US Biotest Protocol #NANOPAC-2016-01

Phase II Study of Four Dose Levels of Intraperitoneal NanoPac® plus IV Carboplatin and Paclitaxel in Patients with Epithelial Ovarian Cancer Undergoing Cytoreductive Surgery

IND Number: 073529

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Sponsor: NanOlogy, LLC
231 Bonetti Drive, Suite 240
San Luis Obispo, CA 93401
805-595-1300

Study Manager: Peter Mast
US Biotest, Inc.
281-630-6731
E-mail: peter.mast@usbiotest.com

Medical Director: Gere diZerega, MD
US Biotest, Inc.
805-630-2800
E-mail: gere.dizerega@usbiotest.com

SPONSOR REPRESENTATIVE AGREEMENT AND SIGNATURE FORM

I have read the attached protocol number 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*, Version 05 dated 19 April 2019, and agree to comply with the contents of this document.

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

The Sponsor for IND 073529, 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.

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The signature of the Sponsor Representative below constitutes his/her agreement.

Gere diZerega
Gere diZerega (Apr 23, 2019)

Signature of Sponsor Representative

Apr 23, 2019

Date

Gere S. diZerega, MD

Printed Name of Sponsor Representative

INVESTIGATOR AGREEMENT AND SIGNATURE FORM

I have read the attached protocol number 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*, Version 05 dated 19 April 2019, and agree to comply with the contents of this document.

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

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

1 PROTOCOL SYNOPSIS

Title	Phase II Study of Four Dose Levels of Intraperitoneal NanoPac® plus IV Carboplatin and Paclitaxel in Patients with Epithelial Ovarian Cancer undergoing Cytoreductive Surgery
Sponsor	NanOlogy, LLC
Study Number	NANOPAC-2016-01
Phase	II
Primary Objective	• Dose Finding Phase: Determine the two best dose levels for further study • Efficacy Phase: Estimate progression-free survival (PFS) at 12 months
Secondary Objectives	• Determine the safety of IP NanoPac immediately following cytoreductive surgery • Perform routine monitoring of plasma paclitaxel concentrations following IP administration of NanoPac • Compare duration of PFS between time-to-initial recurrence and time-to-recurrence following second cytoreductive surgery plus IP NanoPac • Determine possible predictive factors to be used as stratification factors or covariates in subsequent studies
Safety Monitoring Committee	Prior to the enrollment of the first subject, a Safety Monitoring Committee (SMC) Charter will be authored and signed off by the committee members; the Charter will contain the data requirements and the decision rules for monitoring subject safety during the initial post-surgery outcome assessment stage for the escalated doses as well as throughout the trial.
Study Design	Phase II study comparing four dose levels of IP NanoPac (100, 200, 300, and 400 mg/m^2) instilled immediately post-cytoreductive surgery, followed by IV chemotherapy (SOC), with SOC only. IV dosing should be as per institutional standards. The study will include a dose finding phase and an efficacy phase. All subjects will have a minimum 12-month follow-up period. Subjects that have completed the 12-month follow-up period will be contacted every 6 months for disease status until disease progression has occurred in 50% of the subjects or until 12 months after the last subject completes their IV chemotherapy, whichever comes first.

	During the dose finding phase, subjects will be enrolled in dose-escalated cohorts of three subjects. All subjects will receive IP NanoPac at 100, 200, 300, or 400 mg/m^2 plus SOC. Subjects will be monitored post-surgery for signs of toxicity (e.g., severe abdominal pain after 5-7 days, neutropenia, thrombocytopenia, bowel dehiscence, prolonged ileus) and PK plasma samples will be taken. The SMC will review all available data up to a maximum of four weeks prior to dose escalation. Dose escalation of NanoPac will be determined by the SMC per the charter, which will be in place prior to the first subject entering the study. This will be repeated for each escalated dose until all dose levels have been enrolled or a dose is determined to be unsafe. As the IP NanoPac is an adjunctive therapy with the same mode of action as the IV chemotherapy, the SMC will be reviewing all accumulating information regarding safety. The two best dose levels of NanoPac will be included in the efficacy phase of the study. In the efficacy phase, subjects will be randomized 1:1:1 to one of two dose levels of NanoPac plus SOC or SOC alone. Randomization will be determined centrally up to three days prior to surgery. Enrollment will be stratified by center, disease stage, whether the ovarian cancer is primary or recurrent, and whether they receive neoadjuvant chemotherapy. The study will continue until disease progression has occurred in 50% of the subjects or 12 months after the last subject completes their IV chemotherapy, whichever comes first. Disease progression will be demonstrated by onset of symptoms, doubling of CA-125, and/or an increase in the volume of presumptive tumor burden seen on imaging.
Population	Subjects with epithelial ovarian cancer considered appropriate for treatment with IV platinum and paclitaxel undergoing cytoreductive surgery will be included.
Study Plan & Duration	Pharmacokinetic (PK) samples will be collected from all subjects who received NanoPac on the day of cytoreductive surgery if clinically feasible, at 1, 2, 4, 8, and 24 hours post-instillation, weekly until IV chemotherapy begins and at follow-up visits (Months 9 and 12). Subjects will be monitored post-surgery through the treatment period for safety based on adverse events and laboratory values. Hematology and biochemistry will be done weekly until IV chemotherapy begins.

	PK, hematology, and biochemistry samples will be collected from every subject prior to each cycle of post-surgery IV chemotherapy. Imaging will be performed prior to initiation of post-surgery IV chemotherapy to establish baseline tumor burden, after cycle 3, and at the end-of-treatment (EOT) visit. Baseline CA-125 levels will be established prior to post-surgery cycle 2, and subsequent CA-125 testing will be performed at each cycle and following the last cycle. If the CA-125 level is double the baseline level for 2 consecutive cycles, or if progression is suspected, imaging will be conducted. During the minimum 12-month follow-up period, subjects will return to the clinic every 3 months for CA-125, PK sample collection, as well as clinical evaluation of the subject for signs or symptoms of disease progression. Imaging will be performed when a subject develops symptoms, has a doubling of CA-125, or every 6 months, whichever is sooner. After 12 months of follow-up, subjects will be contacted every 6 months until disease progression has occurred in 50% of the subjects or 12 months after the last subject completes their IV chemotherapy, whichever comes first. The duration of the study will be approximately 6 months of treatment with a minimum of 12 months' follow-up per subject.
Medication/Dosage	NanoPac 100, 200, 300, and 400 mg/m^2 administered IP immediately post cytoreductive surgery followed by IV chemotherapy (SOC), or SOC alone.
Sample Size	Dose finding phase: Approximately 16 subjects Efficacy phase: Approximately 45 subjects
Safety Variables	• Adverse events • Laboratory assessments • ECOG performance status
Efficacy Variables	• CA-125 level • Tumor burden (residual disease) shown by imaging and calculated per RECIST (version 1.1) criteria • Progression-free survival (PFS) • Survival • Cancer-related symptoms (including bowel obstruction, ascites)

