Phase 1/2 Trial Evaluating the Safety and Tolerability of NanoDoce® Injection and Intravesical Instillation in Subjects with Urothelial Carcinoma

Protocol Identifying Number: NANODOCE-2017-02

Principal Investigator: Donald Lamm, MD, FACS

IND Sponsor: NanOlogy, LLC

IND #: 137404

Version Number: 7.0
18 June 2020

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
BCG	Bacillus Calmette–Guérin
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Comprehensive Metabolic Panel
CO2	Carbon Dioxide
CR	Complete Response
CRO	Clinical Research Organization
CT	Computed Tomography Scan
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture System
eCRF	Electronic Case Report Form
EMR	Electronic Medical Record
FDA	The U.S. Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
Hct	Hematocrit
Hgb	Hemoglobin
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISF	Investigator Site File
IT	Intratumoral
ITV	Intravesical
IV	Intravenous
LDH	Lactate Dehydrogenase
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume

MedDRA	Medical Dictionary for Regulatory Activities
MIBC	Muscle Invasive Bladder Cancer
MFD	Maximum Feasible Dose
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NDA	New Drug Application (Marketing Application)
NF	National Formulary
NMIBC	Non-Muscle Invasive Bladder Cancer
NOAEL	No-Adverse Effect Level
OS	Overall Survival
PCA	Precipitation with Compressed Antisolvents
PFS	Progression-free Survival
pH	Potential of Hydrogen
PI	Principal Investigator
PK	Pharmacokinetics
Plt	Platelet
PT	Prothrombin time
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDLC	Systems Development Life Cycle
SOC	Standard of Care
SOP	Standard Operating Procedure
TEAE	Treatment-emergent Adverse Event
TURBT	Trans-urethral resection of bladder tumor
ULN	Upper Limit of Normal
UP	Unanticipated Problem
USP	United States Pharmacopeia
UTI	Urinary Tract Infection
WBC	White Blood Cell
WHO	World Health Organization

SPONSOR SIGNATURE PAGE

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Protocol Number: NANODOCE-2017-02

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IND Number: 137404

Investigational Product: NanoDoce (sterile nanoparticulate docetaxel) Powder for Suspension

Sponsor: NanOlogy, LLC
231 Bonetti Dr., Suite 240
San Luis Obispo, CA 93401-7310
805-595-1300

The Sponsor for IND 137404, 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.

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

Gere diZerega
Gere diZerega (Jun 23, 2020 09:27 PDT)
_____
Signature of Sponsor's Representative

Jun 23, 2020
_____
Date

STATEMENT OF COMPLIANCE

I have read the attached protocol 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 1/2 Trial Evaluating the Safety and Tolerability of NanoDoce® Injection and Intravesical Instillation in Subjects with Urothelial Carcinoma

Précis: In this open-label, dose rising, phase 1/2 trial, subjects with high-risk non-muscle invasive bladder cancer (NMIBC) or muscle invasive bladder cancer (MIBC), will receive NanoDoce (sterile nanoparticulate docetaxel) Powder for Suspension as a direct injection to the bladder wall and intravesical instillation(s). Subjects will be stratified into two treatment groups, Group 1 (NMIBC) and Group 2 (MIBC). At Visit 2, all subjects will receive NanoDoce injected into the index tumor resection site on the bladder wall, immediately following transurethral resection of the bladder tumor (TURBT), followed by an initial NanoDoce intravesical instillation (within 2 hours of the direct injection).

Group 1 (NMIBC) and Group 2 (MIBC) Subset

Subjects will be assessed for recovery (TURBT resection site healing) at Visit 4, at which point the Investigator will evaluate subject symptoms, pathology (if available), gross hematuria or urinalysis findings. If the Investigator determines that the subject has sufficiently recovered, the subject will enter a 3-month Induction period. If the Investigator determines that the subject has not recovered at Visit 4, evaluations will be repeated at least every 2 weeks until the subject has recovered and moves forward to the induction period.

The 3-month Induction period will consist of 6 weekly NanoDoce intravesical instillations, followed by 6 weeks of rest. After the Induction period, subjects will proceed to a 3-month Maintenance period, consisting of 3 weekly NanoDoce intravesical instillations, followed by 9 weeks of rest. Subjects will return at Visit 13 for the End of Treatment visit. Any subject terminating early will be required to complete all End of Treatment assessments. An additional Safety visit will be required 45 days after the last administration of NanoDoce if the End of Treatment visit is not conducted.

Progression, progression-free survival (PFS) and post-study concomitant therapy will be collected at 9 and 12 months following the Day 1 NanoDoce injection for subjects who have retained their bladders (non-cystectomy subjects).

Subjects will be evaluated for tumor recurrence or disease progression with cystoscopy and urine cytology at Visit 10, End of Treatment, or at any time, at the discretion of the Investigator. Biopsy is to be performed at any time at the discretion of the Investigator for positive or suspicious cytology or cystoscopic findings. Subjects will be followed through End of Treatment visit for safety, PFS and tumor response to therapy. Institution pathology data will be collected for any resection, cystectomy or biopsy specimen (to include, but not limited to bladder resection, cystectomy or node tissue) at any time during the study or early withdrawal.

Group 2 (MIBC)

At the end of Visit 3, Group 2 (MIBC) subjects will proceed to institutional standard of care treatments and return for the End of Treatment study visit 45 days (+/- 5 days) after Visit 2.

At Visit 3, a subset of subjects, as determined by the treating investigator, who are deemed ineligible for cystectomy and intolerant to existing standard of care chemotherapy or treatment, may be offered intravesical chemotherapy in the Induction and Maintenance periods as described for Group 1 in this study (referred to hereafter as the "Group 2 Subset"). Progression, PFS and post-study concomitant therapy will be collected at 6, 9 and 12 months following the Day 1 NanoDoce injection, for subjects who have retained their bladders (non-cystectomy subjects).

Groups 1 and 2

The study will consist of a dose escalation phase and a dose confirmation phase for the direct injection of NanoDoce concentrations (0.75, 1.5, 2.5, or 3.75 mg/mL) for Groups 1 and 2. In the direct injection dose escalation phase, subjects will be enrolled in sequential cohorts of three subjects starting at the lowest concentration.

The study will also dose escalate Groups 1 and 2 for the intravesical instillation of NanoDoce concentrations (2.0 and 3.0 mg/mL). In the intravesical instillation dose escalation phase, all subjects in Group 1 will be enrolled at the lowest concentration of 2.0 mg/mL for the Visit 2 instillation. If the dose is well-tolerated, Group 1 subjects will continue to receive 2.0 mg/mL until Induction visit #6, then escalate to 3.0 mg/mL intravesical instillations for the subsequent Induction and Maintenance intravesical instillations. Group 2 subjects will be enrolled at the lowest concentration of 2.0 mg/mL for the Visit 2 instillation for all Direct Injection doses. If the dose is well-tolerated, Group 2 subjects will escalate to 3.0 mg/mL intravesical instillations for the dose confirmation portion of the study. For the subset of Group 2 subjects proceeding to the Induction and Maintenance regimen, intravesical instillation escalation to 3.0 mg/mL will also be determined after Visit 6.

Following Data Safety Monitoring Board (DSMB) review of the cohort data, with the exception of the PK data, the DSMB will determine whether to: (a) escalate to the next dose level cohort (no DLT); (b) add three additional subjects to the current cohort (one DLT); (c) if still at the first cohort, stop the study (2 or more DLT); (d) if at higher cohorts, return to the previous (lower) dose cohort and expand by three subjects (more than one DLT). The dose determined to be most suitable for further evaluation, defined as the highest dose with an acceptable safety and tolerability profile (as determined by the DSMB) will enroll additional subjects to total up to 9 subjects at that direct injection dose level.

Objectives:

Primary objective:

- To evaluate the safety and tolerability of NanoDoce injected directly into the bladder wall and instilled intravesically.

Secondary objectives:

- To characterize the PK of docetaxel when injected directly into the bladder wall, in the presence of NanoDoce intravesical instillation.
- To determine whether any of the NanoDoce concentrations (0.75, 1.5, 2.5, or 3.75 mg/mL) in the presence of NanoDoce intravesical instillation concentration dose of 2.0 or 3.0 mg/mL, shows signs of preliminary efficacy.

Endpoints:

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

	Secondary endpoints: • Concentration of docetaxel in the systemic circulation post-injection, in the presence of intravesical instillation (as determined by PK analysis); • PFS defined as tumor recurrence or disease progression at Visit 10 and Visit 13; • Overall survival (OS) determined by survival time up to 12 months following Visit 4.
Population:	Group 1: Up to 42 subjects with NMIBC; Group 2: Up to 33 subjects with MIBC.
Phase:	Phase 1/2
Number of Sites enrolling participants:	Five
Description of Study Drug:	NanoDoce (sterile nanoparticulate docetaxel) Powder for Suspension at concentrations of 0.75 1.5, 2.5, or 3.75 mg/mL administered by direct injection; 2.0 mg/mL or 3.0 mg/mL administered by intravesical instillation.
Study Duration:	Up to 30 months.
Participant Duration:	Group 1: Estimated up to 33 weeks, including safety assessments. Group 2: Estimated up to 64 days, including safety assessments. Group 2 Subset: Estimated up to 33 weeks, including safety assessments. Data collection only: at 6 (Group 2), 9 and 12 months.

