STATISTICAL ANALYSIS PLAN (SAP)

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

Protocol Number:	NANODOCE-2017-02	**Study Phase**	I/II
Trial Design:	Open-label, Single dose direct injection followed by intravesical instillations, 3+3 Dose Escalation Study with both Dose-Escalation and Dose Confirmation Phases		
Medication/dosage:	Nanodoce (Sterile Nanoparticulate Docetaxel) at concentrations of 0.75, 1.5, 2.5, or 3.75 mg/mL in the direct injection dose and at concentrations of 2 or 3 mg/mL for the intravesical instillation.		
Population	Up to 75 male/female subjects with urothelial carcinoma (NMIBC or MIBC).		
Study/Treatment duration:	Study duration will be up to 30 months. Group 1 and Group 2 Subset: Estimated up to 33 weeks. Group 2: Estimated up to 64 days. Follow-ups are scheduled up to 1 Year.		
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Version:	final
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1 of 2

Date of Final Protocol (including all amendments)	18-Jun-2020 v7.0

Date of Final Plan: 25-Nov-2021

I have reviewed the Statistical Analysis Plan. My signature below confirms my agreement with the contents and intent of this document.

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SIGNATURE APPROVAL PAGE

2 of 2

Date of Final Protocol (including all amendments) 18-Jun-2020 v7.0

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I have reviewed the Statistical Analysis Plan. My signature below confirms my agreement with the contents and intent of this document.

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LIST OF ABBREVIATIONS AND TERMS

Abbreviations

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse Event
APR	Analysis Programming Requirements - detailed programming specifications required to convert the EDC data into analysis/presentation data sets.
ATC	Anatomical Therapeutic Chemical Classification System
BLQ	Below the Limit of Quantification / Below Limit of Quantitation
BMI	Body Mass Index
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
DLC	Data Logic Check- A combination of programmed and visual checks based on the CRF, protocol, and sponsor input, designed to identify incomplete or illogical data.
DMP	Data Management Plan - details of how data are managed throughout the trial
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
LLOQ	Lower Limit of Quantitation
MedDRA	Medical Dictionary for Regulatory Activities (coding for AEs)
MIBC	Muscle Invasive Bladder Cancer

Abbreviation	Definition
NMIBC	Non-Muscle Invasive Bladder Cancer
OS	Overall Survival
PFS	Progression Free Survival
PK	Pharmacokinetics
PT	Preferred Term (from MedDRA coding dictionary)
RFS	Recurrence-Free Survival
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SOC	System Organ Class (from MedDRA coding dictionary)
SOP	Standard Operating Procedure
TEAE	Treatment Emergent Adverse Event
WHODD	World Health Organization Drug Dictionary

Definition of Terms

Term	Definition
McDougall	McDougall Scientific Ltd - CRO contracted to perform the data management, statistical programming and analysis functions
NanoDoce	Sterile Nanoparticulate Docetaxel. The investigational product.
Cohort	In this document, Cohort refers to dose level of direct injection of NanoDoce concentrations: 0.75, 1.5, 2.5, or 3.75 mg/mL. All treated subjects can be classified into one and only one Cohort.

Treatment Group	In this document, Treatment Group refers to the combination of direct injection dose level and intravesical instillation dose level. There are eight planned Treatment Groups: 0.75/2.0, 0.75/3.0, 1.5/2.0, 1.5/3.0, 2.5/2.0, 2.5/3.0, 3.75/2.0, 3.75/3.0 mg/mL. All treated subjects can be classified into one and only one Treatment Group, but some treatment groups may have no subject.

1 BACKGROUND

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 non-muscle invasive bladder cancer (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.

Investigational drug product NanoDoce (sterile nanoparticulate docetaxel) Powder for Suspension is being developed by NanOlogy, LLC (NanOlogy) for the treatment of NMIBC and MIBC.

In this open-label, dose rising, phase 1/2 trial, subjects with high-risk NMIBC or 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 study treatment Day 1 (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).

After assessment for recovery (TURBT resection site healing), subjects from Group 1 and a subset of Group 2 will move forward to the induction period and maintenance period with more NanoDoce intravesical instillations. Other Group 2 subjects will proceed to institutional standard of care treatments.