Inclusion Criteria	• Epithelial ovarian cancer which is contained within the abdomen, but may include pleural effusion if that is the limit of non-peritoneal cavity disease. If subject has recurrent epithelial ovarian cancer, the disease must be platinum-sensitive (recurrence >6 months from prior chemotherapy regimen that included a platinum agent and cytoreductive surgery) • Subject appropriate for cytoreductive surgery and treatment with IV platinum and paclitaxel • Minimal or non-symptomatic ascites • ≥18 years old • Signed informed consent
Exclusion Criteria	• Epithelial ovarian cancer outside of the peritoneal cavity, with the exception of pleural effusions • Anticipated use of concomitant chemotherapy (other than the protocol-specified agents), immunotherapy, or radiation therapy • Treatment with a prior investigational agent within 30 days of planned instillation of NanoPac, with the exception of subjects participating in poly (ADP-ribose) polymerase (PARP) inhibitor trials. These subjects must discontinue the investigational agent prior to surgery • Known sensitivity to any of the study medication components or the chemotherapy regimen • History of prior malignancy other than ovarian that has not been in remission for >5 years, with the exception of basal cell or squamous cell carcinoma or cervical carcinoma in situ on biopsy • Ileostomy or hepatic resection during current cytoreductive surgery • Women of childbearing potential not practicing adequate forms of birth control
Statistical Methods	Prior to the enrollment of the first subject, a Safety Monitoring Committee (SMC) Charter will be authored and signed off by the committee members; the Charter will contain the data requirements and the decision rules for monitoring subject safety during the initial post-surgery outcome assessment stage for the escalated doses as well as throughout the trial. The data will be summarized in two periods – the dose finding phase, where the highest doses which are considered safe will be assessed, and the comparative phase. The comparative phase is the primary period for defining the success of the addition of IP NanoPac to the SOC.

	The data from the dose finding phase will be summarized descriptively by dose level. The PK data will be reviewed and the data presented to determine a possible relationship to safety, e.g., frequency of pre-specified AEs. Any efficacy data available (e.g., CA-125 and/or RECIST criteria as well as PFS and survival, if available) will be presented in a similar manner. The comparative part of the trial, with approximately 15 subjects per treatment arm, has not been powered for inferential statistics; however, comparisons to SOC-only may be performed to provide guidance for the clinical interpretation of an effect which is clinically better than the control. It is recognized that all these inferential results should be viewed and interpreted with caution. The criteria defining the NanoPac dose to move forward for further study will be based on both safety and indications of efficacy. In addition, the subjects will enter a post-treatment follow-up phase and be monitored for a minimum of 12 months post-chemotherapy to determine short-term PFS and survival status. The data will at a minimum be displayed as a Kaplan-Meier plot; appropriate descriptive summary statistics will also be presented. Patients will be monitored throughout chemotherapy to assess the adverse experiences associated with the mode of administration and the toxicity of the chemotherapy. The events from the monotherapy stage (surgery to initiation of IV chemotherapy) and the adjunctive therapy stage (from initiation of post-surgery IV chemotherapy until the end of the trial) will be presented separately; the start date will be the indicator of the stage that the event is associated with. Special focus will be on those events which lead to termination of IV chemotherapy.

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3 LIST OF ABBREVIATIONS

AUC	Area under the Curve
AE	Adverse Event
C_{max}	Maximum (Peak) Plasma Concentration of a Drug
DLT	Dose Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EOT	End-of-Treatment
FDA	The U.S. Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
IND	Investigational New Drug Application
IP	Intraperitoneal
IV	Intravenous
MTD	Maximum Tolerated Dose
NDA	New Drug Application
PCA	Precipitation with Compressed Antisolvents
PFS	Progression-Free Survival
PK	Pharmacokinetics
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SMC	Safety Monitoring Committee
SOC	Standard of Care
TEAE	Treatment-Emergent Adverse Event
T_{max}	Time at which Maximum (Peak) Plasma Concentration of a Drug (C_{max}) is observed
TTP	Time to Progression

4 INTRODUCTION

4.1 Background

Ovarian cancer has a high rate of recurrence, even when treated with the current standard of care. When ovarian cancer recurs, treatment is challenging and disease-free intervals are brief. The addition of intraperitoneal (IP) therapy is an attractive option for primary or recurrent ovarian cancer. The basic goal of intraperitoneal antineoplastic therapy is to expose cancer confined to the peritoneal cavity to higher concentrations of drug for longer periods of time than is possible with systemic therapy. Intraperitoneal therapy is designed to maximize drug delivery to the tumor while sparing the patients many of the systemic toxicities associated with the drug. A number of Phase II trials have documented the feasibility and clinical activity of the intraperitoneal approach in epithelial ovarian cancer.

Paclitaxel has broad antitumor activity and may provide a therapeutic advantage with IP administration. Paclitaxel is a naturally occurring diterpenoid isolated from the bark of the Pacific yew tree, and has exhibited some success in the treatment of several types of cancers, including ovarian, breast, and lung cancer. Paclitaxel drug substance has been available in commercial drug products in the United States for over 20 years (Taxol®, NDA 20-262, Bristol-Myers Squibb, approved for marketing on December 29, 1992; also generic paclitaxel drug product). The formulation of Taxol is a 6 mg/mL solution in a 50:50 (v/v) mixture of Cremophor® EL (polyethoxylated castor oil) and dehydrated ethanol. However, significant side effects, including severe anaphylactic hypersensitivity reactions, hyperlipidemia, abnormal lipoprotein patterns, aggregation of erythrocytes, and peripheral neuropathy, have been observed with this commercial formulation. These side effects have been attributed to the Cremophor EL excipient. Due to paclitaxel's significant potential as an effective chemotherapeutic, the search for alternative formulations that may be safer and better tolerated has been extensive.

4.2 Investigational Agent NanoPac

NanOlogy, LLC, has produced a formulation of nanoparticulate paclitaxel, identified as NanoPac® (Sterile Nanoparticulate Paclitaxel) Powder for Suspension ("NanoPac"), which is the subject of this protocol. NanoPac is manufactured using a Precipitation with Compressed Antisolvent (PCA) technique that employs supercritical carbon dioxide and acetone to generate paclitaxel nanoparticles within a well-characterized particle-size distribution. Following PCA, 306 mg of the paclitaxel nanoparticle powder is filled into a 60 mL Type 1, USP, clear-glass vial, closed with a stopper, sealed with an aluminum crimp seal, and sterilized by gamma irradiation.

Prior to administration at the hospital/clinic, the dry, sterilized NanoPac will be reconstituted with 1% polysorbate 80 reconstitution solution and 0.9% Sodium Chloride for Injection, USP, to

form a suspension. The suspension should be kept at room temperature and must be administered within 8 hours of reconstitution; the suspension must not be frozen or refrigerated. Detailed instructions are included in the dose kit.

4.2.1 Clinical Trials with NanoPac

The safety of NanoPac, previously called Nanotax®, was investigated in Protocol HSC#11140, "A Phase I Study of Intraperitoneal Nanoparticle Paclitaxel in Patients with Peritoneal Malignancies." To date, this is the only clinical study that has been conducted with NanoPac. The results of this study were published in the journal *Cancer Chemotherapy and Pharmacology* (*Williamson 2015*).