FIGURE 1: COHORT SCHEDULE – GROUP 1 – NMIBC

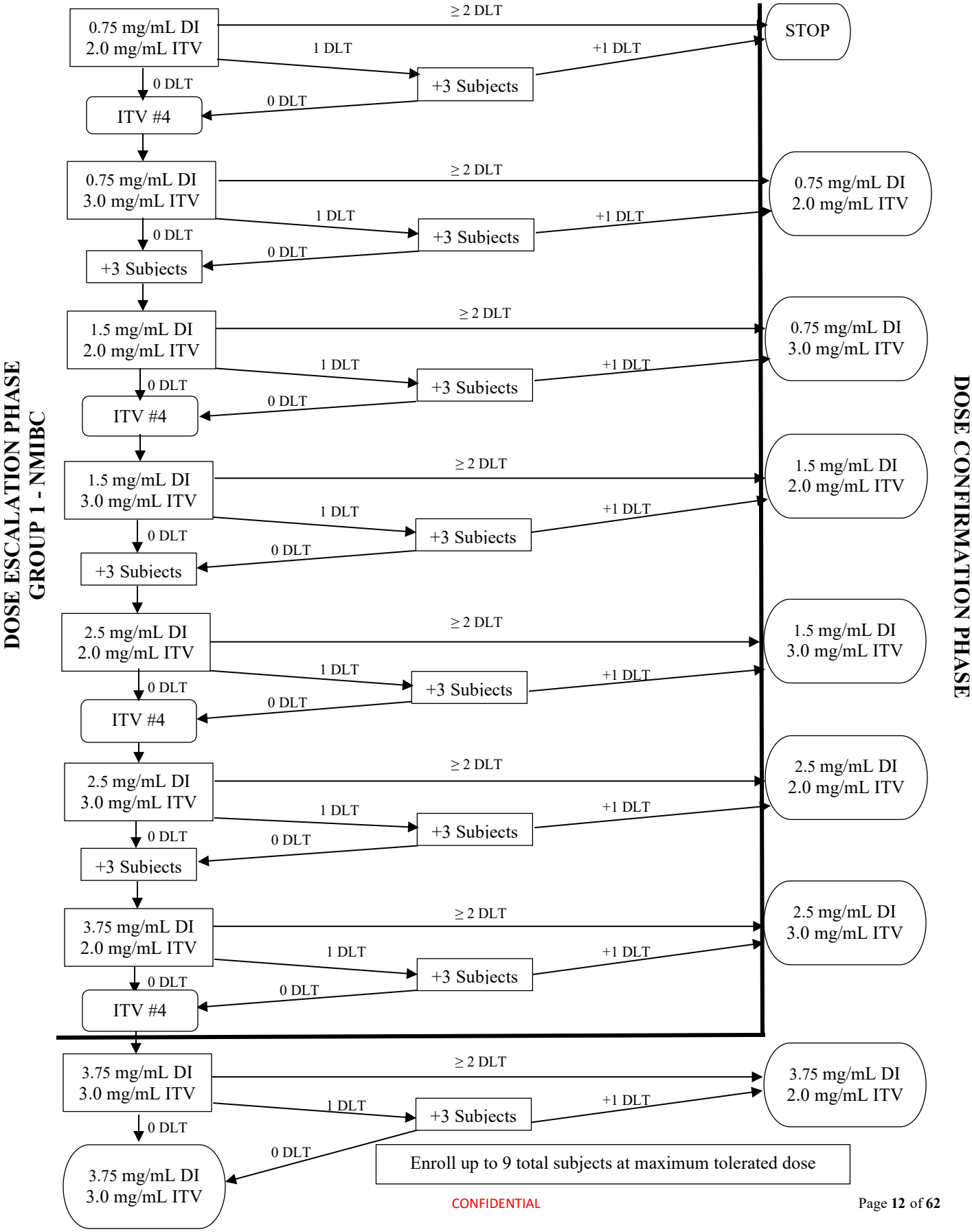
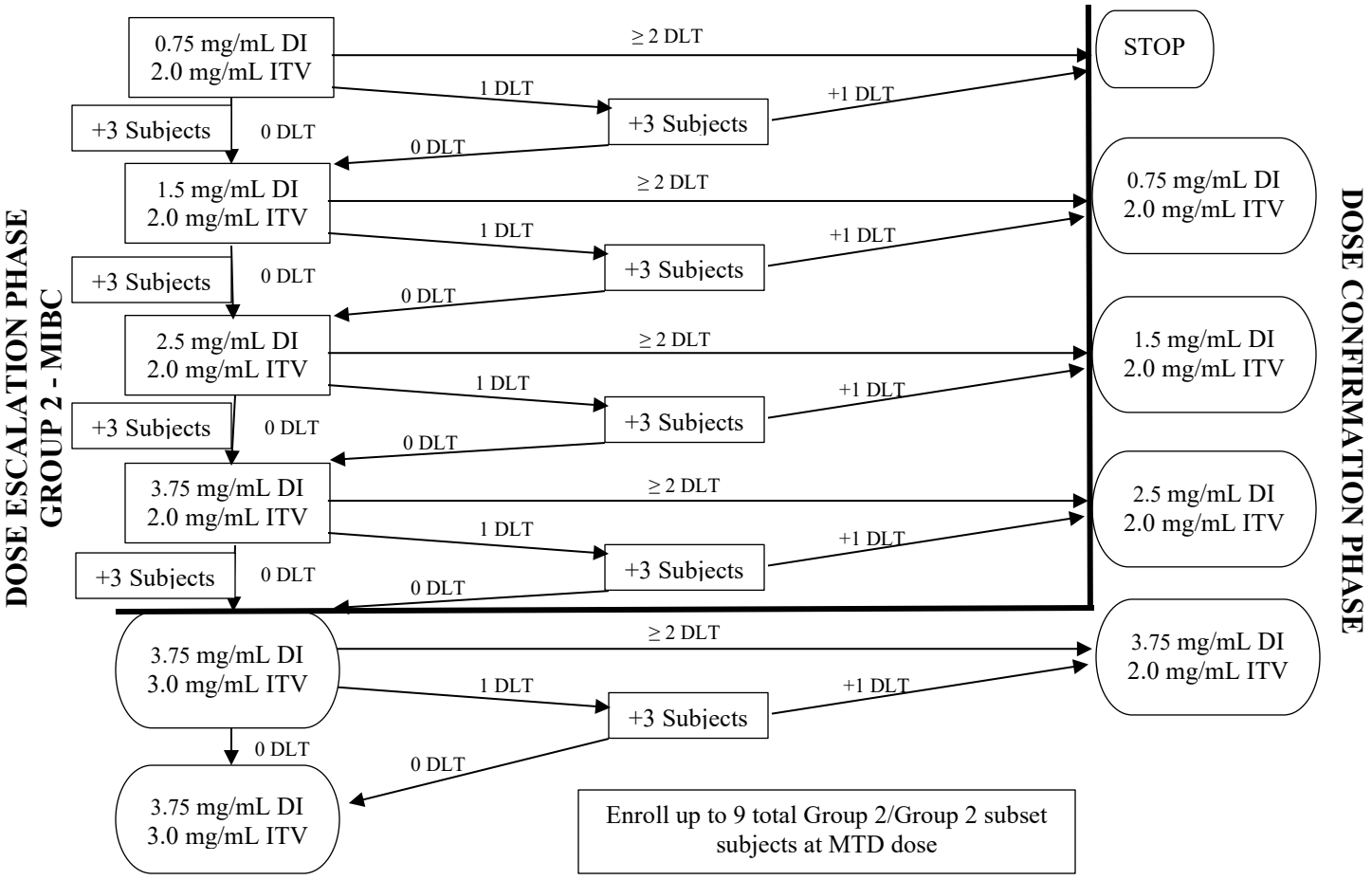


FIGURE 2: COHORT SCHEDULE – GROUP 2 – MIBC



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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 BACKGROUND INFORMATION

The Sponsor for IND 137404, NanOlogy, LLC (NanOlogy), has transferred responsibility for all obligations set forth in 21 CFR Part 312 to US Biotest, Inc. (US Biotest), 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 drug:

NanOlogy, LLC has produced a formulation of nanoparticulate docetaxel, identified as NanoDoce® (sterile nanoparticulate docetaxel) Powder for Suspension (NanoDoce). NanoDoce is manufactured using a Precipitation with Compressed Antisolvent (PCA) technique that employs supercritical carbon dioxide and acetone to generate docetaxel nanoparticles within a well-characterized particle-size distribution. Following PCA, NanoDoce is filled into a clear 60mL Type 1, *USP*, clear-glass vial (100 mg/vial) as a powder fill of nanoparticulate docetaxel, closed with a bromobutyl rubber stopper and aluminum crimp seal, and sterilized by gamma irradiation. Prior to administration, NanoDoce will be reconstituted with Sterile Reconstitution Solution (1% Polysorbate 80 and 8% Ethanol in 0.9% Sodium Chloride for Injection, *USP)*, to form a suspension. The suspension will be further diluted with different volumes of 0.9% Sodium Chloride for Injection, *USP* to achieve the final dose formulations. The reconstitution and dilution will be performed at the investigation site pharmacy.

Nonclinical Summary:

NanOlogy conducted one *in vivo* nonclinical pharmacology study to determine the effects of intratumoral (IT) injection of NanoDoce on a urinary bladder transitional cell carcinoma subcutaneous xenograft in an immunocompromised nude mouse model. The objective of Study D-PBl-02-2017, *Effect of IT administered NanoDoce on growth of Subcutaneous (SC) UM-UC-3 Bladder Cancer in Immunocompromised (Hsd:Athymic Nude-Foxn1nu nude) Mice,* was to evaluate the effect of one, two, or three weekly IT administrations of NanoDoce (100 mg/kg) on tumor growth in comparison to IT vehicle and intravenous (IV) chemotherapy (docetaxel; 30 mg/kg) controls. Treatment outcome was based on differences in tumor volume. Two or three weekly IT NanoDoce administrations were more effective than IV docetaxel in inhibiting the progression of urinary bladder carcinoma. Systemic toxicity leading to weight loss occurred in animals treated with three cycles of IV docetaxel or three cycles of IT NanoDoce; one or two cycles of IT NanoDoce did not affect weight gain. Evaluation of tissue from the tumor sites showed that IT administration of NanoDoce provided appreciable docetaxel levels for durations of up to 44 days following administration.

NanOlogy conducted two *in vivo* nonclinical pharmacology study to determine the effects of NanoDoce on renal cell carcinoma. The objective of Study PD-Pre-03-2018, *A drug efficacy study in the Sprague-Dawley Rag2; Il2rg null (SRG) rat xenograft model of Human renal cell Adenocarcinoma (786-O),* was to evaluate the effect of one, two, or three weekly IT administrations of NanoDoce (20 mg/kg) on tumor growth in comparison to IT vehicle and IV chemotherapy (docetaxel; 2.5-5 mg/kg) controls. Treatment outcome was based on differences in tumor volume. One, two, and three weekly IT NanoDoce administrations were more effective than IV docetaxel in inhibiting the progression of renal cell carcinoma. The IT NanoDoce groups (female) showed almost no/no evidence of tumor on completion of study. NanOlogy also conducted Study Number D-PRe-05-2018, *Evaluation of the Efficacy of Intratumoral NanoDoce against Primary and Secondary Renca Renal Cell Carcinoma in BALB/c Mice*. The Renca model of mouse renal cell carcinoma was used to evaluate the efficacy of IT NanoDoce against primary and secondary tumors compared to untreated and vehicle-treated mice and mice treated with IV docetaxel. NanoDoce

administered IT and intratumoral/peritumoral at 30 mg/kg and 60 mg/kg achieved potential therapeutic activity, defined as tumor growth inhibition > 60%. With the exception of 60 mg/kg administered IT, all NanoDoce had significantly greater tumor growth inhibition compared to IV docetaxel ($p < 0.01$).

To support development of NanoDoce for an indication of treatment of genitourinary neoplasms, seven nonclinical toxicology studies were conducted. Two studies (non-GLP Study D-TR-03-2017 and GLP Study D-TR-04-2017) evaluated the effects of up to four weekly repeat-dose intravesical instillations of NanoDoce suspensions at 1.6 mg/mL (3.2 mg/kg), 5 mg/mL (10 mg/kg), 15 mg/mL (30 mg/kg) or 40 mg/mL (80 mg/kg) into the urinary bladder of female rats. The maximum tolerated dose (MTD) and no-observed-adverse-effect-level (NOAEL) for four weekly NanoDoce intravesical instillations was determined to be 40 mg/mL, which is also the maximum feasible dose (MFD) based on NanoDoce solubility. Two studies (non-GLP Study D-TRab-02-2017 and GLP Study D-TRab-03-2017) were conducted to evaluate the effects of a single direct intramural injection of NanoDoce into the urinary bladder wall in male and female rabbits. NanoDoce was administered at the following doses: 1.6 mg/mL (0.48 mg/kg), 5 mg/mL (1.5 mg/kg), 15 mg/mL (4.5 mg/kg), or 40 mg/mL (12 mg/kg). The MTD was determined to be 40 mg/mL and a NOAEL was not determined. Non-GLP Study D-TR-02-2017 was conducted to evaluate the effects of intra-prostatic administration of NanoDoce. Male rats were administered a single dose of NanoDoce at 5 mg/mL (4 mg/kg), 10 mg/mL (8 mg/kg), 20 mg/mL (16 mg/kg), or 40 mg/mL (32 mg/kg) as two 100 uL injections to each lobe of the prostate and the MTD was determined to be 40 mg/mL. Two studies (non-GLP Study D-TR-06-2018 and GLP Study D-TR-07-2019) evaluated the effects of a single injection of NanoDoce into the kidney of male and female rats. NanoDoce suspensions were delivered as four distinct injections into the renal cortex at the following doses: 0.625 mg/kg (0.5 mg/mL), 2.5 mg/kg (2.0 mg/mL), 12.5 mg/kg (10 mg/mL), 25 mg/kg (20 mg/mL), and 50 mg/kg (40 mg/mL). Toxicity and toxicokinetic evaluations were performed for 8 (Study D-TR-06-2018) and 28 days (Study D-TR-07-2019) after injection. The MTD at 8 days was determined to be 12.5 mg/kg and the NOAEL at 28 days was established to be 12.5 mg/kg with a corresponding $AUC_{0\text{-}672}$ of 1,440 ng*hr/mL.

Clinical Summary:

NanoDoce has not been administered to humans in a clinical trial to date. An extensive series of clinical studies were conducted to assess the safety of docetaxel formulated as Taxotere. In addition, intravesical administration of docetaxel in patients with bladder cancer has demonstrated safety and tolerability (McKiernan 2006; Laudano 2010; Barlow 2009a, Barlow 2009b, Barlow 2013).

NanOlogy provided NanoDoce drug product to an Investigator under Investigator-sponsored single patient expanded access. The patient was an 82-year-old man with recurrent, muscle-invasive urothelial carcinoma of the bladder. The subject was not a candidate for cystectomy and treatment with chemo-radiation resulted in continued bleeding. Under the individual patient expanded access IND, a direct injection procedure and three intravesical instillations with NanoDoce were administered. The subject died due to metastatic disease unrelated to the investigational product.

Relevant Literature:

Although docetaxel is not approved for the indication of urothelial carcinoma, it has been used off-label intravenously and intravesically for patients with bladder cancer.

- Intravenous docetaxel is a widely accepted systemic treatment for advanced bladder cancer. Regulatory authorities worldwide have accepted docetaxel as a community standard and the National Comprehensive Cancer Network recommends docetaxel as second-line therapy for metastatic bladder cancer (Albany 2015).

