is 40 mL. In the

case of a primary lesion of 6 cm diameter, the volume of the lesion will be 113.1 mL, allowing for an injection volume of 22.62 mL of 15 mg/mL NanoPac. This leaves 17.38 mL (40 mL – 22.62 mL) of NanoPac available for injection into local/regional lymph nodes (LNs) and/or the second tumor where applicable. For a primary lesion with a 3 cm diameter, 2.83 mL of NanoPac may be injected into the primary, leaving 37.17 mL of NanoPac available for injection of draining LN's and/or a second tumor.

The sequence of injections of tumor lesions will be prioritized according to the general principle of treating the primary lesion and associated metastatic node(s) before treatment of a second lesion and its associated metastatic node(s). The sequence of prioritization is therefore the following:

1) Primary tumor + local LN drainage i.e. N1 nodes first, then N2, then N3 if no contralateral nodules (M1a);
2) Ipsilateral second tumor, where relevant, + local drainage i.e. N1 nodes first, then N2, then N3 if no contralateral nodules (M1a); **or**
3) Contralateral second tumor (M1a except pleural/pericardial nodules or effusions), where applicable, + local drainage i.e. N1 nodes first, then N2.

The Investigator may use his/her discretion, on a subject-by-subject basis, to inject the entire tumor volume available or to use a lesser amount as he/she deems necessary for each individual subject's safety, subject to the above limits.

Plasma samples will be taken on each day of injection, prior to injection and at 1, 2, and 4 hours after the start time of NanoPac injection, as well as at all other study visits up to Week 24 to characterize the PK of ITU NanoPac.

Blood will also be drawn and sent to a central laboratory for flow cytometric (FCM) analysis of immune markers prior to each injection (Day 1, Week 4, and Week 8) and at the follow-up visits occurring at Week 12, Week 18, and Week 24.

Lung lesion biopsies for histopathology may be obtained at the time of injection, prior to administration of NanoPac. Biopsies must not, however, be obtained from any lesions that are in proximity to cardiac or any vital neurovascular structures. Routine processing for histopathology may be performed at the local institution; if only one biopsy is obtained, slides will be provided to the central laboratory for IHC staining and reporting, and a portion of the biopsy material will be stored frozen for batch shipping to a central laboratory for evaluation of paclitaxel presence.

4.2 ENDPOINTS

4.2.1 PRIMARY ENDPOINT

The primary endpoint will be safety and tolerability, as assessed by AEs, changes in vital signs, laboratory results, and changes in physical examination following NanoPac injection up to Week 24.

4.2.2 SECONDARY ENDPOINTS

The secondary endpoints will be:

- Concentration of paclitaxel in the systemic circulation post-injection (as determined by PK analysis);
    - If tissue biopsy samples are obtained prior to any NanoPac injection tissue will also be evaluated for the presence of paclitaxel;
- PFS as assessed using (RECIST v1.1; Eisenhauer 2009) and OS to Week 52 with a focus on the week 24 summaries;
- Assessment of tumor response (dimensions, volume) as determined by CT scan imaging, at Weeks 12, 24, 38, and 52 compared to baseline;
    - Any changes in characteristics of lesion/nodes as determined via CT scan.

4.2.3 EXPLORATORY ENDPOINTS

- Change in Eastern Cooperative Oncology Group (ECOG) Performance Status at Weeks 12 and 24 compared to baseline;
- Changes in pain (as measured by the visual analog scale [VAS]);
- Changes in QOL as measured by the EQ-5D Quality of Life Scale at baseline and at Weeks 4, 8, 12, 18, 24, 38, and 52;
- Immune markers will be assessed in the blood via FCM, and in the tissues via IHC.