Protocol HSC#11140 was a dose-escalating study evaluating IP-administered Nanotax 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 Protocol HSC#11140, 21 patients received Nanotax, and a total of 43 doses of Nanotax were administered at doses up to 275 mg/m^2. IP administration of Nanotax did not lead to increases in systemic toxicity over that typically associated with IV paclitaxel. No Grade 2 or higher neutropenia and/or Grade 3 or higher neurologic toxicities were reported. Grade 3 thrombocytopenia, considered unlikely to be related to study medication, occurred in one 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 twelve patients had progressive disease. Five of 21 patients with advanced cancers survived longer than 400 days after initiation of IP Nanotax treatment.

Additional data from this clinical trial is presented in the NanoPac Investigator's Brochure.

4.3 Rationale for the Study

The rationale for administration of NanoPac via the intraperitoneal route is three-fold: 1) greater concentrations of paclitaxel will be achieved within the peritoneal cavity compared to IV administration of this agent; 2) nanoparticulate paclitaxel will undergo prolonged dissolution resulting in greater paclitaxel concentrations at the tumor site for a longer period of time compared to IV paclitaxel alone; and 3) substantially less systemic exposure to paclitaxel will result from IP NanoPac administration as compared to IV paclitaxel, thus reducing the risk of additional systemic toxicity.

This Phase II study will include patients with epithelial ovarian cancer undergoing cytoreductive surgery. The study design allows for a safety evaluation of IP NanoPac immediately following surgery as well as preliminary efficacy determination of IP NanoPac in combination with IV paclitaxel and carboplatin versus IV paclitaxel and carboplatin alone. The population selected is expected to benefit from the IP NanoPac.

4.4 Dose Justification

The most common dose of paclitaxel used via the IP route is 60 mg/m^2, with toxicities linked to the Cremophor EL as well as systemic toxicities. In the Phase I NanoPac study, doses up to 275 mg/m^2 were found to be safe. The proposed starting dose in the dose finding phase of this study is 100 mg/m^2, rising to 200, 300 and 400 mg/m^2. The dose finding phase is designed to determine the best tolerated dose of IP NanoPac in the pre-defined series of doses, and establish the safety of instilling NanoPac at the time of surgery as well as the safety of IP instillation followed by IV treatment.

5 STUDY OBJECTIVES

The primary objectives of this study are (a) to determine the two best dose levels of IP NanoPac given at the time of surgery; and (b) to determine progression-free survival (PFS) at 12 months. Secondary objectives are to determine the safety of IP NanoPac immediately following cytoreductive surgery, to compare duration of PFS between time-to-initial recurrence and time-to-recurrence following second cytoreductive surgery plus IP NanoPac in those subjects with recurrent cancer, to determine plasma paclitaxel concentrations following IP administration of NanoPac, and to determine possible predictive factors to be used as stratification factors or covariates in subsequent studies.

6 INVESTIGATIONAL PLAN

6.1 Overall Study Plan

This is a Phase II study of four dose levels of IP NanoPac plus IV carboplatin and paclitaxel (SOC) in patients with epithelial ovarian cancer undergoing cytoreductive surgery.

6.1.1 Study Design

Subjects with epithelial ovarian cancer considered appropriate for treatment with IV platinum and paclitaxel undergoing cytoreductive surgery will be included. The study will include a dose finding phase and an efficacy phase.

Dose Finding Phase

Subjects will be enrolled in dose-escalated cohorts and will receive IP NanoPac at a dose level of 100, 200, 300, or 400 mg/m^2 plus SOC. During the dose finding phase the study will follow a standard 3+3 dose-ascending design, commencing treatment on Day 1 with 100 mg/m^2. If a single dose limiting toxicity (DLT) is identified in 1 of 3 subjects in the cohort, a further 3 subjects will be enrolled at the same dose level. If ≥ 1 more of the same DLT occurs in the 3 extra subjects enrolled in the cohort, dose escalation will stop and the prior dose level will be regarded as the Maximum Tolerated Dose (MTD) and taken forward into the dose expansion phase. If no further DLT are identified, dose escalation will continue, until either a DLT is identified at a higher dose or the top dose of 400 mg/m^2 is reached.

Subjects will be monitored post-surgery for signs of toxicity (e.g., severe abdominal pain after 5-7 days, neutropenia, thrombocytopenia, bowel dehiscence, and prolonged ileus) and PK plasma samples will be taken. The Safety Monitoring Committee (SMC) will review the accumulating data for up to a maximum of four weeks per subject prior to dose escalation and approve moving to the next dose cohort or adding subjects to the current dose level if an IP NanoPac-related adverse effect is determined to be dose-limiting. This will be repeated for each escalated dose until all dose levels have been enrolled or a dose is determined to be unsafe. As the NanoPac is an adjunctive therapy with the same mode of action as the IV chemotherapy, the SMC will be reviewing all accumulating information regarding safety. The two best dose levels of NanoPac will be included in the efficacy phase of the study.

Examples of what might be regarded as a DLT are listed below:

Non Hematologic:

- Grade 3 or higher non-hematological toxicity, excluding nausea, vomiting, diarrhea;
- Grade 3 or higher nausea, vomiting, or diarrhea uncontrolled by maximal antiemetic/ antidiarrheal therapy for greater than 24 hours;
- Any toxicity which in the judgment of the Medical Monitor, Principal Investigator, Sponsor Medical Director, or SMC is considered a DLT;
- Hypersensitivity reactions to NanoPac that cannot be controlled with standard treatment.

Hematologic:

- Grade 3 or higher anemia and/or neutropenia;

- Thrombocytopenia of any Grade if associated with clinically significant bleeding (clinically significant as determined by the investigator, or results in a transfusion of red blood cells.), or Grade 4 thrombocytopenia without bleeding.

Efficacy Phase

Subjects will be randomized 1:1:1 to one of two dose levels of NanoPac plus SOC, or SOC alone. The study will continue until disease progression has occurred in 50% of the subjects or 12 months after the last subject completes post-surgery IV chemotherapy, whichever comes first. Disease progression will be demonstrated by onset of symptoms, doubling of CA-125, and/or a 20% increase in the volume of presumptive tumor burden seen via imaging.

Pharmacokinetic (PK) samples will be collected from all subjects who received NanoPac on Day 1, at 1, 2, 4, 8, and 24 hours post-instillation, if clinically feasible, weekly until post-surgery IV chemotherapy begins, prior to each post-surgery cycle of IV chemotherapy and at the Month 9 and Month 12 follow-up visits. Imaging will be done prior to initiation of post-surgery IV chemotherapy to establish baseline tumor burden. A baseline CA-125 level will be established prior to cycle 2, post-surgery, and subsequent testing will be performed at each cycle and following the last cycle. If the CA-125 level is double the baseline level for 2 consecutive cycles, or if progression is suspected imaging will be conducted.