- Intravesical administration of docetaxel in patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) has been reported. A Phase 1 trial investigated intravesical docetaxel in 18 subjects with recurrent high-grade Ta, T1 and Tis NMIBC for whom BCG had failed (*McKiernan 2006*). Barlow (2009) included the Phase 1 subjects in a retrospective analysis. Laudano (2010) followed-up by reporting long-term results from the Phase 1 trial. Barlow (2013a) rolled the Phase 1 results and the retrospective review into a long-term analysis focused on survival outcomes, with an emphasis on maintenance treatment. Barlow (2009b) conducted a study to evaluate the durability of response for patients with BCG-unresponsive NMIBC treated with intravesical docetaxel in a combined induction and maintenance regimen. In general, these studies report low grade local bladder adverse events (AE) including Grade 1 dysuria, Grade 1 hematuria, Grade 2 hematuria, Grade 1 frequency, and Grade 1 urgency. Systemic toxicity was not reported. Initial complete response (CR) rates in these studies ranged from 22% to 76.9% (with median follow-up ranging from 13 months to 48.3 months).

Importance of the study:

Bladder cancer is the sixth most common cancer in the United States, with an estimated 79,030 new cases and 16,870 deaths from the disease predicted in 2017. Most patients (approximately 75%) with bladder cancer are diagnosed with disease confined to the mucosa or submucosa, classified as NMIBC (Babjuk *2015*). NMIBC is further stratified as low, intermediate or high-risk. Most patients with high-risk NMIBC are treated with transurethral resection of the bladder tumor (TURBT) followed by intravesical chemotherapy. The three therapies currently approved by FDA for intravesical use, bacillus Calmette-Guérin (BCG), Valrubicin, and thiotepa, are imperfect. Many patients do not respond to treatment, do not achieve a lasting response, and/or encounter serious treatment-related toxicities (TICE BCG Package Insert 2009, Barlow 2013b, Babjuk 2017, Dinney 2013, Steinberg 2000, Hollister 1980). BCG is the current gold standard for intravesical therapy; however, 50% of patients treated with BCG experience recurrence (*Barlow 2013*). Patients experiencing BCG failure have a 50% chance of disease progression (*Barlow 2013; McKiernan 2006; Babjuk 2015*). Therefore, BCG failures represent the highest-risk subgroup of high-risk NMIBC.

Approximately 25% of patients with bladder cancer present with a tumor invading the muscle layer of the bladder wall. Muscle invasive bladder cancer (MIBC) is associated with a high rate of recurrence and poor overall prognosis despite aggressive local and systemic therapies. For decades, radical cystectomy has been the mainstay of treatment for muscle invasive bladder cancer. Despite providing excellent local control, surgery alone does not result in optimal survival rates. Further, radical cystectomy is associated with considerable morbidity and mortality, as well as notable long-term complications and negative impacts on quality of life. There is increasing support for bladder sparing approaches to muscle invasive bladder cancer treatment for those who cannot or will not undergo radical cystectomy (*Park 2014, Smith 2013, Mak 2014*).

2.2 RATIONALE

This Phase 1/2 study will include subjects with NMIBC and MIBC. It is hypothesized that the intravesical instillation of NanoDoce will establish a depot of drug within the bladder, providing sustained release of docetaxel within the bladder over time. Direct injection of NanoDoce to the tumor bed after TURBT may, in the short term, kill residual tumor cells missed by surgery and, in the long term, slowly release drug throughout the resection site over time to prevent recurrence.

2.3 POTENTIAL RISKS AND BENEFITS

2.3.1 KNOWN POTENTIAL RISKS

There are no known potential risks from NanoDoce injection into the bladder wall of humans.

Based on published studies of docetaxel, intravesical instillation toxicities include dysuria, hematuria, frequency, and urgency. Other adverse reactions are facial and body flushing/erythema, limb cramps, rash, UTI, exhaustion, pain, incontinence, nocturia, general flu-like symptoms, decreased appetite, lightheadedness and premature docetaxel void.

The risks associated with intravenous docetaxel are described in the Taxotere Package Insert. The most common adverse reactions across all Taxotere indications are infections, neutropenia, anemia, febrile neutropenia, hypersensitivity, thrombocytopenia, neuropathy, dysgeusia, dyspnea, constipation, anorexia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia. Incidence varies depending on the indication.

2.3.2 KNOWN POTENTIAL BENEFITS

There are no known potential benefits of direct bladder wall injection or intravesical administration of NanoDoce in humans.

Published studies of docetaxel administered as an intravesical instillation to subjects with BCG-unresponsive NMIBC demonstrated an initial CR rate of between 22% and 76.9%, with median follow-up ranging from 13 months to 48.3 months.

3 OBJECTIVES AND PURPOSE

The primary objective of this study is to evaluate the safety and tolerability of NanoDoce injected directly into the bladder wall and instilled intravesically.

Secondary objectives are (a) to characterize the pharmacokinetics (PK) of docetaxel when injected directly into the bladder wall in the presence of intravesical instillation; and (b) to determine whether any of the NanoDoce concentrations (0.75, 1.5, 2.5, or 3.75 mg/mL administered by injection; 2.0 or 3.0 mg/mL administered by intravesical instillation) show signs of preliminary efficacy.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

This open-label Phase 1/2 study will enroll subjects with pathological or cytological diagnosis of high-risk NMIBC or MIBC. Subjects will be stratified into two treatment groups, Group 1 (NMIBC) and Group 2 (MIBC). The study drug will be delivered by direct injection into the bladder wall and by intravesical instillation. At Visit 2, all subjects will receive NanoDoce injected into the index tumor resection site on the bladder wall, immediately following TURBT, followed by an initial NanoDoce intravesical instillation (within 2 hours of the direct injection).

Group 1 (NMIBC) and Group 2 (MIBC) Subset

After a recovery period, Group 1 subjects will proceed to the 3-month Induction period. Subjects will be assessed for recovery (TURBT resection site healing) at Visit 4, at which point the Investigator will evaluate subject symptoms, pathology (if available), gross hematuria or urinalysis findings. If the Investigator determines that the subject has not recovered at Visit 4, evaluations will be repeated at least every 2 weeks until the subject has recovered and intravesical NanoDoce can be administered.

The 3-month Induction period consists of 6 weekly NanoDoce intravesical instillations, followed by 6 weeks of rest. After the Induction period, subjects will proceed to a 3-month Maintenance period, consisting of 3 weekly NanoDoce intravesical instillations, followed by 9 weeks of rest. Subjects will return at Visit 13 for an End of Treatment study visit. Plasma samples will be collected at Visit 2 (prior to NanoDoce injection and at 1, 2, 6, and 24 hours post-injection), at Visit 3, at Visit 4 (prior to NanoDoce intravesical instillation and at 1, 2, 6, and 24 hours post- intravesical instillation), at Visits 5-12 prior to the NanoDoce intravesical instillation, and at End of Treatment to characterize the PK of docetaxel.

Subjects will be evaluated for tumor recurrence or disease progression with cystoscopy and urine cytology at Visit 10, and End of Treatment, and at any time at the discretion of the Investigator. Biopsy is to be performed at any time at the discretion of the Investigator for positive or suspicious cytology or cystoscopic findings. Any subject terminating early will be required to complete all End of Treatment assessments. An additional Safety visit will be required if the End of Treatment visit is not conducted 45 days after the last administration of NanoDoce. A PK plasma sample will be collected at the End of Treatment visit. Institution pathology data will be collected for any resection, cystectomy or biopsy specimen (to include, but not limited to bladder resection, cystectomy or node tissue) at any time during the study or early withdrawal.

Progression, PFS and post-study bladder treatment or concomitant therapy will be collected at 9 and 12 months following the Day 1 NanoDoce injection, for subjects who have retained their bladders (non-cystectomy subjects).

Group 2 (MIBC)

At the end of Visit 3, Group 2 (MIBC) subjects may proceed to institutional standard of care (SOC) treatments and return for the End of Treatment study visit 45 days (+/- 5 days) after Visit 2. Alternately, at Visit 3, a subset of subjects, as determined by the treating Investigator, who are deemed ineligible for cystectomy and intolerant to existing standard of care chemotherapy or other treatment, may be offered the option to receive Induction and Maintenance intravesical NanoDoce (according to the regimen described for Group 1) (referred to hereafter as the "Group 2 Subset"). The Investigator must determine and document there are no existing or available, standard of care treatment options for the subject. Only at that time, will the Induction and Maintenance treatment be offered to the subject for consideration.

Plasma samples will be collected at Visit 2 (prior to NanoDoce injection, at 1, 2, 6, and 24 hours post-injection), Visit 3 and at the End of Treatment visit to characterize the PK of docetaxel.

Progression, PFS and post-study bladder treatment concomitant therapy will be collected at 6, 9 and 12 months following the Day 1 NanoDoce injection, for subjects who have retained their bladders (non-cystectomy subjects). Subjects who proceed to cystectomy will no longer have data collected after that point.

Dose Escalation: Groups 1 and 2

The study will consist of a dose escalation phase and a dose confirmation phase for the direct injection of NanoDoce concentrations (0.75, 1.5, 2.5, or 3.75 mg/mL) for Groups 1 and 2; dose escalation will also occur for the intravesical instillation of NanoDoce concentrations (2.0 and 3.0 mg/mL) for Groups 1 and 2. See Section 6.1.7 Starting Dose and Dose Escalation for details.

4.2 ENDPOINTS

4.2.1 PRIMARY ENDPOINT

The primary endpoint will be safety and tolerability as demonstrated by AE, changes in laboratory assessments, physical examination findings and vital signs.

4.2.2 SECONDARY ENDPOINTS

The secondary endpoints will be:

- Concentration of docetaxel in the systemic circulation post-injection in the presence of intravesical instillation (as determined by PK analysis);
- PFS defined as tumor recurrence or disease progression at Visit 10 and Visit 13;
- OS determined by survival time following NanoDoce injection.

4.2.3 EXPLORATORY ENDPOINTS

The exploratory endpoints will be to determine whether exposure to NanoDoce will affect:

- Tumor-specific antigens (IHC);
- Immunophenotyping of T cells, B cells and monocytes.

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;
- Patients with pathological or cytological diagnosis of:
    - High risk NMIBC[1];
        - High grade (HG) T1;
        - Any recurrent, HG Ta;
        - HG Ta, >3 cm (or multifocal);
        - Any carcinoma *in situ* (CIS);
        - Any BCG failure[2] in HG patient;
        - Any variant histology;
        - Any lymphovascular invasion (LVI), to include any HG prostatic urethral involvement;
    - MIBC;

- Urothelial carcinoma confirmed by biopsy, urine cytology, computed tomography scan (CT) or other institution-approved diagnostic methodology;
- All visible tumors removed during TURBT (as is reasonable, ensuring patient safety);
- Performance Status (ECOG) 0-2 at study entry;
- Life expectancy of at least 6 months;
- Adequate marrow, liver, and renal function;
    - ANC ≥ 1.5 x 10^9/L;
    - Hemoglobin ≥ 9.5 grams/dL;
    - Platelets ≥ 75 x 10^9/L;
    - Total bilirubin ≤ 1.5x institutional ULN;
    - AST/ ALT ≤ 2.5x institutional ULN;
    - Creatinine ≤ 1.5x institutional ULN;
- Adequate method of birth control.

1. As defined in the AUA/SUO Guideline (Chang 2016)
2. BCG failure to be determined using the definition of BCG-unresponsive NMIBC as in "BCG-Unresponsive Nonmuscle Invasive Bladder Cancer: Developing Drugs and Treatment Guidance for Industry."
a. BCG-unresponsive disease is defined as being at least one of the following:
i. Persistent or recurrent CIS alone or with recurrent Ta/T1 (noninvasive papillary disease/tumor invades the subepithelial connective tissue) disease within 12 months of completion of adequate BCG therapy
ii. Recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG therapy
iii. T1 high-grade disease at the first evaluation following an induction BCG course.
b. In this context, adequate BCG therapy is defined as at least one of the following:
i. At least five of six doses of an initial induction course plus at least two of three doses of maintenance therapy;
ii. At least five of six doses of an initial induction course plus at least two of six doses of a second induction course.

5.2 PARTICIPANT EXCLUSION CRITERIA

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

- Metastatic disease;
- Previous (within 12 months) or concurrent history of non-bladder malignancy, except for non-melanoma skin cancer;
- Intravesical therapy within 4 weeks prior to consent (chemotherapy or immunotherapy including BCG administered directly into the bladder);
- Resection surface area greater than 8 cm^2;
- Upper tract and urethral disease within 18 months;
- Known hypersensitivity to any of the study drug components or reconstitution components;
- Pregnant or breastfeeding;
- Participation in the treatment phase of another clinical trial within 3 months prior to consent;
- Investigator's opinion of subject's probable noncompliance or inability to understand the trial and/or give adequate informed consent;
- Ongoing drug or alcohol abuse.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Subjects will be recruited at 5 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.