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 and able to tolerate the EBUS-TBNI procedure;
- Histologically/cytologically confirmed lung cancer. Eligible subjects may include, for example: primary or recurrent non-resectable disease, locally advanced stages II and III with nodal disease, stage IV advanced disease
- At least one lesion documented via imaging (within 4 weeks of Screening) which can be accessed using EBUS-TBNI;
- Subject is not a candidate for surgery;
- Has received or plans to receive SOC chemotherapy; adequate hematologic recovery must be confirmed according to the institution's SOC;
- Performance Status (ECOG) 0-2 at study entry;
- Life expectancy of at least 6 months;
- Adequate marrow, liver, and renal function at study entry;
    - ANC ≥ 1.5 x 10^9/L;
    - Hemoglobin ≥ 9.0 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:

- Significant cardiac disease (Class III or IV per New York Heart Association guidelines);
- Active bacterial, viral, or fungal infections (including active AIDS, hepatitis B or hepatitis C);
- Symptomatic central nervous system (CNS) metastasis which are neurologically unstable, or CNS disease requiring increase in steroid dose (treated metastatic disease and stable steroid use are not excluded);
- Known hypersensitivity to study agent;
- Pregnant or breastfeeding women.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Sufficient subjects will be screened to allow up to 18 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.

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 EDC. The final study visit is planned for six months after NanoPac injection. For subjects wishing to pursue other treatment options (such as other clinical trials) sooner than 12 months after NanoPac injection, the final study visit may be conducted sooner.

- The Investigator, at their discretion, may elect not to administer the second or third injection or reduce the volume of the injection. All subjects will be followed for safety for the duration of the trial unless informed consent is withdrawn. 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, or if another clinical trial is being considered for the subject, 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 before Week 24 they would complete all assessments for Week 24; if they withdraw after Week 24, they would complete the assessments which would be performed at either the Week 38 or Week 52 visit.

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 Safety Review Committee (SRC), and/or routine SRC reviews, will allow for termination of study based on unacceptable risk, which will consider all safety evaluations and DLTs.
- 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 (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, 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.: XXXXXXXXXX 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 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 volume at 15mg/mL the injection volume will be withdrawn, as described in the IFU, from the vial(s) into one or more syringes up to a maximum volume of 40 mL.

The maximum volume for the first injection will be calculated from the baseline CT measurements prior to first injection. Actual amounts injected to the various lesions will be detailed in the source and in the EDC.

The syringe(s) for administration will be labeled with the subject ID and the date and time of preparation.

6.1.5 DOSING AND ADMINISTRATION

Subjects will receive NanoPac on three occasions: on the Day 1, Week 4, and Week 8 visits.

On the day of NanoPac administration, the subject will receive parenteral antibiotic prophylaxis at the discretion of the Investigator. The subject will be sedated by standard institutional anesthetic procedure for the bronchoscopic procedure and injection of NanoPac. At each injection visit tumor size(s) will also be measured using EBUS-TBNI, and the tumor(s) and node/nodal sizes recorded.

EBUS-TBNI of the tumor(s) and node(s) within the lung will be used to inject 15 mg/mL NanoPac at a volume up to 20% of tumor and node volume for each individual lesion or metastatic node (as calculated in Section 4.1), up to a maximum volume of 40 mL during each injection procedure.

For the first injection procedure, the tumor volume (lung and nodal lesions) will be calculated from the baseline CT information. The injection volume for the second and third injection procedures should be identical to the first injection procedure, but may be reduced per Investigator discretion. The volume of NanoPac injected, total and/or lesional, will at no time be increased beyond the maximum as calculated by the baseline CT measurement(s) and may be reduced at discretion of Investigator.

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. NanoPac will be injected ensuring that NanoPac is dispersed evenly throughout the entirety of the tumor.

6.1.6 ROUTE OF ADMINISTRATION

NanoPac will be administered directly into the tumor(s) and node(s) within the lung via EBUS-TBNI.

6.1.7 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

Enrollment of the first three subjects will be sequential. After the first subject has completed the 2-week follow-up visit after their first injection procedure, the SRC will convene a teleconference with the Principal Investigator to review the safety of NanoPac and approve dosing of the second subject provided there are no safety issues of note. The second subject may be consented and undergo Screening activities prior to SRC approval but may not be treated with NanoPac until the SRC has given approval. The SRC may also determine at their discretion, upon review of routine data, that dose/volume reduction is required for the remaining subjects in this study. This sequence of safety review will be repeated for the second and third subjects, after which enrollment will be open for all remaining subjects.