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.

Following Data Safety Monitoring Board (DSMB) review of the cohort data, a 3+3 design will be applied to determine the most suitable direct injection dose for further evaluation. Additional subjects will be enrolled to provide up to a total of 9 subjects dosed at that dose level.

The study will also dose escalate Groups 1 and 2 for the intravesical instillation of NanoDoce concentrations (2.0 and 3.0 mg/mL). The dose of intravesical instillation

depends on the study period (Day 1, induction period, or maintenance period) of each subject, and the study phase (dose escalation phase or dose confirmation phase). Please see details in section 3.1.2.

2 OBJECTIVES

2.1 Primary Objective

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

2.2 Secondary Objectives

The secondary objectives are:

- 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.

3 STUDY DESIGN AND ENDPOINTS

3.1 Study Design

This is a Phase I/II, open-label, dose rising trial with two phases: an initial dose escalation phase following a design like traditional 3+3 designs, and a dose confirmation phase with 9 subjects enrolled at the most suitable dose determined in the dose escalation phase.

3.1.1 Subject Groups

All subjects are stratified into two treatment groups based on disease status at enrollment: Group 1 (NMIBC) or Group 2 (MIBC). At Visit 2 (Study Day 1), 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).

At Visit 3 (Study Day 15), a subset of Group 2 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”).

Group 1 and Group 2 Subset subjects will have same schedule of visits and assessments. They will have 1) one direct injection followed by one intravesical instillation on Study Day 1, 2) a 3-month Induction period consisting of 6 weekly NanoDoce intravesical instillations, followed by 6 weeks of rest, and 3) a 3-month Maintenance period, consisting of 3 weekly NanoDoce intravesical instillations, followed by 9 weeks of rest.

Other Group 2 subjects (referred to hereafter as the "Group 2") will proceed to institutional standard of care treatments after their direct injection and intravesical instillation on Day 1.

3.1.2 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 (NMIBC) and 2 (MIBC).

During direct injection dose escalation, cohorts will be enrolled sequentially starting at the lowest concentration. 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. 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.

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 (Study Day 1) instillation, i.e., the first instillation within 2 hours of the direct injection. If the dose is well-tolerated, Group 1 subjects will continue to receive 2.0 mg/mL through Visit 6 (the 3rd instillation of the induction period), 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.