At any time during the study, if there is tumor recurrence or disease progression, decision to remove from study will be a consensus between the Investigator, Medical Monitor and Study Director.

The reason for withdrawal will be documented in the source notes and in the Electronic Data Capture system (EDC).

Any potential or confirmed-related event, (clinical AE, laboratory abnormality, or other medical condition/situation) occurring, and/or DSMB determination which may be attributed to the withdrawal, must be documented and followed for the safety of the subject.

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

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

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

When a subject is terminated after the first study drug dose, all efforts will be made to ensure the End of Treatment procedures are performed.

Subjects that refuse or fail to appear for clinic visits following Visit 2 and fail to respond to or cooperate with reasonable and diligent attempts at contact, will be discontinued from the study and 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 Group 1 subject repeatedly misses study visits or is non-compliant following Visit 2, and where the majority of data is not collected or most of follow-up induction or maintenance visits are not completed, Sponsor may exercise the option to replace that subject in the cohort. All data reported and collected will be included in the assessment of safety.

5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated, if there is sufficient reasonable cause. Written notification, documenting the reason for the study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the Investigator(s) will promptly inform the IRB(s) 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 subjects;

- Routine Medical Monitoring determining a requirement for an ad hoc meeting of the DSMB, and/or routine DSMB reviews, will allow for termination of study based on unacceptable risk, which will consider all safety evaluations and DLTs.
- Groups 1, 2 and Group 2 subset will be considered independently for purposes of termination.
- In the direct injection dose escalation phase, the study may be terminated for a group, at the lowest dose, if at least two of six subjects in that group experience DLT (as defined in Section 6.1.7).
- In the intravesical instillation dose escalation phase, the study may be terminated for a group if, at the lowest dose, at least two of three or two of six subjects in that group experience DLT (as defined in Section 6.1.7).

- 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 DRUG

6.1 STUDY DRUG(S) AND CONTROL DESCRIPTION

6.1.1 ACQUISITION

NanoDoce is manufactured by CritiTech, Inc. (Lawrence, KS) and provided for use in this study. Study drug will not be shipped to the study site until all regulatory documentation has been provided to Sponsor by the site and the site is ready for study initiation, at which time the study drug will be released by US Biotest for shipment. Shipment will be via courier, temperature controlled at 59˚ to 86˚F (15˚ to 30˚C) just prior to the site initiation visit. Study drug will be shipped to the institution pharmacy where it will be stored according to the conditions required (see Section 6.1.3).

6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

The NanoDoce Suspension kits (Clinical Supplies Kit) provided to the study sites will contain study drug for all treatments and dosage groups in the study.

Each ‘Clinical Supplies Kit for NanoDoce Clinical Trials’ contains one vial of NanoDoce and one vial of Sterile Reconstitution Solution (1% Polysorbate 80 and 8% Ethanol in 0.9% Sodium Chloride for Injection, *USP*). The NanoDoce 60 mL vial contains sterile nanoparticulate docetaxel (100 mg/vial), appearing as a white powder. When ready for use, the powder is suspended using the Sterile Reconstitution Solution provided in the kit.

The Clinical Supplies Kit will be labeled as:

Clinical Supplies Kit for NanoDoce Clinical Trials

Each kit contains:

- 1 vial of NanoDoce (sterile nanoparticulate docetaxel) Powder for Suspension, 100 mg per vial

- 1 vial of Sterile Reconstitution Solution for NanoDoce Powder for Suspension, 5 mL per vial

Caution: New Drug – Limited by federal law to investigational use –
For single use only **#####**

The NanoDoce vial will be labeled as:

NanoDoce (sterile nanoparticulate docetaxel) Powder for Suspension, 100 mg vial
Lot.: _____
Prior to reconstitution, Store at 59° to 86°F (15° to 30°C).
Reconstitute according to the Instruction Sheet and the procedure in the clinical protocol.
After reconstitution, store the suspension per Instruction Sheet.
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
Manufactured for: US Biotest, Inc., 231 Bonetti Drive, Suite 240, San Luis Obispo, CA 93401 XXXXX

The reconstitution solution vial will be labelled as:

Sterile Reconstitution Solution for NanoDoce (sterile nanoparticulate docetaxel) Powder for Suspension
Lot No.: _____
Contains: 5 mL of 1% Polysorbate 80 (NF) and 8% Ethanol (USP) in 0.9% Sodium Chloride for Injection (USP) per vial
Prior to use, store at 59° to 86°F (15° to 30°C).
For single use only
Caution: New Drug – Limited by federal law to investigational use
Manufactured by: The University of Iowa Pharmaceuticals, 115 S Grand Ave., Iowa City, IA 52242
Manufactured for: US Biotest, Inc., 231 Bonetti Drive, Suite 240, San Luis Obispo, CA 93401 XXXXXX

6.1.3 PRODUCT STORAGE AND STABILITY

Clinical Supplies Kits containing NanoDoce 100 mg powder vials and sterile reconstitution solution must be stored at the institution pharmacy, under limited access conditions and temperature controlled at 59˚ to 86˚F (15˚ to 30˚C).

Reconstitution will be performed in the pharmacy. Once the NanoDoce has been reconstituted, it will be delivered for injection or instillation at the desired location (treatment area, clinic or operating room). If the reconstituted drug is not delivered immediately, the syringe may be stored according to pharmacy manual instructions until delivery. Each vial and each syringe must be labelled according to institution requirements as well with the subject study number.

6.1.4 PREPARATION

A prescription (drug order) will be provided to the pharmacy for each subject detailing the subject study number, the assigned cohort dose, and the date and time required for administration, as well as any institution-required instructions for study drug identification. The drug order should be provided to the Pharmacy at least 24 hours prior to administration time, or per institution requirements. The site will provide 0.9% Sodium Chloride for Injection, *USP*, a sterile syringe with a sterile 18-gauge needle (or larger bore) for sterile injectable drug preparation and a suitable sterile container to prepare secondary dilutions, as necessary.

Direct Injection: Once the drug has been reconstituted to the required cohort-assigned dose for injection (3.0, 6.0, 10.0 or 15.0 mg), the maximum injection volume of 4.0 mL will be withdrawn from the vial into a syringe.

Intravesical Instillation: Once the drug has been reconstituted to 2.0 mg/mL or 3.0 mg/mL, the appropriate volume of the NanoDoce suspension will be withdrawn from the vial and transferred to an appropriate delivery receptacle for instillation.

Each Clinical Supplies Kit, including entire contents, is for a single-subject use only. Reconstitution will be performed by study-delegated pharmacy staff and the final study drug concentration (whether for direct injection or intravesical instillation) will be delivered by the pharmacy to the Investigator, or designee. Sponsor will provide separate written instructions in the pharmacy manual and an instructional video will be provided by CritiTech to each site at the Initiation Visit for training.

NanoDoce must be administered no more than 4 hours after the initial reconstitution.

6.1.5 DOSING AND ADMINISTRATION

Groups 1 and 2: Direct Injection

NanoDoce will not be injected if there is any evidence of bladder perforation (visible fat or bowel). Confirmed or suspected perforation prior to NanoDoce injection will terminate participation in the study and the subject will be considered a Screen Fail. If perforation is **not** detected during the resection and the subject proceeds to NanoDoce injection and/or instillation, the subject will terminate participation in the study at the time the perforation is detected and proceed to the End of Treatment and safety visit, 45 days after the last study drug dose. The sponsor may replace that subject in the cohort.

Subjects will receive the assigned NanoDoce injection dose into the base of the index tumor resection site on Visit 2 immediately post-TURBT. The index tumor resection site is defined as the largest resection site (should not exceed 8.0 cm^2) if multiple resections are performed. If multiple resections are performed, only the index tumor resection site will receive NanoDoce injections.

Adjustable tip-length cystoscopy needles are to be used for injection into the resected bladder wall. The needle tip to be adjusted to 2 mm (per manufacturer recommendation) for injections in the dome area of the bladder and 3 – 4 mm for injections in the side area of the bladder. A total volume of 4.0 mL of NanoDoce will be injected in 0.5 mL

increments, approximately 1 cm apart, with up to 8 injections into the index tumor resection site. Injections will be performed in a tangential approach (grid-like pattern to cover the resection site) so the needle tip is viewable under direct visualization by cystoscope. The investigator will inject up to 5 mm outside of the resection margin.

The total dose administered will not exceed the assigned cohort dose of 3.0 (0.75 mg/mL), 6.0 (1.5 mg/mL), 10.0 (2.5 mg/mL), or 15.0 (3.75 mg/mL) mg.

Groups 1 and 2: Visit 2 Intravesical Instillation

The initial intravesical instillation will immediately follow the NanoDoce direct injection (≤2 hours). NanoDoce will be instilled intravesically in the bladder for a maximum of 30 minutes (+/- 5 min).

The total dose administered will not exceed the assigned cohort dose 50 mg in 25 mL of saline for a final concentration of 2.0 mg/mL or 75 mg in 25 mL of saline for a final concentration of 3.0 mg/mL.

The subject will be in supine position. Local anesthetic gel is allowed for catheter placement. The urinary catheter will be inserted into the bladder using sterile technique. Isotonic saline or sterile water is the only distending medium which will be allowed in this study. Following intravesical instillation, the subject will be asked to change position every 15 minutes to ensure uniform coating of study medication to the bladder wall. On Visit 2, at the end of the 30-minute dwell time, the instillate will be drained by catheter into an appropriate receptacle; the catheter will be removed, and the drained fluid and catheter will be disposed of, per institution requirements.

Group 1 and Group 2 Subset: Induction and Maintenance Intravesical Instillation

If Induction and Maintenance intravesical instillations are administered in a hospital setting, the instillate will be drained by catheter into an appropriate receptacle; the catheter will be removed, and the drained fluid and catheter will be disposed of, per institution requirement. If the subject is not catheterized, the subject will void in the toilet. Total instillate retention time will be recorded for study purposes.

Visits 4-9 Induction: NanoDoce will be instilled in the bladder once/week for 6 weeks for a maximum of 120 minutes (+/- 10 min).

Visits 10-12 Maintenance: NanoDoce will be instilled in the bladder once/week for 3 weeks for a maximum of 120 minutes (+/- 10 min).

6.1.6 ROUTE OF ADMINISTRATION

NanoDoce will be administered by two routes: as a direct injection to the bladder wall and as intravesical instillation(s) in the bladder.

6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

Direct Injection

The study will consist of a dose escalation phase and a dose confirmation phase for the direct injection of NanoDoce concentrations (0.75, 1.5, 2.5, or 3.75 mg/mL) for Groups 1 and 2.

Table 1: NanoDoce Direct Injection Dose-Escalation

Cohort	NanoDoce Suspension Concentration	Maximum # of Injections	Total NanoDoce Administered 'Not to Exceed'
1	0.75 mg/mL	8	3.0 mg
2	1.5 mg/mL	8	6.0 mg
3	2.5 mg/mL	8	10.0 mg
4	3.75 mg/mL	8	15.0 mg

During direct injection dose escalation, cohorts will be enrolled sequentially starting at the lowest concentration (0.75 mg/mL) (Table 1). Cohorts will enroll separately for Groups 1 and 2. Each cohort will have a planned minimum of three subjects for Group 1 and three subjects for Group 2. Escalation to the next cohort for Group 2 will proceed following review of Group 1 data by the DSMB. All clinical data from subjects in each cohort, including all DLTs described in this section and excluding PK, will be reviewed and evaluated by the Medical Monitor and DSMB (based on the DSMB charter) on an ongoing basis, in addition to at Visits 4, 6 and 9, to determine if the dose received is considered safe and tolerable, and to determine if dose escalation may occur.

If the DSMB determines cohort 1 (0.75 mg/mL) is safe (no DLT), escalation to the next dose level, cohort 2 (1.5 mg/mL), will occur. If >2 DLT occurs in the first three subjects, the study will stop. If 1 DLT occurs at cohort 1, three additional subjects will be added to cohort 1. If $\geq$1 DLT occurs in the additional three subjects, the study will stop. If no additional DLT occurs in the additional three subjects, the study will escalate to the next dose level, cohort 2 (1.5 mg/mL).