It is possible that the full 20% tumor (or lymph node) volume for a particular subject will not be able to be administered; the Investigator will determine this at the time of injection. In the event that not all of the calculated volume of NanoPac can be administered, particularly with respect to the primary target lesion, the amount not injected will be available for use in other lesions or nodes identified on the baseline CT, provided that the maximum volume injected into any lesion or node is not more than 20% of the volume of the lesion or node, up to a maximum of 40 mL in total per bronchoscopic procedure.

All lesions to which NanoPac is delivered will be documented in the source and in the EDC, and only the lesions injected at the first procedure may be injected at the second and third procedure, however the amount delivered may differ but must not exceed 20% of lesion volume as calculated from the baseline CT scan.

6.1.8 DURATION OF THERAPY

NanoPac will be administered on up to three occasions 4 weeks apart.

6.1.9 TRACKING OF DOSE

Volume of NanoPac injected to any lesion or node will be documented within the source and the EDC.

6.1.10 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 study agent, 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.

The Investigator will document the amount of NanoPac injected into each lesion and node, and any volume of NanoPac remaining unused, 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.

- Screening procedures/evaluations as described in Section 7.3.1.

- Confirmation of adequate hematologic recovery (see Section 5.1 Participant Inclusion Criteria) must be obtained prior to NanoPac administration and filed in the subject's study record;
- Comprehensive physical examination, including ECOG Performance Status assessment (Appendix A), and vital signs (blood pressure, heart rate, temperature, body weight and height);
- A CT scan will be conducted during the screening period prior to first injection, in order to calculate tumor and node volume(s). CT scans will also be conducted prior to the second and third injections (Weeks 4 and 8) and at follow-up visits at Weeks 12, 18, 24, 38, and 52. Should the subject withdraw from the study at any time, a scan will be conducted as part of the End of Study procedures if possible. 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. The baseline CT scan will be provided to the Medical Monitor for review/approval with the completed pre-injection form prior to first injection for all subjects. All imaging will be filed in the subject record and identifiers removed before images are shared with the Sponsor.
- Samples will be collected and processed for PK evaluation (Section 7.2.2);
- Samples will be collected and processed for routine clinical laboratory assessment (Section 7.2.1).
- Samples will be obtained and sent to a central laboratory for FCM evaluation of immune markers (Section 7.2.2).
- A biopsy specimen from the primary target lesion may be obtained at each injection visit; biopsies must not, however, be obtained from any lesions that are in proximity to cardiac or any vital neurovascular structures. If available, a portion will be prepared on slides to be sent to a central laboratory for IHC assessments and a portion will be stored frozen prior to bulk shipment to a central laboratory for evaluation of paclitaxel levels.
- QOL will be assessed using the EQ-5D QOL questionnaire (Section 7.2.2).
- Pain will be assessed with the VAS at screening, on the days of NanoPac administration (pre- and post-injection), and at all other study visits up to Week 24.
- NanoPac administered via EBUS-TBNI-guided fine needle injection (Section 6.1.5).

7.1.2 STANDARD OF CARE STUDY PROCEDURES

The subjects being enrolled to this study will have received or will be receiving concomitant SOC as required for their care; platelet and neutrophil recovery is required to meet inclusion criteria for participation.

Following administration 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.).