All subjects will have a minimum 12-month follow-up period, during which subjects will return to the clinic every 3 months for CA-125 determination, PK sample collection, as well as clinical evaluation for signs or symptoms of disease progression. Imaging will be performed when a subject develops symptoms, has a doubling of CA-125, or every 6 months, whichever is sooner. After 12 months of follow-up, subjects will be contacted every 6 months until disease progression has occurred in 50% of the subjects or 12 months after the last subject completes their IV chemotherapy, whichever comes first.

6.2 Sample Size

During the dose finding phase, approximately 16 subjects will be enrolled. During the efficacy phase, approximately 45 subjects will be randomized.

6.3 Investigational Sites

Up to 12 investigational sites in the United States will be used for this study. Sites will be selected based on the experience of the Investigator in the treatment of epithelial ovarian cancer, the number of appropriate potential study subjects available from the center's patient population

and the experience of the site's Investigator and study staff with the treatment of clinical research subjects.

6.4 Study Duration

The overall study duration is estimated to be 30 months: 12 months' enrollment, approximately 6 months of treatment, and a minimum of 12 months of follow-up for each subject.

7 SELECTION AND ENROLLMENT OF STUDY POPULATION

7.1 Eligibility Considerations

7.1.1 Inclusion Criteria

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

1) Signed informed consent
2) Epithelial ovarian cancer which is contained within the abdomen, but may include pleural effusion if that is the limit of non-peritoneal cavity disease. If subject has recurrent epithelial ovarian cancer, the disease must be platinum-sensitive (recurrence >6 months from prior chemotherapy regimen that included a platinum agent and cytoreductive surgery)
3) Subject appropriate for cytoreductive surgery and treatment with IV platinum and paclitaxel
4) Minimal or non-symptomatic ascites
5) ≥18 years old

7.1.2 Exclusion Criteria

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

1) Epithelial ovarian cancer outside of the peritoneal cavity, with the exception of pleural effusions
2) Anticipated use of concomitant chemotherapy (other than the protocol specified agents), immunotherapy, or radiation therapy
3) Treatment with a prior investigational agent within 30 days of planned instillation of NanoPac, with the exception of subjects participating in poly (ADP-ribose)

polymerase (PARP) inhibitor trials. These subjects must discontinue the investigational agent prior to surgery

4) Known sensitivity to any of the study medication components or the chemotherapy regimen

5) History of prior malignancy other than ovarian that has not been in remission for >5 years, with the exception of basal cell or squamous cell carcinoma or cervical carcinoma in situ on biopsy

6) Ileostomy or hepatic resection during current cytoreductive surgery

7) Women of childbearing potential not practicing adequate forms of birth control

7.2 Enrollment and Randomization

After written informed consent is obtained, the subject will be assigned a subject number and will be considered enrolled in the study. Subject numbers will be assigned sequentially by the site and used to identify the subject on all study documents, including the Case Report Form (eCRF). If a subject does not qualify for the study or is withdrawn from the study, the subject number will not be reassigned.

In the dose finding phase, subjects will be assigned to IP plus IV chemotherapy. In the efficacy phase subjects will be randomized 1:1:1 to the two best NanoPac dose levels plus IV chemotherapy, or to IV chemotherapy alone. Randomization will be determined centrally. Enrollment will be stratified by center, disease stage, whether the ovarian cancer is primary or recurrent, and whether they receive neoadjuvant chemotherapy. Subjects will be monitored post-surgery for signs of toxicity (e.g., severe abdominal pain after 5-7 days, neutropenia, thrombocytopenia, bowel dehiscence, prolonged ileus), and hematology, biochemistry, and PK plasma samples will be taken. The SMC will review the accumulating data for up to a maximum of four weeks prior to dose escalation per subject. Dose escalation of NanoPac will be determined by the SMC per the charter, which will be in place prior to the first subject entering the study.

7.3 Removal of Patients from Assessment

All subjects removed from the study due to adverse events will remain under investigation until conditions requiring removal are resolved or stabilized and will continue to be followed for at least 6 months after instillation of NanoPac to assess adverse events and disease status.

Subjects may be discontinued from the study for any of the following reasons:

1. Lack of cooperation with the requirements of the study;

2. Intercurrent illness that, in the opinion of the Investigator, will affect the patient's ability to conform to the study protocol;
3. Withdrawal of consent; or
4. At the direction of the Medical Monitor.

The Sponsor should be notified immediately when a subject is removed or withdrawn from the study after treatment with Investigational Agent has commenced.

Subjects who refuse or fail to appear for clinic visits and fail to respond to or cooperate with reasonable and diligent attempts at contact should be considered lost-to-follow-up. Attempts at contact should be recorded in subject records.

8 STUDY PROCEDURES AND TREATMENTS

8.1 Study Procedures

8.1.1 Screening and Baseline

Prior to enrollment in the study, the following procedures and assessments must be completed, documented and reviewed by the Investigator within 14 days prior to cytoreductive surgery:

- Written informed consent including comprehensive discussion of the study schedule, procedures and subject protocol requirements;
- Complete medical history, including review of previous medical records, demographics and parity;
- Review and documentation of epithelial ovarian cancer diagnosis, highest recorded CA-125 level, and previous treatments including surgical, radiotherapy, and chemotherapeutic records. A copy of the pathology report confirming the *de novo* diagnosis of epithelial ovarian cancer or the diagnosis of recurrent platinum-sensitive epithelial ovarian cancer must be filed in the subject's study record;
- Review and documentation of all concomitant prescription and non-prescription medications, at the time of screening;
- Comprehensive physical examination, including ECOG Performance Status assessment (see Appendix A), gynecological exam and vital signs (blood pressure, heart rate, respiration rate, temperature, body weight and height);
- Sample collection and processing for clinical laboratory assessments as follows:
    - Blood urea nitrogen (BUN), creatinine, total bilirubin, direct bilirubin (if total is abnormal), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin;

- Red blood cell count (RBC), hemoglobin (Hgb), hematocrit (Hct), white blood cell count (WBC) including differential, reticulocyte count, and platelet count;
- Urinalysis including hydrogen ion concentration (pH), RBC, WBC, protein, and glucose;
- Serum pregnancy test, if the subject is not surgically sterile or post-menopausal;

- Review of inclusion and exclusion criteria and determination of eligibility.

8.1.2 Treatment Cycles

Subjects receiving NanoPac will have IP instillation of the NanoPac at the time of cytoreductive surgery (see Section 8.3.1). Full debulking is not required (if not feasible), however Investigator assessment of residual disease is required following surgery. All subjects are expected to initiate IV carboplatin and IV paclitaxel treatment following cytoreductive surgery. IV carboplatin and IV paclitaxel will be administered, either every 21 days or on a dose dense schedule for six cycles (SOC). Bevacizumab may be added to the SOC regimen at the Investigator's discretion, as long as it is initiated at least 6 weeks post-surgery.

The SOC is expected to remain the same for all cycles of treatment. However, the regimen can be modified after cycle 1 if, in the investigator's opinion, that change is best for the subject and the new treatment does not involve an investigational agent. Dosing and dose adjustments should be as per institutional standards.