Three subjects will be dosed at cohort 2 (1.5 mg/mL). If the DSMB determines cohort 2 is safe (no DLT), escalation to the next dose level, cohort 3 (2.5 mg/mL), will occur. If >2 DLT occurs in the first three cohort 2 subjects, the study will return to the previous (lower) dose, cohort 1 (0.75 mg/mL), and proceed to dose confirmation. If 1 DLT occurs at cohort 2, three additional subjects will be added to cohort 2. If $\geq$ 1 DLT occurs in the three additional cohort 2 subjects, the study will return to the previous (lower) dose, cohort 1 (0.75 mg/mL), and proceed to dose confirmation. If no additional DLT occurs in the additional three subjects, the study will escalate to the next dose level, cohort 3 (2.5 mg/mL).

Three subjects will be dosed at cohort 3 (2.5 mg/mL). If the DSMB determines cohort 3 is safe (no DLT), escalation to the next dose level, cohort 4 (3.75 mg/mL), will occur. If > 2 DLT occurs in the first three cohort 3 subjects, the study will return to the previous (lower) dose, cohort 2 (1.5 mg/mL), and proceed to dose confirmation. If 1 DLT occurs at cohort 3, three additional subjects will be added to cohort 3. If $\geq$ 1 DLT occurs in the three additional cohort 3 subjects, the study will return to the previous (lower) dose, cohort 2 (1.5 mg/mL), and proceed to dose confirmation. If no additional DLT occurs in the additional three subjects, the study will escalate to the next dose level, cohort 4 (3.75 mg/mL).

Three subjects will be dosed at cohort 4 (3.75 mg/mL). If the DSMB determines cohort 4 is safe (no DLT), dose confirmation at cohort 4 (3.75 mg/mL) will occur. If > 2 DLT occurs in the first three cohort 4 subjects, the study will return to the previous (lower) dose, cohort 3 (2.5 mg/mL), and proceed to dose confirmation. If 1 DLT occurs at cohort 4, three additional subjects will be added to cohort 4. If $\geq$ 1 DLT occurs in the three additional cohort 4 subjects, the study will return to the previous (lower) dose, cohort 3 (2.5 mg/mL), and proceed to dose confirmation. If no additional DLT occurs in the additional three subjects, the study will complete enrollment at cohort 4 (3.75 mg/mL) in dose confirmation.

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

Once the dose deemed appropriate for further evaluation has been determined by the DSMB, additional subjects will be enrolled to provide up to a total of up to 9 subjects dosed at that dose level.

Intravesical Instillation

The study will also dose escalate Groups 1 and 2 for the intravesical instillation of NanoDoce concentrations (2.0 and 3.0 mg/mL). In the intravesical instillation dose escalation phase, all subjects in Group 1 will be enrolled at the lowest concentration of 2.0 mg/mL for the Visit 2 instillation. If the dose is well-tolerated, Group 1 subjects will continue to receive 2.0 mg/mL through Visit 6, then escalate to 3.0 mg/mL intravesical instillations for the subsequent Induction and Maintenance intravesical instillations following ongoing data review by the Medical Monitor and the DSMB. Group 2 subjects will be enrolled at the lowest concentration of 2.0 mg/mL for the Visit 2 instillation for all direct injection doses. If the dose is well-tolerated for the Group 1 subjects (following ongoing data review by the Medical Monitor and the DSMB) Group 2 and Group 2 subset subjects will escalate to 3.0 mg/mL intravesical instillations for the dose confirmation phase of the study.

Escalation to 3.0 mg/mL in each group will proceed, independent of the other group. If no subjects in cohort 1 at 2.0 mg/mL experience a DLT, the intravesical dose will escalate to 3.0 mg/mL for that group as described below. If two or more subjects in cohort 1 experience a DLT at 2.0 mg/mL, then the study will stop. If one of the three subjects in cohort 1 experiences a DLT at 2.0 mg/mL, then an additional three subjects will be enrolled to cohort 1 at 2.0 mg/mL. If, in the additional three subjects at 2.0 mg/mL, no subjects experience a DLT, then the dose will remain at 2.0 mg/mL as described below. If ≥1 DLT occurs in the additional three subjects, the study will stop.

Definition of DLT

Included in the DSMB's review of AEs and general study data pertaining to safety (laboratory results, vital signs, physical examination findings) there will be rules for non-escalation. Any AE that is considered related or probably related to NanoDoce is potentially a DLT. The definition of a DLT will be determined by the DSMB and the Sponsor for AEs. DLTs will, in addition, include the following:

- Procedure-related events that require hospitalization or surgical intervention and some procedure-related events that require medical intervention;
- All Grade 3-4 AE which are possibly related to study drug will be considered DLT **except**:
    - Grade 3 nausea or Grade 3-4 vomiting and diarrhea that persist for less than 48 hours in patients who have not received optimal anti-emetic or anti-diarrhea prophylaxis;
    - Grade 3 fatigue less than 5 days;
    - Grade 3 laboratory abnormalities that are not clinically significant and return to normal (with or without intervention) within 48 hours;
- Grade 3 thrombocytopenia with clinically significant hemorrhage;
- Grade 2 toxicity that prevents further treatment or persists for at least 3 weeks;
- Any life-threatening event (unless there is a clear alternative explanation that the event is not related to the procedure or the investigational product itself).

6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

Group 1 and Group 2 Subset

At any time during Induction or Maintenance, intravesical instillations will be withheld in weekly increments in the event of Grade 2 thrombocytopenia, anemia, neutropenia, hematuria (visible gross hematuria) or laboratory-confirmed urinary tract infections until the infection is resolved. The hematuria and abnormal CBC values must resolve to a maximum of Grade 1.

Group 2

The study will evaluate one single NanoDoce intravesical instillation in each subject; therefore, there will be no dose adjustment or modification.

6.1.9 DURATION OF THERAPY

At Visit 2, NanoDoce will be injected directly into the index tumor resection site followed by a single intravesical instillation.

Group 1 and Group 2 Subset

Up to six Induction NanoDoce intravesical instillations and up to three Maintenance NanoDoce intravesical instillations will be administered. It is estimated that individual subject participation could last up to 33 weeks. Survival data will be collected up to 12 months; clinic visits will not be required.

Group 2

It is estimated that individual subject participation could last up to 64 days. Survival data will be collected up to 12 months; clinic visits will not be required.

6.1.10 TRACKING OF DOSE

Not applicable.

6.1.11 DEVICE SPECIFIC CONSIDERATIONS

Not applicable.

6.2 STUDY DRUG ACCOUNTABILITY PROCEDURES

The Investigator will maintain adequate records showing the receipt, dispensing, return, or other disposition of the investigational drug, including the date, quantity, lot number, and identification of subjects (number, initials as allowed) receiving study medication.

Accountability will be conducted by the Pharmacy including details on the Clinical Supplies Kits, the individual NanoDoce vials, and the sterile reconstitution solution. No used vials will be kept for accountability purposes, they will be disposed of according to the institution destruction procedures.

If Investigator determines that the full volume of NanoDoce cannot be administered, the Investigator will document the amount of NanoDoce injected or instilled and the volume remaining in the vial, in the source document and in the EDC.

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

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES/EVALUATIONS

7.1.1 STUDY SPECIFIC PROCEDURES

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

- Complete medical history and demographics collection and documentation;
- Concomitant prescription and non-prescription medication collection and documentation;
- Urothelial carcinoma diagnosis and treatment documentation;
- Comprehensive physical examination, including ECOG; vital signs, body weight and height;
    - Respiratory rate may not be measured at all institutions as SOC; this will not be a deviation. For those institutions providing the measurement, the data will be collected as described in Section 7.3.
- 12-lead ECG;
- PK sampling;
- Routine clinical laboratory sampling;
- Diagnostic biopsy and/or imaging with CT scans including, but not limited to histological reports to include lymph node data. A copy of the pathology report confirming the diagnosis must be filed in the subject's study record;
- Bladder tissue slides for immunohistochemistry staining collected during the course of the trial;
- NanoDoce injection of the index tumor resection site post-TURBT;
- Intravesical NanoDoce instillation(s);
- Subject diary completion.

7.1.2 STANDARD OF CARE STUDY PROCEDURES

Group 1 and Group 2 Subset

At any point after the first administration of study drug, the care of the subject will be as dictated by the protocol but will allow for any other standard care routinely provided (such as pain relief, additional clinic visits, etc.).

Group 2

After the Visit 3 NanoDoce direct injection and intravesical instillation, subjects may proceed to SOC.

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.

Laboratory Assessments include:

- Biochemistry analysis to be performed at Visits 1, 4, 10 and End of Treatment for Group 1 and Visits 1 and End of Treatment for Group 2 to include: Sodium, potassium, chloride, carbon dioxide (CO_2), calcium, phosphorus, glucose, blood urea nitrogen (BUN), creatinine, serum lipase, serum amylase, alkaline phosphatase (ALP), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), total protein, albumin, triglycerides, cholesterol, uric acid and calculated creatinine clearance;
- Complete blood count (CBC) at each visit (except Visit 3 for Group 1 subjects) to include: Red blood cells (RBC), white blood cells (WBC) including complete differential, hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), platelet (Plt) and reticulocyte count;
- Urinalysis at each visit (except Visit 3 for Group 1 subjects) including specific gravity, hydrogen ion concentration (pH), RBC, WBC, protein, and glucose;
- Activated partial thromboplastin time (aPTT) and prothrombin time (PT) to be performed at Visits 1, 4, 10 and End of Treatment for Group 1 and Group 2 subset and at Visits 1 and End of Treatment for Group 2;
- Fibrinogen assay to be performed at Visits 1, 4, 10 and End of Treatment for Group 1 and Group 2 subset and at Visits 1 and End of Treatment for Group 2.

Blood for routine laboratory assessments will be collected and processed per institution requirements and guidelines.

7.2.2 OTHER ASSAYS OR PROCEDURES

7.2.2.1 PATHOLOGY EVALUATIONS

Any tissue sample collected during the study will be processed per institution pathology standards, to include but not limited to: pathologist review of tissue blocks and histological quality check; pathologist clinical data review, including stage confirmation; and H&E staining.

Additionally, once study eligibility is confirmed at Visit 2 (see Section 7.3.2), biopsy samples collected during the study (starting with initial TURBT) will be mounted on slides and shipped to a central laboratory for immunohistochemistry (IHC) research. Shipment process for the IHC slides to NeoGenomics will be described in the IHC Laboratory manual.

7.2.2.2 PHARMACOKINETICS

Plasma samples will be collected to characterize the PK of docetaxel. Visit 2 (Day 1) PK samples will be collected as of 'stop time' of the last injection; Visit 4 (Day 1) PK samples will be collected as of 'stop time' of instillation.

Group 1 and Group 2 subset

Plasma samples will be collected at Visit 2 (prior to NanoDoce injection and at 1, 2, 6, and 24 hours post-injection), at Visit 3, at Visit 4 (prior to NanoDoce intravesical instillation and at 1, 2, 6, and 24 hours post- intravesical instillation), at Visits 5-12 prior to NanoDoce intravesical instillation, and at the End of Treatment visit. Allowable visit 2 and visit 4 windows will be: 10-minutes for hours 1 and 2, 20-minutes at 6 hours post and 30-minutes at 24 hours post.

Group 2

Plasma samples will be collected at Visit 2 (prior to NanoDoce injection and at 1, 2, 6, and 24 hours post-injection), Visit 3, and at the End of Treatment visit. Allowable Visit 2 windows will be: 10-minutes for hours 1 and 2, 20-minutes at 6 hours post and 30-minutes at 24 hours post.

7.2.2.2.1 PK SPECIMEN PREPARATION, HANDLING, AND STORAGE

PK samples will be drawn at the specified time for each visit, processed and stored frozen on-site until instructed to ship by the sponsor, at which time they will be batch-shipped to Covance Laboratories (Madison, WI) for analysis of docetaxel. Procedures for storage processing will be described in the PK Laboratory Manual provided at study initiation.

7.2.2.2.2 PK SPECIMEN SHIPMENT

Shipment process for the PK samples to Covance Laboratories will be described in the PK Laboratory manual provided at study initiation.