Information on SOC and treatment post-injection(s), until the End of Study visit, 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 days of NanoPac injection, 2 weeks after each injection, and at the Weeks 12, 18 and 24 visits. The samples to be collected are: sodium, potassium, chloride, carbon dioxide (CO2), calcium, phosphorus, glucose, blood urea nitrogen (BUN), creatinine, alkaline phosphatase, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total protein, albumin, and calculated creatinine clearance;
- Red blood cell count (RBC), hemoglobin (Hgb), hematocrit (Hct), 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; and urine pregnancy test (if applicable at Screening, Week 12 and Week 24);
- Prothrombin time (PT), activated partial thromboplastin time (PTT), and international normalized ratio (INR).
- Serology testing will be performed for HIV, Hepatitis B and Hepatitis C prior to first injection

7.2.2 OTHER ASSAYS OR PROCEDURES

PK samples will be taken at scheduled injection visits (Day 1, Week 4, and Week 8), prior to NanoPac injection, and at 1, 2, and 4 hours +/- 10 minutes post injection start time.. A single sample will be obtained during all other study visits, up to and including Week 24.

Imaging with CT scan will occur prior to each injection of NanoPac, and at Weeks 12, 18, 24, 38, and 52. Should the subject withdraw from the study at any time, a scan will be conducted as part of the End of Study procedures if possible. Additional imaging may be performed at the Investigator's discretion and all resulting images will be collected for the subject's record. The baseline CT scan will be forwarded to the Medical Monitor for review/approval with the completed pre-injection form prior to first injection for all subjects. All imaging will be collected for the subject's record and identifiers removed before sharing copies with the Sponsor.

Pain assessment will be conducted with the VAS at all study visits to Week 24. On the day(s) of NanoPac administration the pain assessment will be conducted prior to NanoPac injection, and at 4 hours post-injection or just prior to discharge following the procedure to allow for residual anesthetic effects to wear off.

QOL assessment will be conducted using EQ-5D QOL instrument at baseline, at each injection visit prior to the procedure, and again at Weeks 12, 18, 24, 38, and 52.

Blood samples will be collected for flow cytometric evaluation of immune markers at each injection visit and again at Weeks 12, 18, and 24.

Biopsy specimens may be collected at each or any injection visit and a portion will be prepared on slides for IHC assessment and a portion will be stored frozen for paclitaxel assessment.

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 batch-shipped to Covance Laboratories (Madison, WI) for analysis. Procedures for processing for storage will be provided prior to study initiation.

Biopsy specimens for paclitaxel assessment, when available, will be stored frozen on-site until batch-shipped to Covance Laboratories (Madison, WI) for analysis.

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

Blood samples for FCM will be drawn into tubes provided for this purpose, and shipped to NeoGenomics on the day the sample is obtained; samples may remain at ambient temperature until shipped.

Biopsy specimens for IHC evaluation, when available, will be sent to the site's pathology laboratory for preparation of tissue block/slides to be shipped to NeoGenomics. A manual will be provided by NeoGenomics detailing the instructions for both slide preparation and for FCM sample preparation.

7.2.4 SPECIMEN SHIPMENT

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

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

7.3 STUDY SCHEDULE

7.3.1 SCREENING

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, and demographics;

- Review and documentation of lung cancer, including documentation of lesion size(s) 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 (Section 7.2.1);
- Urine pregnancy test for women of child-bearing potential;
- Imaging with CT scan will be performed prior to the next study visit; the scan may be performed any time within 28 days of the injection visit, allowing for sufficient time to obtain the dimensions for all lesions and nodes planned to be injected. This information is required for the NanoPac requisition to Pharmacy indicating the volume required for Day 1 procedures. The baseline redacted CT scan will be forwarded to the Medical Monitor for review/approval with the completed pre-injection form prior to first injection for all subjects.

Visit dates will be scheduled/projected forward from the first injection visit at Day 1.

Visits from Week 1 to Week 10 will have a +/- one day window; Weeks 12, 18 and 24 will allow for a +/- 1-week window; Weeks 38 and 52 will allow for a +/- 2-week window

7.3.2 DAYS OF NANOPAC INJECTION – DAY 1, WEEK 4, WEEK 8

Day 1: All Screening assessments must have completed prior to this visit, and all results and inclusion/exclusion criteria must have been confirmed.