FIGURE 1: COHORT SCHEDULE – GROUP 1 – NMIBC

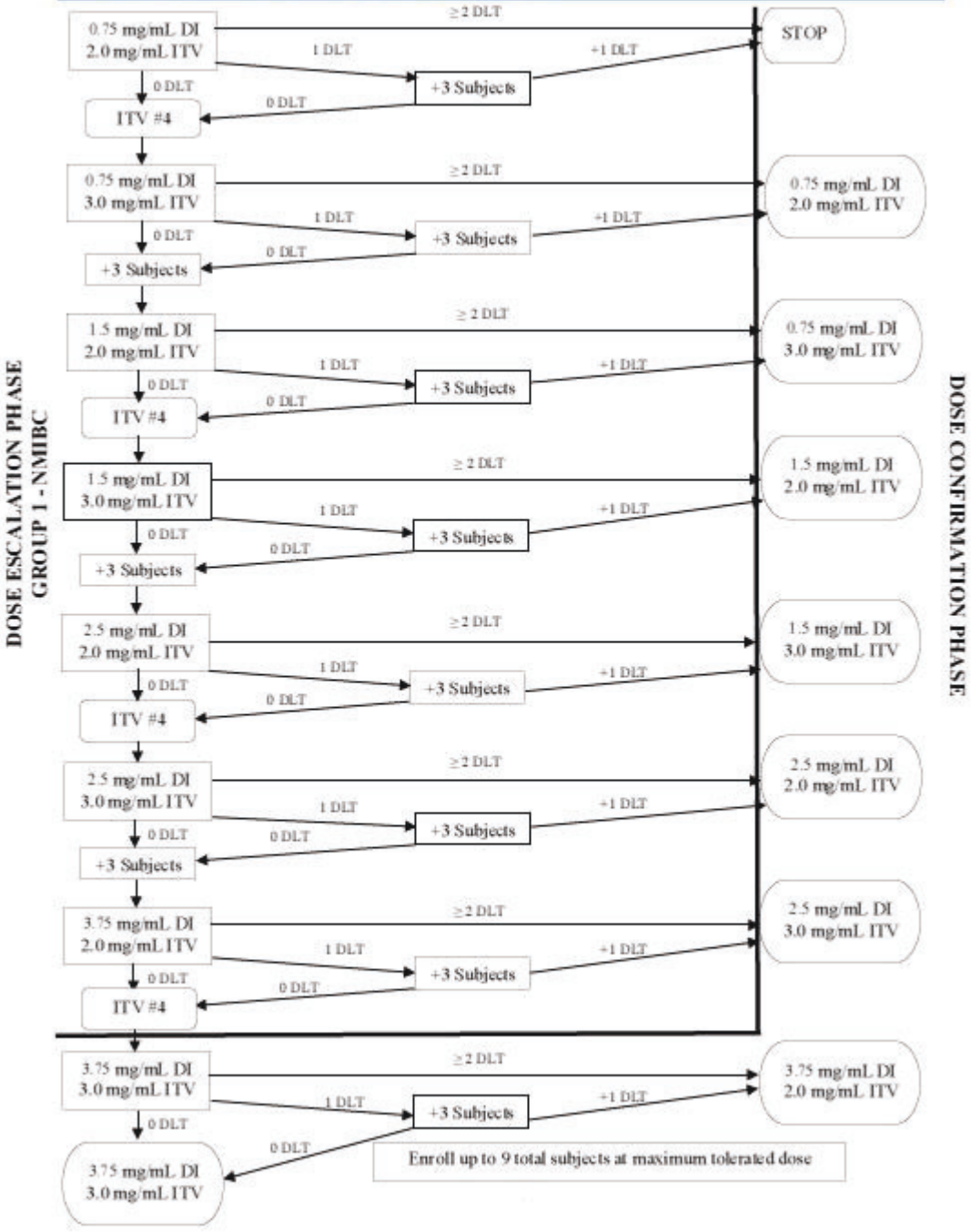
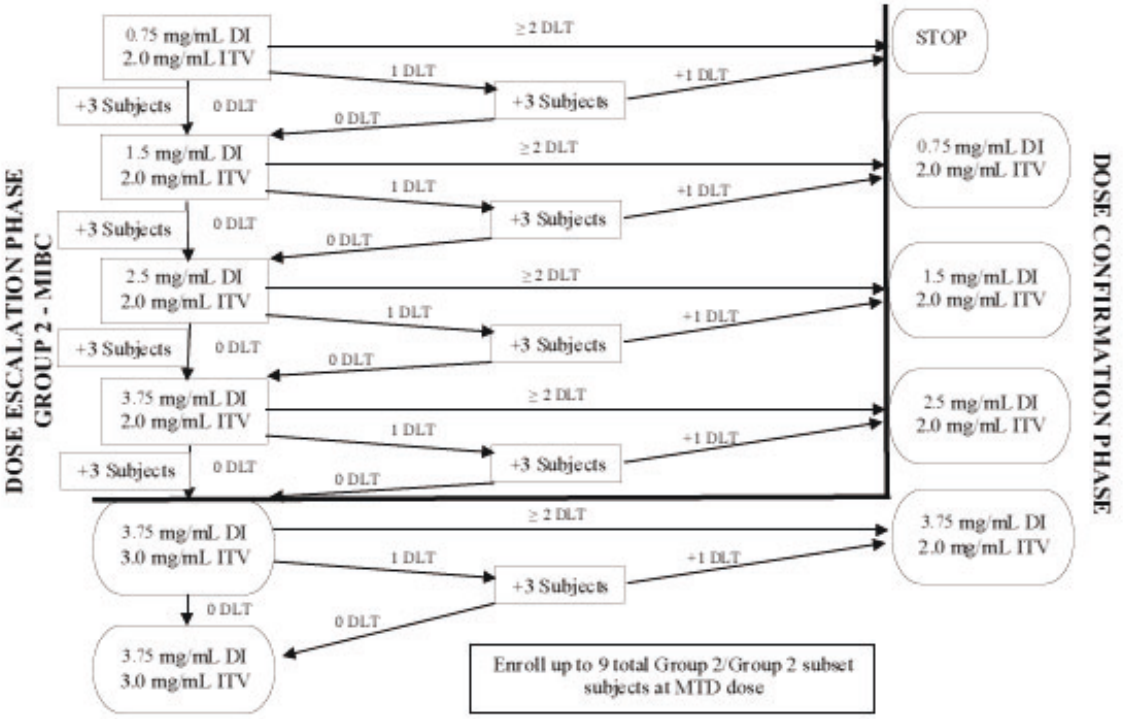