7.3 STUDY SCHEDULE

7.3.1 SCREENING (VISIT 1)

Groups 1 and 2 will complete the Screening visit (Visit 1). Assessments, visits, and other assays performed prior to consent to the study for NanoDoce injection, will be performed according to the institution SOC and are not considered part of this study. The following procedures and assessments must be completed, documented and reviewed by the Investigator during the screening period, within 30 days prior to NanoDoce Visit 2 injection, unless otherwise indicated:

- 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 urothelial carcinoma diagnosis (diagnostic biopsy and/or imaging, cystoscopy and or cytology) obtained within three months of consent. A copy of the pathology report confirming the diagnosis must be filed in the subject's study record;
- Review and documentation of previous treatments including surgical, chemotherapy and immunologic records;
- Review and documentation of all concomitant prescription and non-prescription medications;
- Comprehensive physical examination within the 14 days prior to Visit 2;
- ECOG Performance Status (Appendix A) within the 14 days prior to Visit 2;

- 12-lead ECG;
- Vital signs (blood pressure, heart rate, respiratory rate and temperature) within the 14 days prior to Visit 2;
- Body weight and height;
- Pregnancy test (urine) for females of child-bearing potential;
- Sample collection and processing for clinical laboratory assessments (see Section 7.2.1)

7.3.2 TRANS URETHRAL RESECTION OF BLADDER TUMOR (VISIT 2)

Groups 1 and 2 will complete Visit 2.

- Medical history confirmation (AE occurring prior to NanoDoce injection will be considered history);
- Comprehensive physical examination (if not completed within the 14 days prior to Visit 2);
- ECOG Performance Status assessment (if not completed within the 14 days prior to Visit 2);
- Final review of inclusion and exclusion criteria and determination of eligibility prior to NanoDoce injection;
- TURBT;
    - Confirmation of non-bladder perforation during TURBT must be documented and filed in the subject's study record;
    - Trans-urethral resection surface area to be recorded (< 8 cm^2);
    - If subject does not qualify or bladder perforation is confirmed, subject will <u>not</u> proceed to NanoDoce injection and will be considered a Screen Fail;
- If continuation to NanoDoce injection is confirmed, the bladder resection tissue sample collected will be processed according to Section 7.2.2.1;

7.3.3 NANODOCE TREATMENT - INJECTION & INTRAVESICAL INSTILLATION (VISIT 2 CONTINUED)

Groups 1 and 2 will complete Visit 2.

- Baseline PK sample will be drawn prior to NanoDoce injection;
    - May be collected at any time during screening prior to TURBT procedure;
- Vital signs (blood pressure, heart rate, respiratory rate) will be monitored and collected prior to NanoDoce injection;
    - Vital signs will be monitored and collected per SOC; it is expected during surgery and recovery, continuous vitals monitoring will be conducted;
- NanoDoce injection of the resected bladder tumor;
    - Start time of first injection and stop time of last injection will be recorded;
- Vital signs (blood pressure, heart rate, respiratory rate) will be monitored and collected post NanoDoce injection;
- NanoDoce intravesical instillation;
    - Start time of instillation and time at end of void will be recorded;
- Vital signs (blood pressure, heart rate, respiratory rate) will be monitored and collected post NanoDoce intravesical instillate (catheter removed and instillate voided);

- Collection of AE (start time of first NanoDoce injection) will be documented separately as treatment-emergent adverse events (TEAE);
- Collection of concomitant medication;
- PK samples will be drawn at 1, 2, 6, and 24 hours post NanoDoce injection stop time;
- Subject will be provided a diary to record AE and concomitant medications until the next study visit.

7.3.4 VISIT 3

Groups 1 and 2

- One PK sample will be drawn.

Group 2

- Directed physical exam;
- CBC and urinalysis sample collection
    - PK samples can be collected and processed at the same time as CBC samples.
- AE review;
- Concomitant medication review;
- Review of eligible treatment options;
- The Investigator will document all treatment options following review of subject records and institution standard of care protocols, and if it is determined that the subject is not a candidate for cystectomy or standard of care treatment, the Investigator will discuss with the subject the option of participating in the Group 2 Subset for Visits 4-9 Induction and Visits 10-12 Maintenance instillations, as an alternative choice.

Group 2 Subset

- Written informed consent including comprehensive discussion of the study schedule, procedures and subject protocol requirements may be conducted at any time from Visit 3 up to Visit 4 (prior to the first Induction instillation).

7.3.5 INDUCTION PERIOD (VISITS 4 – 9)

Only Group 1 and Group 2 subset subjects will complete the Induction Period (Visits 4-9). Subjects will be assessed for recovery (TURBT resection site healing) at Visit 4, at which point the Investigator will evaluate subject symptoms, pathology (if available), and gross hematuria or urinalysis findings. If the Investigator determines that the subject has not recovered at Visit 4, evaluations will be repeated at least every 2 weeks until the subject has recovered, at which time intravesical NanoDoce can be administered.

At any time during the Induction Period, if intravesical instillation is delayed, the next instillation visits will be recalculated based on the new/rescheduled instillation date and per visit timelines and windows (see Schedule of Events: Table 2b).

The 3-month Induction period will consist of 6 weekly NanoDoce intravesical instillation treatments, followed by 6 weeks of rest. The following procedures will be performed:

- Vital signs;
- Directed physical exam;

- Sample collection and processing for clinical laboratory assessments (Section 7.2.1);
    - Non-clinically significant CBC and urinalysis must be confirmed prior to each intravesical instillation to rule out infection or DLT. A 48-hour window is allowed for sample collection and processing to ensure results are available prior to the intravesical instillation.
    - If applicable, chemistry, fibrinogen, aPTT, PT and PK samples can be collected and processed at the same time as CBC samples.
    - Visit 4 only:
        - Chemistry, fibrinogen, aPTT and PT;
        - PK samples will be drawn prior to NanoDoce instillation and at 1, 2, 6, and 24 hours post NanoDoce instillation stop time;
    - Visits 5-9:
        - PK samples will be drawn prior to NanoDoce instillation;
- Intravesical NanoDoce instillation (Section 6.1.5);
- AE review;
- Concomitant medication review;
- In addition to the Visit 4 cystoscopy and cytology, at any time during the induction period, the Investigator may perform cytology, cystoscopy or biopsy **(**for positive or suspicious cytology or cystoscopic findings);
    - Any tissue sample collected will be processed according to Section 7.2.2.1;
- Subject diary will be reviewed to confirm it is adequately completed. The subject will be questioned regarding discrepancies, missing entries and errors. Any discrepancy will be documented in the subject source documents by a delegated staff; and a new diary to be provided to the subject to record instillate void time and for daily completion to record adverse events and concomitant medications.

7.3.6 MAINTENANCE PERIOD (VISITS 10 – 12)

Only Group 1 and Group 2 subset subjects will complete the Maintenance Period (Visits 10-12). Visit 10 will occur after subjects complete the last day of the 3-month Induction period. If biopsy is indicated, maintenance therapy with NanoDoce is to be withheld until the histopathology results are available. NanoDoce intravesical instillation may be delayed up to 3 weeks.

At any time during the Maintenance Period, if intravesical instillation is delayed, the next instillation visit will be recalculated based on the new/rescheduled maintenance instillation date and per visit timelines and windows (See schedule of Events: Table 2b).

At Visit 10, subjects will proceed to a 3-month Maintenance period consisting of three NanoDoce intravesical instillations to be administered once weekly, in the first three weeks.

The following procedures will be performed at Visits 10 - 12:

- Directed physical exam may be performed;
- ECOG – Visit 10 only;
- Vital signs;
- Sample collection and processing for clinical laboratory assessments (Section 7.2.1);
    - Chemistry, aPTT and PT at Visit 10 only
    - Non-clinically significant CBC and urinalysis must be confirmed prior to each intravesical instillation to rule out infection or DLT;

- A 48-hour window is allowed for sample collection and processing to ensure results are available prior to the intravesical instillation.
- Chemistry, fibrinogen, aPTT, PT and PK samples can be collected and processed at the same time as CBC samples.

- Intravesical NanoDoce instillations (Section 6.1.5);
- PK samples will be drawn pre- NanoDoce instillation;
- In addition to the Visit 10 cystoscopy and cytology, at any time during the maintenance period, the Investigator may perform cytology, cystoscopy or biopsy **(**for positive or suspicious cytology or cystoscopic findings);
  - Any tissue sample collected will be processed according to Section 7.2.2.1;
- AE review;
- Concomitant medication review;
- Subject diary will be reviewed to confirm it is adequately completed. The subject will be questioned regarding discrepancies, missing entries and errors. Any discrepancy will be documented in the subject source documents by a delegated staff; and a new diary to be provided to the subject to record instillate void time and for daily completion to record adverse events and concomitant medications.

7.3.7 END OF TREATMENT

The End of Treatment visit (Visit 13) will be conducted after a subject completes the Day 1 NanoDoce injection and will always be conducted 45 days after the last study drug dose for early termination subjects, regardless of Group. For subjects completing the study, Visit 13 is conducted 180 days after Visit 4 for Group 1 and Group 2 Subset and 45 days after Visit 2 for Group 2. If the End of Treatment visit is less than 45 days after the last NanoDoce instillation for Group 1 and Group 2 subset, due to instillation delays, a safety visit or phone call will be conducted 45 days after the last treatment to assess ongoing or new AEs.

At the visit, the following procedures will be performed:

- Comprehensive physical exam;
- ECOG;
- Vital signs;
- 12-lead ECG;
- Clinical laboratory sample collection (Section 7.2.1);
- PK Sample collection (one sample collection only);
- Cystoscopy, urine cytology;
- Biopsy;
  - Performed for positive or suspicious cytology or cystoscopic findings;
  - Any tissue sample collected will be processed according to Section 7.2.2.1;
- AE collection;
- Concomitant medication;
- Subject diary will be reviewed to confirm it is adequately completed. The subject will be questioned regarding discrepancies, missing entries and errors. Any discrepancy will be documented in the subject source documents by a delegated staff.

7.3.8 SAFETY ASSESSMENT VISIT

For early termination subjects, if the End of Treatment visit is not conducted, a follow up Safety visit will be completed to assess adverse reactions 45 days after the last study drug is administered (injection and/or instillation). The visit can be combined with the End of Treatment visit if both are conducted 45 days after the last study drug administration. During this visit the site will follow up on any existing AE and record any new AE or reactions as well as collect a PK sample

7.3.9 EARLY TERMINATION VISIT

In the event a subject is withdrawn, End of Treatment assessments, which include the procedures described in Section 7.3.7, are expected to be completed. If a subject is withdrawn at a routine study visit, all evaluations expected at that study visit should be completed in addition to any procedure or evaluation listed in End of Treatment visit. Every effort should be made to inform the subject at the time of consent, that in the event of early termination, a last study visit will be completed, in addition to a visit for safety (see 7.3.8), so they are aware of expectations.

7.3.10 SURVIVAL/PROGRESSION FOLLOW-UP

Data will be collected for all subjects at 6 (Group 2 only), 9 and 12 months after Visit 4 to include progression, PFS and OS. Data will include concomitant therapy for bladder cancer (radiation, chemotherapy, immunotherapy and surgical intervention). An additional subject visit will not be required as data will be collected by chart review. In cases where the subject has moved or lives in another city, data will be requested from the treating physician/institution. If the subject is no longer being followed by a treating physician/institution, a phone call may be conducted to determine survival and to collect the last post-study concomitant treatment data. This data will be collected for information only and will not be used to support a study endpoint.

7.3.11 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 evaluations as determined necessary by the Investigator. All evaluations or procedures performed at the unscheduled visit, will be entered in the EDC.

7.3.10 SCHEDULE OF EVENTS TABLE

Table 2a: Group 1 (NMIBC) and Group 2 Subset Schedule of Events

Procedure	Screening	Treatment		Induction					
	Days (-30 - 0)	Visit 2	Visit 3	Visit 4 [1, 2]	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
		Day 1	Day 15 (+/- 1 day)	Day 1 Week 1 (≥ 4 weeks)	Day 8 Week 2 (+/-2 days)	Day 15 Week 3 (+/-2 days)	Day 21 Week 4 (+/-2 days)	Day 28 Week 5 (+/-2 days)	Day 35 Week 6 (+/-2 days)
Informed Consent	X								
Medical and Surgical History[3]	X								
Demographics	X								
Physical Examination[4]	X	X[5]		X	X	X	X	X	X
ECOG	X	X[5]							
12-Lead ECG	X								
Vital Signs[6]	X	X		X	X	X	X	X	X
Height and Weight	X								
Pharmacokinetic Collection		X[7]	X[7]	X[7]	X[8]	X[8]	X[8]	X[8]	X[8]
Laboratory Tests[9]	X			X	X	X	X	X	X
NanoDoce Direct Injection		X							
NanoDoce Intravesical Instillation		X		X	X	X	X	X	X
TURBT[10]		X							
Cystoscopy [10, 11]	X			X					
Cytology [10, 11]	X			X					
Biopsy[10, 11]	X			X[11]					
Immunohistochemistry[12]		X		X	X	X	X	X	X
Diary Distribution		X		X	X	X	X	X	X
Diary Collection				X	X	X	X	X	X
Adverse Events		X		X	X	X	X	X	X
Concomitant therapy	X	X		X	X	X	X	X	X

Table 2 is continued on the next page.