All injection visits – Day 1, Week 4, Week 8, **prior** to the bronchoscopic procedure:

- Subjects will complete an EQ-5D QOL questionnaire
- Comprehensive physical examination, including vitals and ECOG Performance Status assessment (Appendix A);
- VAS for pain assessment will be completed pre- and post-injection. Post-injection scale will be completed at the 4-hour PK sample timepoint.
- AEs occurring in the period between Screening and this visit must be confirmed as either ongoing or completed. AEs 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;
- Laboratory sample collection prior to injection, and processing for clinical laboratory assessments (Section 7.2.1):
    - Routine safety laboratory work and blood sample for FCM

        - Coagulation laboratory assessment results must be confirmed to be within normal limits prior to injection if a biopsy is planned
    - PK samples pre-injection and 1, 2, and 4 hours post-i injection
- Imaging with CT scan will be performed prior to injections at Week 4 and Week 8 and may be obtained up to 3 days prior to the scheduled injection visit.

Subjects will receive NanoPac as described in Section 6.1.5. Immediately prior to NanoPac injection, tissue biopsies will be obtained for routine histopathology at the site (if standard procedure) and for paclitaxel assessment and tissue block/slide preparation for IHC assessment.

7.3.3 FOLLOW-UP VISITS

Follow up visits occur one and two weeks after each injection (Weeks 1, 2, 5, 6, 9, and 10) and then at Week 12 and at Week 18.

At all follow-up visits the following are performed:

- VAS for pain assessment will be completed;
- Vital signs will be assessed;
- A single PK sample will be collected;
- Concomitant medications will be updated;
- AEs will be updated.

At Weeks 2, 6, 10, 12, and 18 routine safety blood samples will be obtained and sent to the local laboratory for assessment (Section 7.2.1). A urine pregnancy test will be performed at Week 12 for women of child-bearing potential.

At Weeks 12 and 18 the following additional assessments will be performed:

- QOL questionnaire will be completed;
- An ECOG score will be obtained;
- A blood sample for FCM analysis of immune markers will be obtained;
- A CT scan will be performed within the visit window.

In the event that an Investigator or subject elects not to receive all three scheduled injections, not all study visits listed in the schedule of events are required. The list below clarifies what visits are to be conducted when injections are missed.

- **Week 4 Scheduled Injection Missed:** Week 5 visit is not required; Week 6 is still required. The subject will then return at Week 8 for their next injection if all criteria for receiving the injection are met.
- **Week 8 Scheduled Injection Missed:** If Week 8 injection procedure is missed, the one-week follow-up (Week 9) is not required but the two-week follow-up (Week 10) is still required.
- **Week 4 and Week 8 Scheduled Injections Missed:** If a subject misses the Week 4 administration, they will follow the visit schedule as outlined above in anticipation that the

scheduled Week 8 injection may still occur. In the event that the Week 8 injection is also missed, the Week 9 and Week 10 visits are no longer required for safety as 2 months have passed since investigational drug administration. In this situation, Weeks 5, 9, and 10 are not required.

7.3.4 PRIMARY ENDPOINT STUDY VISIT (WEEK 24, APPROXIMATELY 6 MONTHS)

This primary endpoint visit will be conducted at Week 24 ± 1 week. For any subject withdrawing prior to Week 24 all assessments as described for this visit would be conducted.

Subjects may decide to withdraw participation prior to this point and at that time this visit should be conducted if possible. For some subjects the Week 12 (3-month) or Week 18 study visit may serve as the final study visit, as this 6-month visit will only be conducted for subjects still willing and able to undergo the assessments.

At this primary endpoint study visit the following procedures will be performed:

- Comprehensive physical examination, including vitals and ECOG Performance Status assessment;
- VAS for pain assessment will be completed;
- QOL questionnaire will be completed;
- Concomitant medications will be updated;
- AE collection up to the Week 24 visit (noted to be resolved or ongoing at this visit);
- Sample collection and processing for clinical laboratory assessments (Section 7.2.1);
    - Routine safety laboratory work and blood sample for FCM;
    - PK sample obtained;
    - Urine pregnancy test for women of child-bearing potential;
- Imaging with CT scan within the visit window.