FIGURE 2: COHORT SCHEDULE – GROUP 2 – MIBC



3.2 Primary Endpoint

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

3.3 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.

3.4 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

3.5 Study Timeline and Schedule of Events

Table 1: 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 1 is continued on the next page.

Table 1 (continued): Group 1 (NMIBC) 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 2 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.

4 DATA MANAGEMENT

4.1 Data Collection and Database Construction

Most data will be collected at the sites via an electronic data capture (EDC) system. The study-specific application will be developed based on the protocol requirements and following the full Systems Development Lifecycle (SDLC). The development and management of the trial application, including security and account administration, will adhere to the Standard Operating Procedures (SOPs) at McDougall. All participants will be trained in the use of the application, and the training documented prior to each site being initiated.

The application design will, where appropriate, provide choice fields in the form of checkboxes, buttons and lists to aid in ensuring high quality standardized data collection. In addition Data Logic Checks (or data Edit Checks) will be built into the application based on variable attributes (e.g. value ranges), system logic (e.g. sequential visit dates) and variable logic (e.g. onset date must be before cessation date). Visual review and data responses will be overseen by a trained data manager.

The database will be locked when all the expected data has been entered into the application, all query responses have been received and validated, the designated data has been noted as monitored in the system and each investigator has signed off the casebook for each of their study subjects. The data coding must be accepted by the Sponsor and any Serious Adverse Events (SAEs) reconciled with the pharmacovigilance data base working with the Medical Monitor.

According to study design, following external/central lab data will not be entered into EDC system. They will be provided as external data:

- Concentration of docetaxel in the systemic circulation
- Immunohistochemistry data

The data management processes are outlined in the project specific Data Management Plan (DMP); this and all related documentation are on file at McDougall and are identified by the project code NA06NDH.

All programming will be performed in SAS version 9.4 or higher.

4.2 Coding

Adverse Events and medical history will be coded in MedDRA version 22.0 and signed off by US Biotest, Inc. All concomitant medications will be coded using WHO Drug Dictionary Global C3 March 1, 2019. All coding will be reviewed and signed off prior to data base lock.

4.3 Pharmacokinetics (PK) Data

The PK analysis of plasma docetaxel concentration will be performed by Covance Madison Laboratories Bioanalytical (BA) Group. The concentration data will be provided to McDougall in Excel data sheets to be read into SAS system for descriptive summaries.

4.4 Immunohistochemistry Data

The immunohistochemistry data will be provided to the Sponsor by the external laboratory, NeoGenomics, for incorporation to the Clinical Study Report as an appendix or addendum.

5 CHANGE TO ANALYSIS AS OUTLINED IN THE PROTOCOL

5.1 Recurrence-Free Survival (RFS)

Protocol section 4.2.2 describes a secondary endpoint:

> *PFS defined as tumor recurrence or disease progression at Visit 10 and Visit 13*

Because of the different disease types and treatment schedules, the treatment efficacy will be assessed and analyzed differently for the two subject groups:

Group 1 (NMIBC)

Each subject's Recurrence-Free Survival (RFS) time will be calculated:

RFS time = months from direct injection to recurrence or death, if the subject had recurrence after initial TURBT, or died within Month 12 follow-up.

= months from direct injection to cystectomy or last alive date if the subject did not have recurrence before cystectomy or last contact.

RFS (yes/no) at Visits 10 and 13, as well as RFS time will be summarized by cohort and for total Group 1 subjects.

Group 2 (MIBC)

Disease progression (yes/no) at Day 45 will be derived for all Group 2 subjects based on their cytology and biopsy assessments. It will be summarized by cohort and for total Group 2 subjects.