Plasma samples for PK analysis will be taken on Day 1 at 1, 2, 4, 8, and 24 hours post-intraperitoneal (IP) instillation of NanoPac, if clinically feasible, and weekly thereafter until IV chemotherapy begins, to provide information on resulting paclitaxel systemic exposure in subjects who receive IP NanoPac. Additionally, a PK sample will be collected prior to each post-surgery cycle of IV chemotherapy and at the month 9 and month 12 follow-up visits. Hematology and biochemistry assessments will be done weekly between surgery and initiation of IV chemotherapy. Imaging will be done prior to initiation of post-surgery IV chemotherapy to establish baseline tumor burden.

Patients who, in the PI's judgement, will benefit from IV carboplatin and paclitaxel chemotherapy in advance of their cytoreductive surgery and who meet all other enrollment criteria may be enrolled in the study. For these subjects, the pre-surgery chemotherapy will be recorded in the prior cancer treatment section of the eCRF and the post-surgery chemotherapy will be recorded in the IV chemotherapy section of the eCRF, with the first post-surgery cycle

designated as cycle 1. Imaging will be done prior to post-surgery IV chemotherapy to establish baseline tumor burden.

Post-surgery IV Chemotherapy

On Day 1 of each post-surgery IV chemotherapy treatment cycle the following procedures will be performed:

- Review of any changes in physical condition or symptoms
- Review of concomitant medications and therapies
- Brief physical exam including vital signs (blood pressure, heart rate, respiration rate and body weight)
- Blood sampling (hematology, biochemistry, and PK)
- Calculation of body surface area for determination of chemotherapy dose and administration of the following chemotherapy regimen:
    - Intravenous carboplatin at a dose of AUC 5 to 6
    - Intravenous paclitaxel at a dose of 175 mg/m^2 given every 21 days, or 80 mg/m^2 given weekly
    - Note that in the case of allergic reaction cisplatin can be used instead of carboplatin. Dosing should be as per institutional standards.
- Review and documentation of adverse events and changes in symptoms.

Imaging will be done following cycle 3 and cycle 6. If 4 cycles, or less, of IV chemotherapy will be given post-surgery, imaging will be conducted following the last cycle. If more than 4 cycles of IV chemotherapy will be given post-surgery, imaging will be conducted following cycle 3 and the last cycle. Tumor burden and response will be determined using RECIST (version 1.1) criteria.

Prior to IV chemotherapy cycle 2, a baseline CA-125 level will be established. Subsequent testing will be performed at each cycle and following the last cycle. If CA-125 level is double the baseline level for two consecutive cycles, or if progression is suspected, imaging will be conducted.

The End-of-Treatment (EOT) visit will take place after the last cycle of IV chemotherapy. This visit will include:

- Review of any changes in physical condition or symptoms
- Review of concomitant medications and therapies
- Brief physical exam including vital signs (blood pressure, heart rate, respiration rate and body weight)

- Blood sampling (hematology, blood chemistry, CA-125)
- Urinalysis
- Imaging

8.1.3 12-Month Follow-Up Period

Following completion of the post-surgery IV chemotherapy, a minimum 12-month follow-up period will occur. The follow-up period will begin at the EOT visit (at the end of the final cycle of chemotherapy). Subjects will return to the clinic every 3 months for CA-125 determination, PK sample collection, as well as clinical evaluation of signs or symptoms of disease progression. Imaging will be performed when a subject develops symptoms, has a doubling of CA-125, or every 6 months, whichever is sooner.

Subjects that have completed the 12-month follow-up period will be contacted every 6 months for disease status until disease progression has occurred in 50% of the subjects or until 12 months after the last subject completes their IV chemotherapy, whichever comes first.

8.1.4 Clinical Laboratory Testing

Clinical laboratory tests required by the protocol will be performed by the local lab. Laboratory testing will be conducted at baseline, at the beginning of every post-surgery IV chemotherapy cycle, and at the EOT visit.

8.2 Schedule of Study Procedures and Events

	Screening	Surgery	Surgery -to-IV	IV Chemotherapy (Q21dx6)[10]						End-of-Treatment[6]	Follow-Up	
				Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6		Q3monx4	Q6mon
Informed Consent	X											
History[1]	X	X										
Concomitant therapy	X	X	X	X	X	X	X	X	X	X		
Physical Exam	X									X		
ECOG	X									X		
Hematology[2,4]	X		X[2]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X		
Biochemistry[2,4]	X		X[2]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X		
Urinalysis	X									X		
CA-125	X[8]				X	X	X	X	X	X	X	
PK Samples[2]		X[9]	X[2]	X	X	X	X	X	X		X	
Surgery, Staging, Residual disease, Randomization		X										
NanoPac[7] Instillation		X										
Radiologic Assessment[3]			X			X				X	X	
IV Chemotherapy[10]				X	X	X	X	X	X			
Adverse Events[5]		X	X	X	X	X	X	X	X	X		
Disease status												X

1 History includes all events before initiation of NanoPac treatment

2 PK (in NanoPac subjects only), hematology, and biochemistry to be done weekly in the period between surgery and the start of IV chemotherapy

3 Radiologic assessment is an abdominal/pelvic CT or MRI and the initial study images should be post-debulking surgery, but prior to the initiation of post-surgery IV chemotherapy. Once IV chemotherapy has started, imaging is to be conducted following cycle 3, at EOT, and when CA-125 is doubled from baseline for two consecutive assessment points or when progression is suspected or every 6 months during the 12-month follow-up period. If ≤4 cycles of IV chemotherapy will be given post-surgery, imaging will be conducted following the last cycle. If >4 cycles of IV chemotherapy will be given post-surgery, imaging will be conducted following cycle 3 and the last cycle.

4 Bloodwork should be done within 24 hours prior to Day 1 of any cycle, but up to 72 hours prior is acceptable

5 Adverse event collection will start immediately following initiation of study treatment and conclude one month following last administration of post-surgery IV chemotherapy

6 End-of-treatment assessments will be done at the point the subject discontinues post-surgery IV chemotherapy (e.g., day 21 (+/- 7 days) of cycle 6 or last cycle administered)

7 NanoPac applies only to those randomized to NanoPac

8 Screening CA-125 is the highest recorded CA-125 level for the subject up until screening for this study

9 PK samples on day of surgery, after NanoPac instillation are 1 and 2 hours (+/- 15 min.), 4 and 8 hours (+/- 30 min.), and 24 hours (+/- 2 hours)

10 The schedule for neoadjuvant and post-surgery chemotherapy will be at the Investigator's discretion and may be different than the planned six cycles post-surgery.

8.3 Treatments

8.3.1 Investigational Agent

Investigational Agent for all treatment groups will be supplied to the site in kits with a 60 cm^3 vial containing 306 mg of NanoPac powder and a smaller vial with 7 mL of reconstitution solution (1% Polysorbate 80 in 0.9% Sodium Chloride for Injection, USP). The site will be responsible for providing 0.9% Sodium Chloride for Injection, USP.