7.3.5 FOLLOW UP VISIT WEEK 38 AND END OF STUDY WEEK 52

These visits are being conducted in subjects still willing and able to undergo assessments for the purposes of determining QOL, PFS, and OS.

The following procedures will be performed:

- Vital signs will be performed;
- ECOG will be assessed;
- QOL questionnaire will be completed;
- Imaging with CT scan within the visit window;
- Concomitant medications – only those used as SOC lung cancer therapies will be captured.

For any subjects withdrawing after the Week 24 visit, their withdrawal visit would include all assessments noted for these visits.

Week 38 and Week 52 visits will be performed with a visit window of +/- 2 weeks.

No further follow-up will be required or requested of subjects after this visit.

7.3.6 EARLY TERMINATION VISIT

In the event a subject is withdrawn prior to Week 24 they would, at minimum, undergo Week 24 evaluations, which include the procedures described in Section 7.3.4. 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. If a subject is withdrawn from the study between Week 24 and Week 52, the assessments for Week 52 will be conducted.

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.

7.3.7 SCHEDULE OF EVENTS TABLE

	Screening[6]	Day 1 NanoPac	Week 1	Week 2	Week 4 NanoPac	Week 5	Week 6	Week 8 NanoPac	Week 9	Week 10	Week 12	Week 18	Week 24 (6 months)	Week 38 (9 months)	Week 52 (12 months)
Informed Consent	X														
History[1]	X														
Physical Exam	X	X			X			X					X		
Pain Assessment[4]	X	X	X	X	X	X	X	X	X	X	X	X	X		
QOL Questionnaire		X			X			X			X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG[2]	X	X			X			X			X	X	X	X	X
Clinical Laboratory Tests[8,9]	X	X		X	X		X	X		X	X	X	X		
PK Samples (blood)[3]		X	X	X	X	X	X	X	X	X	X	X	X		
Blood FCM analysis		X			X			X			X	X	X		
Tissue (biopsy) for IHC and paclitaxel		X			X			X							
Imaging (CT Scans)[5]	X				X			X			X	X	X	X	X
NanoPac Procedure		X			X			X							
Pharmacy		X			X			X							
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X[7]	X[7]
Adverse Events		X	X	X	X	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 PK Samples on Day 1, Week 4, and Week 8 will be drawn prior to injection and at 1, 2, and 4 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.

4 Pain will be assessed with the visual analog scale.

[5] Imaging with CT scan will occur during the screening period, prior to each NanoPac administration, and at Weeks 12, 18, 24, 38, and 52. Should the subject withdraw from the study at any time, a CT 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.

[6] Screening will occur up to four weeks prior to injection.

[7] All concomitant medications will be captured to Week 24. Only SOC lung cancer therapy will be captured at visit Weeks 38 and 52.

[8] Urine pregnancy test for women of child-bearing potential at Screening, Week 12 and Week 24.

[9] Clinical laboratory tests include hematology, chemistry, urinalysis and at screening includes serology (Hepatitis A, Hepatitis B and HIV).

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Sponsor acknowledges that EBUS-TBNI of NanoPac into the tumor(s) and node(s) within the lung, 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 electronic 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

If chemotherapy or radiation therapy is to be initiated during the conduct of the study, particularly during the 4 weeks following the first NanoPac injection, the PI must contact the study Medical Monitor to discuss the assessments made in determining 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.

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:

- AEs, collected at all study visits from the time of dosing to Week 24;
- 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, SRC review will be conducted as follows:

- As described in Section 6.1.7, for only the first three subjects enrolled to the study, the SRC will conduct a review after each of the first three subjects completes the 2-week follow-up visit after their first injection of NanoPac. Additionally, the SRC will conduct a review after each of the first three subjects completes the 2-week follow-up visit after their second injection of NanoPac.

- The baseline redacted CT scan will be forwarded to the Medical Monitor for review/approval with the completed pre-injection form prior to first injection for all subjects.