5.2 Additional Sub-Group Analysis

Protocol section 10.4.8 describes additional sub-group analysis:

> *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.*

To conduct subgroup analysis, either directly compare safety/efficacy between subgroups, or perform safety/efficacy analysis for one or more subgroups, the subgroup(s) should be defined by baseline information, and not by data collected during study conduct, such as AE, therefore, and in consideration of the small number of subjects in this study, these subgroup analyses will not be conducted.

6 STATISTICAL METHODS

Descriptive summaries of continuous data will consist of the mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized with frequencies and percentages. All data will be listed by subject and treatment. This study was not powered for inference, and so no inferential analyses will be included.

6.1 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).

6.2 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.

6.3 Data Conversion for Analysis

To summarize quantitative endpoints, e.g., lab test results, some data collected as text values need to be converted to numeric values for analysis. Following conventional rules will be applied for this study.

- All “< xx” lab results will be converted to 0.99 * xx. The adjustment is -1% of xx.
- All “> xx” lab results will be converted to 1.01 * xx. The adjustment is +1% of xx.
- Some PK concentration values may be marked as Below the Limit of Quantification (BLQ) or reported as “< xx”. Here xx is the Lower Limit of Quantitation (LLOQ). For the summary of docetaxel concentration in this study, all BLQ values will be set to 0.

Above data conversions are only applied to data descriptive summaries. In by-subject data listings, original reported data “< xx”, “> xx”, or “BLQ” will be presented.

For this study’s data submission and analysis, all EDC and external data will be converted to SDTM (Study Data Tabulation Model) and ADaM (Analysis Data Model) datasets. In the creation of SDTM and ADaM datasets, original lab test results from different sites (laboratories) need to be converted to results in SI units (the International System of Units). For some tests, data rounding may be applied during the conversion. The details will be provided in SDTM and ADaM’s define.xml files and their support documents.

6.4 Calculated Outcomes

The following are key endpoints derived from data captured at the sites via the EDC system. Complete documentation of the calculations and data manipulation required to go from the CRF database to the analysis database are contained in the companion document - the study Analysis Programming Requirements (APR) for SDTM and ADaM.

Endpoint	Calculation	Comment

Baseline value	Value reported prior to study treatment, i.e., NanoDoce direct injection	If multiple values collected prior to treatment initiation, non-missing value closest to the date/time of direct injection is considered baseline
Change from Baseline	Value collected at time point (Visit) – Baseline value	
Time in Trial (days)	Study completion/withdrawal date – date of informed consent date + 1 day	
Time on Treatment (days)	Date/End Time of last intravesical instillation – Date/Start Time of NanoDoce direct injection	
Treatment Emergent Adverse Event (TEAE)	= no if onset date/time AE is before the date/time of NanoDoce direct injection, or after the End of Treatment visit, i.e. Month 6 for Group 1 / Group 2 subset; Day 45 for Group 2 = yes otherwise	According to conservative rule, all AEs that cannot be determined as started before NanoDoce injection or after EoT will be considered as TEAE
Age (years)	= Informed Consent Year – Birthdate Year, if consent date was on or after birthday, = Informed Consent Year – Birthdate Year – 1, if consent date was before birthday	

Recurrence Free Survival (RFS) Time (months)	= ((Date of first recurrence or death – Date of NanoDoce direct injection + 1) / 365.25) * 12, if the subject had recurrence or died during the study = ((Date of cystectomy or last alive date – Date of NanoDoce direct injection + 1) / 365.25) * 12, if the subject had no recurrence before cystectomy or last alive date	Note: 1) This RFS time will only be calculated for Group 1 (NMIBC) subjects. 2) Due to the small number of subjects in each cohort or treatment group, RFS time will not be analyzed using K-M analysis and log-rank test.
Disease Progression at Day 45	= Yes. if the subject had disease progression on/before Day 45 visit, which is End of Treatment visit of the Group 2 subjects = No, if the subjects had no disease progression at Day 45 visit.	This variable is only calculated for MIBC subjects, including both Group 2 subset and other Group 2 subjects
Overall Survival (OS) Time (months)	= ((Date of death – Date of NanoDoce direct injection + 1) / 365.25) * 12, if the subject died during the study,	Note: Due to the small number of subjects in each cohort or treatment group, OS time will not be analyzed using K-M analysis and log-rank test. Therefore, OS time for censored subject is not calculated.