Dosing solution will be prepared as follows:

NanoPac suspension procedure:

- Using a syringe with a 27-gauge needle or larger, add 5.0 mL of the sterile 1% polysorbate 80 reconstitution solution into the 60 cc NanoPac powder vial.
- Vigorously hand shake with inversions to make sure all the particles adhering to the interior of the vial and stopper are wetted.
- Continue shaking for 1 minute and examine the suspension for any large clumps of particles.
- Immediately after shaking, use a syringe with a 27-gauge needle or larger to add 46 mL of 0.9% sodium chloride for injection to the vial and hand shake the vial for another 1 minute. Periodically examine the suspension for any large visible clumps. If present, continue hand mixing until the suspension is properly dispersed.
- After mixing, allow the suspension to sit undisturbed for at least 5 minutes to reduce entrapped air and foam.
- The reconstituted suspension should be stored at room temperature and should be administered within 8 hours of suspension. DO NOT freeze or refrigerate.

Dose withdrawal procedure:

- At the time of dose administration, the vial should be inverted twice immediately prior to dose removal to ensure uniformity of the suspension.
- Using a syringe with a 27-gauge needle or larger bore, invert the vial and insert the needle into the septum of the inverted vial. Withdraw just over the amount of suspension needed, remove the needle from the vial, and adjust to the desired volume.

The withdrawn suspension will then be instilled into the peritoneal cavity immediately following cytoreductive surgery. Final methodology for instillation of the NanoPac suspension will be at the surgeon's discretion. The method used should minimize loss of dosing suspension from the peritoneal cavity and allow for the coating of the remaining intraperitoneal tumor implants (if any) and sites of tumor excision. One approach would be to place an indwelling catheter, close the incision, instill the dose suspension via the catheter, and remove the catheter. Another approach could be to close the incision, except for an area for an irrigation syringe which could be used to instill the dose suspension prior to final closure of the incision. The device used for instillation is at the discretion of the surgeon; however, examples of instillation devices include

an irrigating syringe in a laparotomy and an irrigation cannula in a laparoscopic procedure. The device chosen must have apertures that are at least 27-gauge in diameter.

8.3.2 IV Chemotherapy

All subjects are expected to initiate IV carboplatin and IV paclitaxel treatment following cytoreductive surgery. IV carboplatin and IV paclitaxel will be administered, either every 21 days or on a dose dense schedule for up to six cycles post-surgery (SOC). IV chemotherapy must be supplied by the investigational site and administered in accordance with institutional and investigator SOC. Details of the chemotherapy must be recorded in the subject's study record and in the eCRF.

The SOC is expected to remain the same for all cycles of treatment. However, the regimen can be modified after cycle 1 if, in the investigator's opinion, that change is best for the subject and the new treatment does not involve an investigational agent. Bevacizumab may be included in the SOC regimen at the Investigator's discretion, as long as it is initiated at least 6 weeks post-surgery. Dosing and dose adjustments should be as per institutional standards.

The IV chemotherapy regimen for this protocol is:

- Intravenous carboplatin therapy at a dose of AUC 5 to 6 given on Day 1 of the cycle;
- Intravenous paclitaxel at a dose of 175 mg/m^2 given every 21 days, or 80 mg/m^2 given weekly;
- Note that in the case of allergic reaction cisplatin can be used instead of carboplatin. Dosing should be as per institutional standards.

Delays in scheduled chemotherapy treatment for toxicity and recovery are permitted provided the delay period does not exceed 4 weeks between completion of one cycle and commencement of the next. If the subject requires a delay longer than 4 weeks, the Sponsor/Medical Monitor should be contacted for consultation as to whether or not the subject may remain on the study.

8.3.3 Concomitant Medications and Treatments

All medications or treatments the patient is taking at entry and through the end of the treatment period will be recorded in the subject's record and the eCRF. Medications administered should be recorded according to the generic name when possible. Concomitant medications should be limited to those that are medically necessary. Any concomitant medication used should have an indication recorded.

8.3.4 Prohibited, Excluded, and Contraindicated Medications and Treatments

The following medications or treatments will be excluded during the course of the study and must be discontinued within the time frame indicated below before the first treatment cycle begins. Patients requiring these medications or treatments during the course of the study may be discontinued from the study.

- Non-protocol chemotherapy, immunotherapy, radiation therapy, or anti-tumor treatment.
- Any medication or therapy contraindicated in patients treated with paclitaxel or carboplatin as identified in the current version of their package inserts.
- Exposure to any other investigational drugs within 30 days of planned instillation of NanoPac, with the exception of subjects participating in PARP inhibitor trials. These subjects must discontinue the investigational agent prior to surgery

9 ADVERSE EVENT REPORTING

9.1 Adverse Event

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.

Adverse events occurring from the time of surgery through to the end-of-treatment visit (whether or not attributable to the Investigational Agent), will be recorded in the medical record and the eCRF. This includes AEs observed by the Investigator or reported by the subject. The following information will be recorded for all adverse events:

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

- Seriousness

Adverse events should be followed until resolved, stabilized or if ongoing at End-of-Study, for a minimum of 30 days following the termination of the subject's participation from the study for any reason.

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

9.1.1 Relationship to Investigational Agent

Relationship of Adverse Events to the Investigational Agent will be classified by the Principal Investigator using the following definitions:

- No relationship to Investigational Agent: the event is not associated with Investigational Agent.
- Possibly related to Investigational Agent: the event follows a reasonable temporal association with the Investigational Agent administration, however could have been produced by the patient's clinical condition or other therapy.
- Probably related to Investigational Agent: the event follows a) a reasonable temporal association with the Investigational Agent administration, but b) abates upon discontinuation of Investigational Agent and c) cannot be explained by the patient's clinical condition or other therapy.
- Definitely related to Investigational Agent: the event: a) follows a reasonable temporal association with the Investigational Agent administration, but b) abates upon discontinuation of Investigational Agent, c) cannot be explained by the patient's clinical condition or other therapy, and d) reappears on re-exposure to Investigational Agent.

9.1.2 Severity

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

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

- **Fatal:** Death related to the event.

Toxicities and variables that are the specific endpoints of this study should be evaluated according to the NCI CTCAE, version 4.0.
https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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

9.2 Serious Adverse Event (SAE)

An SAE is any adverse event that meets at least one of following criteria:

a) Is fatal;

b) Is life-threatening, meaning the patient 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;

c) Is a persistent or significant disability or incapacity;

d) 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);

e) Is a congenital anomaly or birth defect;

f) Other important medical events may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes as listed in #a-e in this definition.

All SAEs, including death, due to any cause which occurs during this study and until 30 days after the last cycle of IV chemotherapy, whether or not expected and regardless of relationship to the Investigational Agent, must be reported to the Sponsor immediately upon discovery of the event, using a US Biotest SAE reporting form, by fax and, if necessary, by phone to:

US Biotest Medical Monitor:
Dr. Tony Verco
Phone: (805) 762-4615
Fax: (805) 888-4290

24-hour Emergency Contact:

Peter Mast, CCRA	Gere diZerega, MD
Study Manager	Medical Director
(281) 630-6731	(805) 630-2800

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).