- Thereafter, safety reviews will take place on a monthly basis during the conduct of the study. The Medical Monitor will review the data for each subject entered to the database on a monthly basis and communicate the summary findings to the SRC at each review.

- The SRC may also convene at any other time if deemed necessary or requested by any member of the SRC.

Included in the SRC's review of the AEs and general study data pertaining to safety (such as laboratory results and questionnaire responses) consideration will be given to any adverse event that is considered related or possibly related to NanoPac and therefore is potentially a DLT. The definition of a DLT will be

made by consensus by the SRC and Principal Investigator for AEs. DLTs will, in addition, include the following:

- ≥ Grade 3 febrile neutropenia;
- ≥ Grade 3 non-hematological toxicity, unless clearly not attributable to the study agent;
- 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;
- Concomitant elevation of AST/ALT 3x ULN and bilirubin 2x ULN (Hy's Law)
- Any life-threatening event (unless there is a clear alternative explanation that the event is not related with the procedure or the study agent itself); and
- Any clinically important event as defined by the SRC.

DLTs may result in removal of the subject from study treatment, however they will not be discontinued from the study follow-up procedures unless deemed to be in their best interest.

Events of special interest (Section 8.4.4) will be specifically reviewed by the Medical Monitor, and the SRC review will provide and document oversight as detailed in the Safety Plan.

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 2 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 according to the NCI CTCAE v 5 grades; Grades 1 through 5 have unique clinical descriptions of severity for each AE based on the general guideline as follows:

- **Grade 1 - Mild:** Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Grade 2 - Moderate:** Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- **Grade 3 - Severe:** Or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- **Grade 4 - Life-Threatening:** Urgent intervention indicated
- **Grade 5 - Fatal:** Death related to the adverse event.

8.2.2 RELATIONSHIP TO STUDY AGENT

The following five-point scale will be used by the Investigator to rate the relationship of the AE to the study agent:

- **Definitely related:** A clinical event (including laboratory test abnormality) occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitively associated pharmacologically, using a satisfactory re-challenge procedure, if necessary;

- **Probably related:** A clinical event (including laboratory test abnormality) with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition;

- **Possibly related:** A clinical event (including laboratory test abnormality) with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear;

- **Unlikely to be related:** A clinical event (including laboratory test abnormality) whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments);

- **Not related:** An event for which sufficient information exists to conclude that the etiology of the event is unrelated to the study agent. An alternative definitive etiology should be documented by the Investigator.

8.2.3 EXPECTEDNESS

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

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

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

AEs will be recorded throughout the study to Week 24, and at early termination if it occurs sooner. AEs ongoing at the Week 24 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.

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

All AEs (whether or not attributable to the study agent) occurring during the 24 weeks following first NanoPac injection 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 the 24 weeks following first NanoPac injection, 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
Email: tony.verco@usbiotest.com
Phone: 805-235-9193

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

The Study Manager should be copied on all correspondence.

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 first 24 weeks 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. Events of interest include systemic adverse effects known to be caused by paclitaxel e.g. neutropenia, febrile neutropenia, sepsis, anemia, thrombocytopenia, and peripheral neuropathy. Local AEs of interest include chest pain (pleuritic and non-pleuritic, back, shoulder), shortness of breath, cough, wheezing, hemoptysis, pneumonitis/pneumonia, mediastinitis, Superior Vena Cava (SVC) syndrome, Horner's Syndrome, and bronchopleural fistula.

8.4.5 REPORTING OF PREGNANCY

Female subjects must take a pregnancy test before receiving any treatment (Section 5.1 Participant Inclusion Criteria).

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 Sponsor 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 2 study, and review of the safety and tolerability data will be conducted according to the schedule by the SRC. Following review, at any time point, the study may be terminated.

The study will be halted if there is any death, other than disease progression, which is at least possibly related to the study agent, or if two or more Grade 4 events which are at least possibly related to the study agent occur.

Should the study be halted, all subjects who have received treatment will be followed to the completion of their participation to ensure all safety data is collected on all treated subjects.