6.5 Analysis Population

All enrolled subjects who receive NanoDoce injection will be the analysis population for all outcome analyses.

6.6 Interim Analysis/ Data Monitoring

No interim analysis is planned for this trial. The safety data (e.g., Adverse Events, dose limiting toxicities, vital signs, laboratory values, etc.) will be reviewed on an ongoing basis throughout the study by the Data Safety Monitoring Board (DSMB), to evaluate the risk for the subjects and to make dosing recommendations.

The trial statistician will provide safety report to DSMB for each cohort of the dose-finding phase after the first 3 subjects of the cohort complete the study. If additional 3 subjects are enrolled to the same dose level, the safety report will be provided again for all 6 subjects of the cohort.

6.7 Analysis Methods

All calculations and analyses will be performed using SAS version 9.4 or higher under the Windows Server 2012R2 operating system at McDougall Scientific Ltd. in Toronto, Canada. Continuous data will be summarized via PROC MEANS - mean, standard deviation, median, range, and 95% CIs, while categorical data will be presented as counts and percentages (or proportions) via PROC FREQ for the descriptive displays.

No statistical inference will be made for all outcomes.

7 RESULTS

All enrolled and treated subjects will be the analysis population for all analyses. All data collected in EDC will be at a minimum listed.

Because of the different disease types (i.e., NMIBC vs. MIBC) and different treatment schedules, all tables, listings, and graphs will be presented separately for Group 1, Group 2 Subset, and Group 2.

All outcomes will be summarized by cohort, i.e., dose level of direct injection, and visit, if applicable.

All outcomes will also be summarized by treatment group, i.e., combination of direct injection dose and instillation dose (0.75/2.0 mg/mL, 0.75/3.0 mg/mL, 1.5/2.0 mg/mL, 1.5/3.0 mg/mL …).

All outcomes will also be summarized for the total treated subjects.

All available data of screen failures will be provided in a separate listing.

7.1 Study Subjects

7.1.1 Patient Disposition

All enrolled and treated subjects will be accounted for. Number of subjects in the analysis population, study completion status, and time in trial will be summarized by cohort and by treatment group.

All early discontinuations will be summarized by primary reason of discontinuation.

7.1.2 Demographics and Baseline Characteristics

Demographic (age, sex, ethnicity, and race), baseline body measurements (height, weight, and calculated BMI), and vital signs (blood pressures, heart rate, and body temperature) will be summarized.

7.1.3 Medical History

Medical history will be coded in MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT).

7.1.4 TURBT

All TURBT information at Study Day 1, including date, start/end time of resection, number of resection sites, target lesion size, etc., will be presented in data listing.

7.1.5 NanoDoce Administration

NanoDoce direct injection data at study Day 1, including dose level, injection date, start/end time, number of injections, total volume (in mL) and dose (in mg) injected, and bladder location of injection, will be listed.

NanoDoce instillation data at study Day 1, induction period, and maintenance period, including dose level, instillation date, start/stop time, void time, instillation volume (in mL) and dose (in mg), will be listed.

Time on treatment and total number of instillations will be summarized.

7.2 Primary Outcomes

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

All primary outcomes will be descriptively summarized by cohort, by treatment group, and for the total treated subjects. No statistical inference will be made for primary endpoint.

7.2.1 Adverse Events

For this study, Treatment Emergent Adverse Events (TEAEs) are limited to AEs during the treatment period. That is, TEAEs are adverse events with onset date on/after the first study dose (injection), and on/before the End of Treatment visit (Month 6 for Group 1/Group 2 subset; Day 45 for Group 2).

The AEs of special interest will be flagged and tabulated. They are signs of systemic toxicity due to docetaxel exposure as well as local reactions; 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.