All SAEs must be followed until the event resolves or, in the opinion of the Investigator, becomes stable. Hospitalization of patients for the administration of chemotherapy will not be considered an SAE.

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

9.3 Pregnancy

Any pregnancy occurring while a subject is enrolled in the study or for 30 days following the last cycle of IV chemotherapy must be reported to US Biotest within 24 hours of the pregnancy being made known to the Investigator.

10 EFFICACY AND SAFETY VARIABLES

This is an exploratory study of the safety profile and effects on epithelial ovarian cancer of intraperitoneal NanoPac administered at the time of cytoreductive surgery.

10.1 Efficacy Variables

- CA-125 level

- Tumor burden (residual disease) shown by imaging and calculated per RECIST (version 1.1) criteria
- Progression-free survival (PFS)
- Survival
- Cancer-related symptoms (including bowel obstruction, ascites)

10.2 Safety Variables

- Adverse events
- Laboratory assessments
- ECOG performance status.

11 STATISTICAL CONSIDERATIONS

This is a prospective, multi-center, randomized, study subject-blinded Phase II study evaluating the safety and efficacy of NanoPac in the treatment of epithelial ovarian cancer. A detailed discussion of study statistical considerations will be part of the Statistical Analysis Plan (SAP), which will be generated and signed off after the data has been reviewed and prior to database lock and unblinding.

The study will be presented descriptively as it has not been powered for inferential analysis. There are two stages for the trial. The goal of the first stage is to screen subjects exposed to four doses of IP NanoPac, escalated by 100 mg (100, 200, 300 and 400 mg/m^2), instilled immediately post cytoreductive surgery and determine two best dose levels to move to the efficacy phase for further investigation. In the next stage, subjects will be randomized to one of the two chosen NanoPac doses plus standard of care (SOC), or SOC alone.

All subjects in the trial will receive their assigned NanoPac dose (or none for those randomized to SOC alone) and when recovered sufficiently from surgery they will also receive up to 6 cycles of post-surgery IV chemotherapy.

To best capture the safety profile of NanoPac, the safety data will be summarized into the monotherapy phase (only NanoPac) followed by the adjunctive SOC therapy phase. The efficacy treatment outcomes will be summarized by the NanoPac treatment received.

All data will be tabulated, listed, and numbered in accordance with the ICH E3 Guidance document for Clinical Summary Reports.

11.1 Sample Size Estimations

Although the sample sizes were chosen clinically, retrospective calculations were performed to provide context for the results of the trial. In the initial dose finding stage, there would be a minimum of 3 subjects per dose (100, 200, 300 or 400 mg/m^2). Using nQuery Advisor (version 6.01) and the procedure confidence interval for observing a rare event it was estimated that for a sample size of 3, the probability of observing at least one event will be 0.834 when the probability of an event is 45%. For the second stage (i.e., 3 groups of 15 where the proportion of subjects progressing at 12 months is the event of interest), the procedure employed was the confidence interval for a proportion using a normal distribution. For a sample size of 15, a two-sided 95.0% confidence interval for a single proportion using the large sample normal approximation will extend 0.253 from the observed proportion for an expected proportion of 0.500.

11.2 Populations

All subjects who enroll in the trial and have at least one dose of study medication, basically the intra-surgical treatment with NanoPac, will be part of the safety and the efficacy populations.

Subject data from the initial dose finding stage (open assignment) will be combined with the same dose data from the second stage as a secondary population for analysis to provide a more robust estimate of the treatment outcomes.

11.3 Missing Data

Data will be presented as observed. No imputation will be performed for missing data.

11.4 Subject Disposition and Characteristics

All subjects who enter the trial and are exposed to treatment will be accounted for. The formal tables and listings will focus on the randomized subjects. Subjects terminating early will be summarized and the reasons for termination noted.

Subject baseline data for the dose finding and efficacy sections will be presented separately by dose group and also combined by dose group. This will include demography, screening laboratory data, medical history (which will be coded to MedDRA terms), disease history, relevant surgical information (e.g., extent of disease, duration of surgery, relevant biomarkers), and medication.

11.5 Primary Safety Outcome

The primary objective of the first part of this trial is to establish safety of the four (4) treatment doses when instilled as part of cytoreductive surgery. Safety will provide the optimal guidance in defining the two best dose levels to move forward with in the next stage of the trial.

Safety will be assessed primarily via the adverse events (AEs) recorded as these will contain any clinically relevant changes in the laboratory values, the vital signs, and physical examination. All AEs will be coded in the latest version of MedDRA. Treatment-emergent AEs for this stage, occur when the date and time of the AE onset is on or after the first application of the Investigational Agent (surgery) and any time up to when the IV therapy commences, will be summarized for each treatment group; an attempt will be made to determine the "within dose" variation between active and control, if the data are amenable. The summaries will include an overall summary of the number of subjects reporting and the number of events reported; summaries of AEs leading to termination or death; summaries by severity and relatedness – separately and combined – the combined display will include the subject identifier.

Of greatest interest will be post-surgery signs of toxicity (e.g., severe abdominal pain after 5-7 days, neutropenia, thrombocytopenia, bowel dehiscence, prolonged ileus).

Other Stage 1 Outcomes

Other outcomes to be reported are the radiological assessment and concomitant medication.

11.6 Primary Efficacy Outcome

The second stage subjects will be randomized to one of three treatments – one of two doses of NanoPac from stage 1 plus standard of care (SOC), or SOC only. Subjects will be monitored every three months for the first 12 months and then every six months thereafter until progression or the last subject in the trial has been monitored for 12 months. All the monitoring information including biomarkers (e.g., CA-125), imaging (tumor burden) and cancer-related symptoms (including bowel obstruction and ascites) will be summarized in tables displaying the treatment group results across time.

Progression will be presented as time to progression (i.e., Kaplan-Meier) as well as percent progressed up to and including 12 months post-IV chemotherapy.

Exploratory Approach

Factors, which will be thoroughly defined in the Statistical Analysis Plan (SAP), will be included in a logistic regression with progression (yes/no) at 12 months as the response. A variety of covariates, including treatment, will be assessed for their association with progression (e.g.,

staging, residual disease, number of IV cycles). These may be used as stratification factors in future trials.

11.7 Treatment-Related Information

The traditional summary of the number of cycles, dose delays, and dose reductions will be provided for the IV part of the treatment.

11.8 Pharmacokinetics

Plasma samples will be collected on Day 1 at 1, 2, 4, 8, and 24 hours post-intraperitoneal (IP) instillation of NanoPac if clinically feasible, and weekly thereafter until IV chemotherapy begins, to provide information on resulting paclitaxel systemic exposure in subjects that receive IP NanoPac. Additionally, a PK sample will be collected prior to each cycle of post-surgery IV chemotherapy, as well as at the Month 9 and Month 12 follow-up visits for determination of paclitaxel concentrations to assess potential NanoPac persistence. Since Day 1 predose plasma samples are expected to be below the limit of quantification (BLQ), predose samples will not be collected and paclitaxel concentrations will be reported as zero.