Table 2b (Continued): Group 1 and Group 2 Subset Schedule of Events

Procedure	Maintenance			End of Treatment	Survival Follow-up
	Visit 10	Visit 11	Visit 12		
	Day 85 Week 13 (+/-3 days)	Day 92 Week 14 (+/-3 days)	Day 99 Week 15 (+/-3 days)	Day 180 Visit 13 (+/- 7 days)	Months 9 & 12
Physical Examination[4]	X	X	X	X	
ECOG	X			X	
Vital Signs[6]	X	X	X	X	
12-Lead ECG				X	
Laboratory Tests[9]	X	X	X	X	
NanoDoce Instillation	X	X	X		
Pharmacokinetic Collection[7, 8]	X	X	X	X	
Cystoscopy[10, 11]	X			X	
Cytology[10, 11]	X			X	
Biopsy[10, 11]	X			X	
Immunohistochemistry[11]	X	X	X	X	
Diary Distribution	X	X	X		
Diary Collection	X	X	X	X	
Adverse Events	X	X	X	X	
Concomitant Therapy	X	X	X	X	X
Survival[12]					X

1. Start of Induction, or Visit 4, to be determined starting at 4 weeks post TURBT; If subject not recovered, evaluations will be repeated every 2 weeks until recovery confirmed.
2. Group 2 subset will start induction treatment on the same schedule as Group 1 at Visit 4
3. History includes all medical and surgical history prior to the first direct injection of NanoDoce;
4. Comprehensive physical examination required at screening and End of Treatment; targeted physical exam at all other visits, if required;
5. Comprehensive physical examination and ECOG to be performed at Visit 2 if not completed within the 14 days prior to Visit 2;
6. Vitals will be performed prior to and post NanoDoce direct injection and intravesical instillations (see Section 7.3); Temperature measurement is not required during the Visit 2 Direct injection and instillation vitals monitoring;
7. See Table 4 for Visits 2, 3 and 4 detailed PK collection schedule;
8. PK samples will be collected within 24 hours prior to study drug intravesical instillation, or can be drawn to coincide with laboratory sample collection prior to the Induction and Maintenance intravesical instillation visit, if within allowable visit window;
9. Laboratory testing (CBC and Urinalysis) to be performed and results reviewed prior to all Induction and Maintenance intravesical instillations. Chemistry and coagulation to be collected only at visits 1, 4, 10 and End of Treatment. Any tissue sample collected during the study will be processed per Institution pathology procedure;
10. Cystoscopy and cytology required at Visits 4, 10 and End of Treatment; ad-hoc cystoscopy, urine cytology, and 'for-cause' biopsy can be conducted at any time during the study as needed, but must be performed prior to any NanoDoce instillation;
11. Any tissue sample collected during the study, starting with eligible TURBT tissue samples to be processed per Section 7.2.2.1;
12. Chart review or subject contact.

Table 3: Group 2 (MIBC) Schedule of Events

Procedure	Screening	Treatment		End of Treatment	Survival Follow-up
	Visit 1	Visit 2	Visit 3		
	Days (-30 - 0)	Day 1	Day 15 (+/- 1 day)	Day 45 (+/- 5 days)	Months 6, 9, 12
Informed Consent	X				
Medical and Surgical History[1]	X				
Demographics	X				
Physical Examination[2]	X	X[3]		X	
ECOG	X	X[3]		X	
12-Lead ECG	X			X	
Vital Signs[4]	X	X		X	
Height and Weight	X				
Pharmacokinetic Collection[5]		X	X	X	
Laboratory Tests[6]	X		X	X	
NanoDoce® Direct Injection		X			
NanoDoce® Intravesical Instillation		X			
TURBT		X			
Cystoscopy[7]	X			X	
Cytology[7]	X			X	
Biopsy[7]	X			X	
Immunohistochemistry[8]		X		X	
Diary Distribution		X		X	
Diary Collection				X	
Adverse Events		X	X	X	
Concomitant therapy	X	X		X	X
Survival[9]					X

1. History includes all medical and surgical history prior to the first direct injection of NanoDoce;
2. Comprehensive physical examination required at screening and End of Treatment or early withdrawal; targeted physical exam at all other visits, if required;
3. Comprehensive physical examination and ECOG to be performed at Visit 2 if not completed within the 14 days prior to Visit 2
4. Vitals will be performed prior to and post NanoDoce direct injection and intravesical instillations (see Section 7.3);
5. See Table 4 for detailed PK collection schedule;
6. CBC and Urinalysis) to be performed and results reviewed prior to the Visit 2 Injection and the intravesical instillations. Chemistry and coagulation to be collected at visits 1 and End of Treatment;
7. Any tissue sample collected during the study will be processed per Institution pathology procedure;
8. Any tissue sample collected during the study, starting with eligible TURBT tissue samples to be processed per Section 7.2.2.1;
9. Chart review or subject contact.

Table 4: Schedule of Pharmacokinetic Sample Collection

Timepoint		Post Dose			
	0 Hour [1]	**1 Hour** (+/-10 min)	**2 Hours** (+/-10 min)	**6 Hours** (+/-20 min)	**24 Hours** (+/-30 min)
Visit 2 [2]	**X** [3]	**X**	**X**	**X**	**X**
Visit 3 [2, 4]	**X**				
Visit 4 [5]	**X** [6]	**X**	**X**	**X**	**X**
Visit 5-13	**X**				

1. PK sample collection to occur prior to administration of study drug for Visit 2 and Visit 4, and during Visit 3 (where no study drug is administered);
2. Groups 1 and 2;
3. PK sample collection within 24-hours prior to the Visit 2 study drug direct injection or anytime during the screening period;
4. Even though there is a 1-day window, every effort should be made to collect the Day 15 sample on Day 15.
5. Group 1 and Group 2 subset only;
6. PK sample collection within 24-hours prior to the Visit 4 study drug intravesical instillation; or can be drawn to coincide with laboratory sample collection prior to the Induction intravesical instillation.

7.4 JUSTIFICATION FOR SENSITIVE PROCEDURES

Sponsor acknowledges that injection of NanoDoce into the resected bladder tumor, including the anesthesia necessary for the injection, may qualify as a sensitive procedure and as such should be mentioned in this section.

7.5 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant prescription medications taken during study participation will be recorded on the case report forms (eCRFs). For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications, and non-prescription medications taken by the subject while on study and historical medication which are continued to be taken while on study for existing condition, whether or not acute.

Medications allowed in the study will include: local anesthetic gel for catheter placement, prophylactic antibiotics (pre-or post TURBT) for infection prevention, methylene blue or other staining agents to enhance diagnostic visualization procedures and institution SOC IV chemotherapy (if required following Visit 2 direct injection and intravesical instillation).

Group 2 subset subjects may receive radiation concurrently during Visits 4-12 induction and maintenance, per institution standard of care.

Although no interaction studies have been conducted using NanoDoce, docetaxel is a CYP3A4 substrate metabolized by cytochrome P450 isozyme CYP3A4 (Taxotere Package Insert). *In vivo* studies showed that the exposure of docetaxel increased 2.2-fold when it was co-administered with ketoconazole, a potent inhibitor of CYP3A4. Protease inhibitors, particularly ritonavir, may increase the exposure of docetaxel. Concomitant use of docetaxel and drugs that inhibit CYP3A4 may increase exposure to docetaxel and should be avoided.

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

Any distending media (conductive fluids, nonconductive or non-electrolyte and gas) other than isotonic saline or sterile water, are not allowed.

For subjects in Group 1, the use of chemotherapy, immunotherapy, or radiation therapy is prohibited during the Induction period (at Visit 4 or later) or anytime during the maintenance period.

7.8 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Dexamethasone or institution standard of care allergy prophylaxis may be administered, at the discretion of the investigator.

Dexamethasone use suggested:

Visit 2: Subjects in Groups 1 and 2 will take one 4 mg dexamethasone tablet 12 hours before NanoDoce direct injection, one 4 mg dexamethasone tablet 1 hour before NanoDoce direct injection, and one 4 mg dexamethasone tablet 8 hours after NanoDoce direct Injection. As both direct injection and intravesical instillation are planned for Visit 2, the timing of dexamethasone pretreatment will be determined by the direct injection dose only.

Induction and Maintenance Intravesical Instillations: Subjects in Group 1 and Group 2 subset will take one 4 mg dexamethasone tablet 12 hours before NanoDoce intravesical instillation, one 4 mg dexamethasone tablet 1 hour before NanoDoce intravesical instillation, and one 4 mg dexamethasone tablet 8 hours after NanoDoce intravesical instillation.

Prophylactic antibiotics and any other prophylactic medications will be administered according to the institution's SOC at any time during the study.

7.9 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Rescue medications, treatments, and procedures are not expected for this study.

7.10 PARTICIPANT ACCESS TO STUDY DRUG AT STUDY CLOSURE

Not applicable.

8 ASSESSMENT OF SAFETY

8.1 SPECIFICATION OF SAFETY PARAMETERS

Safety assessments to be conducted in this study include:

- AE, collected at all study visits from the time of first study drug dose;
- 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.

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

Included in the DSMB's review of the AEs and general study data pertaining to safety there will be rules for non-escalation. Any AE that is considered related or probably related to NanoDoce is potentially a DLT. The definition of a DLT will be made by consensus by the Medical Monitor, Sponsor Medical Director, and Principal Investigator for AEs.

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

8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended change in structure, function, sign, or symptom 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 a physical exam that was not included in the medical history. Clinical conditions attributable to disease progression will be considered AEs.

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; in the opinion of the investigator, the subject was at substantial risk of dying at the time of the adverse event, or use or continued use of the medical product might have resulted in the death of the patient;
3) Is a persistent or significant disability or incapacity;
4) Requires hospitalization or prolongs an existing hospitalization. Hospitalization will be defined as such if > 24 hours, or a hospitalization that requires an intervention to treat emergent symptomatology (non-diagnostic);
5) Exposure prior to conception or during pregnancy may have resulted in a congenital anomaly or birth defect in the child;
6) Other important medical events not noted in events above, but may be considered a serious experience when, based upon appropriate medical judgment, 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 1/2 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 as mild, moderate, severe, life-threatening, or fatal according to the following definitions:

- **Mild:** The AE is transient and does not interfere significantly with the subject's normal functioning level. The AE resolves spontaneously or may require minimal therapeutic intervention;
- **Moderate:** The AE produces limited functional impairment and may require therapeutic intervention. The AE produces no sequelae;
- **Severe:** The AE results in significant impairment of function and may lead to temporary inability to resume

the subject's normal life pattern. The AE produces sequelae which require prolonged therapeutic intervention;

- **Life-Threatening:** The AE results in life-threatening consequences, urgent intervention is indicated, urgent operative intervention is indicated or the patient is at risk of death at the time of the event if immediate intervention is not undertaken;
- **Fatal:** The AE results in death.

Further, toxicities should be evaluated according to the NCI CTCAE, version 4.0 criteria.

8.2.2 RELATIONSHIP TO STUDY DRUG

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

- **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 participant'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 drug. An alternative definitive etiology should be documented by the Investigator.

8.2.3 EXPECTEDNESS

The definition of expectedness is related to the study drug specifically. An event may be unexpected in the subject but that in itself does not qualify as unexpected; review against information available and provided for the study drug 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 drug, in the protocol and within the Investigator's Brochure.

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

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

Subjects will be required to spontaneously report any 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, become stable.

The Sponsor will report any serious, unexpected and drug-related AE to applicable regulatory agencies and provide these reports to the investigative sites. The Investigator must promptly inform the IRB of such events and retain a copy of the notification in the Investigator Site File (ISF).

8.4 REPORTING PROCEDURES

8.4.1 ADVERSE EVENT REPORTING

AE will be captured from first study drug dose (injection) until 45 days after the last study drug dose (injection or instillation) for Group 2 subjects or until the End of Treatment (Visit 13) visit for Group 1 or Group 2 subset subjects. All AEs (whether or not attributable to the study drug) occurring during the study observed by the Investigator or reported by the subject will be recorded on the eCRF. The following information will be recorded for all AEs:

- Event: name/condition/diagnosis/description;
- Onset and resolution time and/or date;
- Severity;
- Relationship to study drug; (assessment by staff trained and authorized to diagnose),
- Action taken;
- Seriousness.