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 SRC. Membership of the SRC will constitute the Sponsor Medical Director, Principal Investigator, Medical Monitor, and an independent specialist physician (Section 8.1 Specification of Safety Parameters).

All subject study data will be captured in an EDC system, allowing real-time access to ongoing safety and tolerability data.

The SRC will convene to review the subject data, and a report will be generated outlining any safety concerns from the data available for review in the EDC. Reviews will take place as described in Section 6.1.7 and Section 8.1.

During the SRC 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 prior to study database lock.

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 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.

The SAP will define intercurrent events (e.g. not completing the full course of treatment (i.e. three injections), use of alternative medication, or stopping treatment due to an AE); different strategies will be developed to address the possible impact on the ability to derive a reliable treatment-related estimate of each of the outcomes of interest.

Given the small number of subjects and the descriptive nature of summary statistics, it is recognized that looking at 'sensitivity' analyses will likely be limited to a variety of summary tables.

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 treatments. The general approach will be to highlight any trends that cause concern for the reviewing medical monitoring team (i.e., DLTs). Events that are related to the mode of administration will be presented separately from those that may have a relationship to the actual study medication.

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 future study, as follows:

- Concentration of paclitaxel in the systemic circulation post-injection (as determined by PK analysis);
- Tumor response (RECIST as per Eisenhauer 2009);
- Reduction in pain (as measured by the VAS).

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

10.4.4 SAFETY ANALYSES

10.4.4.1 ADVERSE EVENTS

AEs 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 recorded. AEs will be recorded from Day 1 to the Month 6 visit only.

Events reported at or after the application of NanoPac will be considered TEAE. All reported events will be listed by subject number and cumulative dose to date, investigator term, Medical Dictionary for Regulatory Activities (MedDRA) coded term, date/study day (from initial treatment) for onset and cessation, severity (using the NCIC severity grading), and relationship to study medication. Only the TEAE will be tabulated.

The primary safety analysis and clinical study report will be based 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 focus of the summary will be on the cumulative dose just prior to the onset of the event for the subject.

AE 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 v 5.0 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). AEs of special interest will be defined in the SAP and 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) 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. Analytes of particular interest (e.g., hematological tests) may be graphed by subject; 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 as defined in the SAP 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 SRC meetings between cohorts as outlined in Section 8.

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 four weeks prior to the injection procedure (, at Weeks 4, 8, 12, 18, 24, 38, and 52, or at any time deemed to be required by the investigator.

These results will be summarized and changes from the pre-dosing measurements highlighted.

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.

10.4.10TABULATION OF INDIVIDUAL RESPONSE DATA

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

10.4.11EXPLORATORY ANALYSES

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 with any difference in the number of doses or cumulative dose, as outlined in the SAP 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.

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

QOL will be measured using the validated EQ-5D QOL instrument

Flow cytometric analysis of blood samples and ICH evaluation of slides will be conducted by NeoGenomics (central laboratory) and they will be responsible for providing reports of these findings. These findings may be presented in a standalone report which will be integrated into the Clinical Study Report (CSR).

10.4.12CONCOMITANT 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

Defining the primary endpoint explicitly requires understanding the primary purpose of the study. If, in this case, the primary purpose of the study is safety, 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 AE is known to occur in only 1% of subjects, there is an 16.5% chance it will appear in a particular cohort of 18 subjects. If the event only occurs in 5% of patients, there is only a 60.3% chance it will appear in a given 18-subject cohort, and for an event with a base occurrence rate of 10%, the probability of observing at least one event will be 85%. 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 Advisor version 8.3.

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.

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.

Copies of imaging data provided to the Sponsor will be filed in a secure cabinet with controlled access and held for review until archiving of the study documents, at which time the redacted imaging data will be archived together with the Trial Master Filed.

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 data is ALCOA-C compliant.

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

For paper source, documentation is expected to be completed in a neat, legible manner to ensure accurate interpretation of data. Black or blue ink is required to ensure clarity of reproduced copies. 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 PK 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 a full Sponsor study team list 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.