Non-compartmental pharmacokinetic parameters will be calculated for paclitaxel if supported by the data:
C_{max} – maximum observed plasma concentration
T_{max} – time of maximum observed plasma concentration
$AUC_{0\text{-last}}$ – area under the plasma concentration-time curve from time zero to time of last measurable concentration

Pharmacokinetic parameters, with the exception of T_{max}, will be summarized using the arithmetic and geometric means, standard deviation, median, range, and % CV (coefficient of variation). T_{max} will be summarized by the median and range of its values. Plasma paclitaxel concentrations will be summarized using the arithmetic mean, standard deviation, coefficient of variation, median, and range. Graphs of Day 1 individual and mean paclitaxel concentration-time data following NanoPac IP instillation will be generated. After a review of the data, the SAP may indicate that no summarization will be performed but rather listings and displays of the 3 subjects in each group will provide more relevant information.

All PK sample data will be summarized descriptively and allow for clinical assessment of persistence (i.e., depot effect) of NanoPac.

11.9 Safety Outcomes

Laboratory outcomes will be listed. Clinically significant laboratory and vital sign changes will be captured as AEs.

11.10 Concomitant Medication

Medication recorded during the trial will be coded using the most recent version of WHO Drug Dictionary (WHODD), summarized by anatomical system and therapeutic class in tables employing treatment group as a factor.

11.11 Safety Monitoring Committee (SMC)

The Safety Monitoring Committee (SMC) will draft and agree to a Charter which outlines the criteria to be applied to the subjects in the trial as well as the final choice of dose groups to be studied further, prior to the first subject being enrolled in the trial. The trial statistician will work with the SMC to produce specific data driven reports to support their decision making.

Subject safety will be the primary driver in all decision making.

11.12 Interim Analysis

No interim analysis has been scheduled for this trial.

12 DATA QUALITY ASSURANCE

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 to attest to the accuracy, authenticity, and completeness of the data.

The eCRF application, TrialMaster, will be licensed from OmniComm. Access to the system is restricted by username and password; these are controlled by the Data Management CRO, McDougall Scientific Ltd. 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. All data, both eCRF and external data (e.g., laboratory data), will be entered into a clinical system.

12.1 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 patient's medical records, regulatory binder, study binder, eCRFs, and source documents as needed to assure the conduct of the study was within compliance. In addition, the FDA or other government agencies may request an inspection following notification to the site. In such an event, the Investigator agrees to notify the Sponsor immediately of the request and will allow Sponsor and inspectors to review records.

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

Routine monitoring visits will be made to assure compliance with the study protocol, to review the patient's eCRF and compare 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.

12.2 Source Documents

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

- The medical history prior to the patient's involvement in the study;
- Date of informed consent;
- The basic identifying information that links the patient'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 patient;

- The medical condition during the patient's involvement in the study;
- All adverse events;
- The patient's exposure to the study medication;
- The patient's exposure to any concomitant therapy;
- All relevant observations and data on the condition of the patient throughout the trial;
- Justification for all entries in the patient's eCRF.

A log of all potentially eligible patients consented but not enrolled for obvious violations of the entry criteria will be kept at the site. The log will contain patients' initials, subject number, diagnosis, and reason for ineligibility.

12.3 Electronic Case Report Forms (eCRFs)

An eCRF is required and must be completed for each consenting 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.

12.4 Disposition of Clinical Supplies

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

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.

13 ETHICS

13.1 Institutional Review Board/Ethics Committee

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 patient is enrolled in the study.

Amendments to the protocol will be subject to the same requirements as the original protocol.

13.2 Ethical Conduct of the Study

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.

13.3 Patient Information and Consent

The Investigator will obtain informed consent from each patient 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 Informed Consent Form (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 patient 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 medication. 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 Protocol Amendments

Any changes to this protocol may only be made in a written protocol amendment approved by US Biotest, the applicable regulatory agencies and the participating IRBs/Ethics Committees. Once the study has started, amendments will be made at the sole discretion of US Biotest.

The Investigator is expected to take any immediate action required for the safety of a study subject, even if this action results in a departure from the protocol. In such cases, the Sponsor and the site's IRB should be notified of the action as soon as is reasonably possible.

13.5 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 their patient number. The subjects will be told that all study findings will be stored and handled in strictest confidence, according to legal requirements, but will be informed that authorized research investigators and agents of the United States Food and Drug Administration (FDA), the National Cancer Institute, and authorized personnel of US Biotest have the right to inspect their medical records.

14 STUDY ADMINISTRATIVE STRUCTURE

14.1 Sponsor Contacts

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 shown on the cover page of this protocol and will be provided to the Investigator in separate study documents.

14.2 Maintenance of Study Records

The Investigator must retain a copy of all study documents, including reports to the IRB and US Biotest in accordance with the FDA or local regulations, whichever are the more stringent.

The Investigator must maintain study documents:

- For a minimum of two years following the date the marketing application (NDA) is approved for the indication for which the drug was investigated for;
- For a minimum of two years following the release date of the final report, if no marketing application is to be filed, or if the marketing application is not approved for the indication of which the drug was investigated or is discontinued and the FDA has been notified; or,

- For a minimum of fifteen 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 disposing of any records.

14.3 Final Report

Upon terminating the study, the Investigator will submit a final report to the IRB and provide a copy to the Sponsor. This report should include any deviations from the protocol, the number and types of subjects evaluated, the number of subjects who discontinued, including reasons, results of the study, adverse events, and a conclusion summarizing the results.

If requested by the Investigator, at the completion of the study and following analysis of the data, US Biotest will supply a tabulated listing of data and a final clinical statistical report.

14.4 Publication and Use of Study Findings

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. This will be a multicenter study. Any publication/presentation of data must include the entire study population. Publication/presentation of data from individual study centers will not be allowed without explicit permission from US Biotest. Submission of data for publication/presentation will be coordinated and approved by US Biotest in collaboration with the Investigator.

14.5 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance coverage in accordance with all local legal requirements. The civil liability of the Investigator, the persons instructed by him, the hospital, practice, or institute in which they are employed, and the liability of the Sponsor in respect of financial loss due to personal injury and other damage, which may arise as a result of the carrying out of this study, are governed by the applicable law. As a precautionary measure, the Investigator, the persons instructed by him and the hospital, practice or institute are included in such coverage in regards to work done by them in carrying out this study to the extent that the claims are not covered by their own professional indemnity insurance. The Sponsor will arrange

for subjects participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study. Such insurance is taken out by the Sponsor in accordance with regulations in the country concerned. To the extent that payments are made under such insurance, the right to claim damages extinguishes.

15 REFERENCES

Williamson S, Johnson G, Maulhardt H, Moore K, et al. A phase I study of intraperitoneal nanoparticulate paclitaxel (Nanotax®) in patients with peritoneal malignancies. *Cancer Chemoth Pharm.* 2015;75(5): 1075-1087.

APPENDIX A: ECOG PERFORMANCE STATUS 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 self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. 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.