8.4.2 SERIOUS ADVERSE EVENT REPORTING

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

Dr. Antony Verco
Medical Monitor
E-mail: tony.verco@usbiotest.com
Phone: 805-235-9193
Fax: 805-980-4897

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

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

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

8.4.3 UNANTICIPATED PROBLEM REPORTING

Unanticipated incidents or events that occur during the conduct of the study and meet the criteria for an AE or SAE will be captured in the source documents and in the EDC as such. See 8.4.1 and 8.4.2.

8.4.4 EVENTS OF SPECIAL INTEREST

Of particular interest will be signs of systemic toxicity due to docetaxel exposure; particularly from bladder injection. NanoDoce has never previously been injected in the bladder; subjects will be monitored for injection site pain and any reported event, in particular, during the first 36 hours after the procedure.

8.4.5 REPORTING OF PREGNANCY

A female patient is 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, all sexually-active patients must make use of double condoms until 45 days after the last study drug administration.

Any pregnancy occurring in a subject or a subject's sexual partner during the study or within 6 months after the last NanoDoce drug dose must be reported to US Biotest as soon as the Investigator is aware of it. The pregnancy will not be considered an SAE; however, information on the event will be collected and the outcome followed to birth or termination of pregnancy.

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 1/2 dose escalation study. Dose escalation will be determined following review of the safety and tolerability data in a cohort by the DSMB. Following review, at any time point, the study may be terminated. Should this occur, all subjects who have received treatment will be followed to the completion of the End of Treatment visit

or 45 days after administration of NanoDoce, whichever occurs later, to ensure all safety data is collected on all treated subjects.

DSMB may determine that a further three subjects should be treated at the same dose as the current cohort, to provide additional safety and/or tolerability information as needed in order to determine if dose escalation should proceed; they may also determine that it is acceptable to proceed with an increased dose in the next cohort; or they may determine that the safety and tolerability profiles are not acceptable and may stop the study.

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

8.6 SAFETY OVERSIGHT

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

All subject study data will be captured in an EDC system, allowing real-time access to ongoing safety and tolerability data. The Medical Monitor will perform ongoing data review for each subject entered in the database and prior to proceeding to dose escalation. See 10.4.7.1

Prior to dose escalation proceeding, the DSMB will convene to review the cohort data, and generate a report outlining any safety concerns from the reviewed EDC data. This review will take place prior to proceeding with either addition of more subjects to a current cohort or proceeding to dose escalation in a new cohort.

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

9 CLINICAL MONITORING

US Biotest monitors, or delegates, will conduct scheduled site visits to the investigational centers for the purposes of monitoring the study. The Investigator agrees to allow monitors and other authorized Sponsor personnel or designees, access to the subject's complete and comprehensive medical and research study records, Investigator Site File, pharmacy document and any other applicable documents as needed to assure that the conduct of the study and the safety of the study subject is maintained and 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, or at the earliest possible opportunity of the request. The clinical trial site will allow access to the inspectors to review requested records.

US Biotest will conduct a site initiation visit to provide the Investigator and study staff with a comprehensive overview of the protocol and study procedures and to review mutual obligations and requirements of regulatory authorities. The Investigator Site File (may be identified as regulatory file or binder) containing required documentation will be up to date throughout the life of the study and maintained at the site for reference and inspection.

Routine monitoring visits will be conducted 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 conduct a final visit to assess the conduct of the study, inform the investigator of ongoing and final regulatory obligations and perform a final inventory of all clinical supplies to be either returned to US Biotest, destroyed or retained at the site.

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 at least one dose of study drug will be included in the descriptive analysis.

The dose populations will be defined in the SAP once the pattern of exposure is determined i.e. the dose and the total number of treatments. The medical team will provide guidance on the groupings. The resulting displays will provide the basis for interpreting possible dose-response outcomes for both safety and any possible signals of efficacy. This will be supported by pharmacokinetic information where available.

10.3.1 MISSING DATA

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

10.4 DESCRIPTION OF STATISTICAL METHODS

10.4.1 GENERAL APPROACH

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

10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

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

10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

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

- Concentration of docetaxel in the systemic circulation post-injection in the presence of intravesical instillation (as determined by PK analysis);
- Disease progression as defined by cystoscopy, cytology, and if indicated, biopsy at Visit 10 (Group1 and Group 2 subset) and Visit 13 in Group 1 or Group 2 subset.
- OS will be determined for all groups at Months 6 (Group 2 only), 9 and 12.

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

10.4.4 SAFETY ANALYSES

10.4.4.1 ADVERSE EVENTS

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

Events reported at or after the first injection of NanoDoce will be considered TEAE. All reported events will be listed by subject number and assigned treatment, investigator term, 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 collected up to the End of Treatment visit. 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 treatment/dose group for the subject.

Adverse event reports will be coded using the most recent version of MedDRA, signed off by the Medical Monitor, and presented by system organ class and preferred term. All AE and abnormal laboratory variables will be assessed according to the NCI-CTCAE v4.0 grading system. The number of subjects reporting, and number of events reported will be presented in frequency tables (overall, by intensity, by relationship and by outcome) for each dose cohort in each group. Adverse events of special interest will be presented separately. The criteria for the most frequently reported events will be determined in the SAP after reviewing the data; due to the small dose cohorts, the traditional 5 and 10% would not be reasonable.

10.4.4.2 LABORATORY ANALYTES

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

10.4.4.3 VITAL SIGNS

Vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate (if measured by the institution), 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 drug application, for each treatment group.

10.4.4.4 ECOG

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

10.4.5 ADHERENCE AND RETENTION ANALYSES

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

10.4.6 BASELINE DESCRIPTIVE STATISTICS

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

10.4.7 PLANNED INTERIM ANALYSES

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

10.4.7.1 SAFETY REVIEW

Safety data will be reviewed in a combination of Medical Monitor reviews and DSMB (based on the DSMB charter) meetings. Safety reviews will be conducted on an ongoing basis to allow for 'real-time' safety assessment.

Group 1:

Reviews will be conducted by the Medical Monitor for all clinical data from subjects in each cohort, on an ongoing basis and once each subject has completed Visit 4, Visit 6, and Visit 9. Additionally, depending on enrollment rate, during direct injection escalation phase, the Medical Monitor will conduct monthly reviews if more than 6 weeks between reviews occurs or is likely to occur. During the maintenance phase the Medical Monitor will conduct monthly reviews. At the end of Visit 9 for each cohort and at every 3 months during the maintenance period, the Medical Monitor will also provide an aggregate data report to the DSMB. A formal DSMB meeting will be conducted, at any time during the study if required or requested by any DSMB member following review of any data provided by the Medical Monitor.

Dose escalation in Group 1 will proceed independent of Group 2 and according to the planned schedule in order to allow adequate safety assessment of multiple intravesical instillates.

At the 1st safety review, all clinical data from each subject, in each cohort, including all DLTs (See section 8.1) and excluding PK, will be reviewed and evaluated to determine if the dose is safe and tolerable, up to and including the first day of the induction period instillation, or Visit 4. The Medical Monitor will provide *an aggregate summary*

report to the DSMB for review and approval for each subsequent direct injection dose escalation (Cohorts 2, 3 and 4). At the 2nd review, all clinical data from each subject in that cohort, including all DLTs (Section 8.1) and excluding PK, will be reviewed and evaluated up to, and including the fourth induction period instillation, or Visit 6. This will allow an assessment of safety prior to increasing the intravesical instillation dose from 2.0 mg/mL to 3.0 mg/mL,

Group 2

Monthly reviews will be conducted by the Medical Monitor for all clinical data from subjects in each cohort, on an ongoing basis. Safety evaluation for Group 1, depending on differing rates of enrollment between Groups 1 and 2, may be used as the basis for dose escalation in Group 2. In the event that the 3rd subject in a Group 2 cohort reaches Day 45 before the same dose is evaluated in Group 1, the dose escalation in Group 2 will be based on the relevant clinical data available in that Group 2 cohort.

Groups 1 and 2

In addition, the Medical Monitor will provide an aggregate data report to the DSMB every 3 months. A formal DSMB meeting will be conducted, at any time during the study if required or requested by any DSMB member following review of any data provided by the Medical Monitor.

10.4.7.2 EFFICACY REVIEW

Cystoscopy and biopsy (if available), and any institution-required diagnostic imaging will be reviewed at End of Treatment visit for Group 1 and Group 2 subset. For Groups 1 and 2, histologic evaluation of tissue samples will be assessed for presence of tumor, if any. Review may be earlier if there is persistence, recurrence and progression of disease.

10.4.8 ADDITIONAL SUB-GROUP ANALYSES

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

10.4.9 MULTIPLE COMPARISON/MULTIPLICITY

Not applicable, as no inferential analyses will be employed.

10.4.10 TABULATION OF INDIVIDUAL RESPONSE DATA

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

10.4.11 EXPLORATORY ANALYSES

Determination of immune response in the bladder lesion due to NanoDoce injection and instillation by IHC staining will be evaluated for all positive tissue/biopsy samples at any time during the study; baseline TURBT samples will be concurrently evaluated.

10.4.12 CONCOMITANT MEDICATION

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

10.5 SAMPLE SIZE

There is no formal sample size calculation for this Phase I/II safety study. To provide a reference for the ongoing safety review of each cohort and the possible expansion of a cohort with safety concerns, the procedure "confidence interval for the probability of observing a rare event" was employed in nQuery Advisor (Version 8) to determine that, for an event with an occurrence rate of 0.33, the probability of detecting it with 3 subjects is 69.9% vs 91.0% for 6 subjects, and for an event rate of 0.05 the probability of detecting the event is 14.3% and 26.5% for 3 and 6 subjects, respectively.

The rationale to expand the final cohort in the Dose Confirmation Phase to 12 subjects, from either 3 or 6 subjects, was based on the "reasonable gain" in detection rate that each additional subject would provide in this early phase exploratory trial. The calculations were performed as the estimates above. With 12 subjects, the probability of detecting the 0.1 event rate is 71.8%, as compared to a 46.9% probability with 6 subjects. This sample size also allows for more acceptable probabilities of detecting much rarer events: for example, a 46% probability of detecting an event with a 0.05 event rate (compared to 26.5% with 6 subjects), and a 11.4% probability for an event with a 0.01 event rate (5.9% with 6 subjects).

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 correction to eCRF entries must be reflected in a validated 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;
- Screening, enrollment, end of treatment and safety visit details including dates and reasons for early termination;
- 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 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 in 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 is certificated with European "Safe Harbor" regulations (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 by the IRB.

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 drug and any prior findings from previous studies; study procedures including the timing of study clinic visits and responsibility to adhere to those timelines; any risks which may be associated with the study drug 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 at the study site. The Investigator will provide the Sponsor with written IRB or Ethics Committee approval, 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 legal representative before any activity or treatment is undertaken, which is not part of routine or SOC. This includes, but is not limited to, the performance of diagnostic or therapeutic procedures and the administration of study drug. 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.

In the event a protocol is amended, the consent form may be revised to reflect those changes; in which case, 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, if required by the IRB.

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 (if allowed by institution, local and/or state requirements), birth date, and subject number. The subjects will be informed 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 or delegates 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 conducted in the study. Samples will not be available for purposes other than as indicated within this protocol. No genetic testing will be performed.

Access to stored samples will be limited to site authorized personnel authorized in the conduct of collecting, processing, storing and shipping to the designated laboratory for analysis. Samples will be stored using codes assigned by the Sponsor or as required by the clinical laboratory.

Samples will only be retained until analyses are complete, after which they will be disposed of according to the laboratory SOPs. No samples will be retained for any future use.

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

13.5 FUTURE USE OF STORED SPECIMENS

Not applicable.

14 DATA HANDLING AND RECORD KEEPING

14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The Investigator is responsible for ensuring the data is ALCOAC compliant.

For electronic source, the institution must provide a secure, validated electronic medical record (EMR) data management system that is 21CFR 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.

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 on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions are required and expected to be implemented promptly by the site.

These practices are consistent with ICH E6:

- 4.5: Compliance with Protocol, Sections 4.5.1, 4.5.2, 4.5.3 and 4.5.4
- 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. All deviations must be addressed in study source documents, and reported to the Sponsor, the Data Management group and to the local IRB, per guidelines. The site PI/study staff is responsible to adhere to any IRB reporting requirements.

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

14.4 PUBLICATION AND DATA SHARING POLICY

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

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

15 STUDY ADMINISTRATION

15.1 STUDY LEADERSHIP

The study will be overseen by the Sponsor Study Lead or designee 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 Site Monitor designated by the Sponsor.

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 form FDA 1572 for this study, filed at the site and by the sponsor in the Trial Master File.

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.:
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