Summaries of AEs will be prepared by treatment group, and include:

- Overview of all AEs - include the total number of TEAEs, serious TEAEs, death, and AEs leading to early discontinuation.
- AEs by MedDRA System Organ Class (SOC) and Preferred Term (PT)
- AEs by MedDRA SOC, PT, and relationship to NanoDoce treatment.
- AEs by MedDRA SOC, PT, and severity.
- SAEs by MedDRA System Organ Class (SOC) and Preferred Term (PT).
- AEs with fatal outcome.
- AEs leading to early discontinuation.
- AEs of Special Interest
- DLTs

All these summaries will include the counts and frequencies of events, and of subjects who had events.

All AEs will be listed by subject. Death, DLT, and other SAEs will be listed separately.

7.2.2 Laboratory Assessments

Laboratory assessments, including assessments at each visit and change from baseline at post-baseline visits, will be summarized by visit and analyte.

Each non-missing lab result's normal/abnormal status (e.g. normal/low/high for quantitative results, and normal/abnormal for qualitative results) will be calculated based on the normal reference ranges provided by the lab. The status will be summarized using shift tables from baseline to each post-baseline time point.

All lab data will be presented in by-subject data listing. Separate listings will be provided for subjects with abnormal lab values which are judged by the investigator to be clinically significant.

Following lab tests are required for the study:

Chemistry: Sodium, potassium, chloride, carbon dioxide (CO2), 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.

Hematology: 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;

Coagulation and Fibrinogen assay: Prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen;

Urinalysis: Specific gravity, hydrogen ion concentration (pH), RBC, WBC, protein, and glucose.

7.2.3 Physical Examination

All abnormal findings from the physical examination after study treatment will be recorded as AEs. The analysis of physical examination will be included in AE summaries. See section 7.2.1.

7.2.4 Vital Signs

Vital Signs (blood pressure, heart rate, temperature, respiratory rate) will be summarized for each visit.

Vital Signs' change from baseline values will be summarized at all post-treatment visits.

Unscheduled vital signs will only be presented in by-subject data listing.

7.2.5 12-Lead ECG

12-Lead ECG assessed at Screening and End of Treatment visit will be descriptively summarized.

7.3 Secondary Outcomes

7.3.1 Plasma Docetaxel Concentration

All numeric docetaxel concentration data above the Lower Limit of Quantitation (LLOQ), i.e. the detectable limit, will be tabulated by visit/time point using the arithmetic mean, standard deviation, coefficient of variation, median, and range.

All docetaxel concentration data (individual subjects and mean of treatment group) will be visually presented in spaghetti plots by treatment group.

7.3.2 Recurrence-Free Survival and Disease Progression

Group 1 (NMIBC) subjects

Each NMIBC subject's Recurrence-Free Survival (RFS) time will be calculated based on the disease recurrence data and death information. The recurrence data is a composite of all cytology and tumor biopsy assessments. For subjects who had no recurrence before cystectomy or alive at last contact, i.e., censored subjects, their RFS time will be the time from initial treatment to the date of cystectomy or last alive date.

RFS status (yes/no) at Visit 10 (1st maintenance instillation) and Visit 13 (End of Treatment visit), as well as RFS time will be summarized by cohort and for total Group1 subjects.

Group 2 (MIBC) subjects

Disease progression status at Day 45 will be summarized for MIBC subjects. Time to cystectomy, death, or last alive contact will be listed.

7.3.3 Overall Survival

Overall survival (OS) time will be calculated for subjects who died during the study. Death date, overall survival time, and cause of death will be listed.

The surviving (yes/no) at 6, 9, 12-month follow-ups will be summarized.

7.3.4 Cystoscopy, Cytology, and Biopsy

Cystoscopy and cytology data are 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.

Cytology categorical data, like types and results, will be descriptively summarized.

All cystoscopy, cytology, and biopsy data collected in EDC will be listed.

7.3.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

ECOG performance scale collected at screening, Day 1, and during study will be summarized by cohort and by treatment group.

7.3.6 Immunohistochemistry Data

All immunohistochemistry data will be reported separately and inserted as an appendix or addendum to the Clinical Study Report.

7.4 Safety Outcomes

All safety analyses will be presented as the primary outcome analysis. See section 7.2.

7.5 Other Outcomes

7.5.1 Prior and Concomitant Medications

A summary of all concomitant medications taken during the course of the study will be presented in tabular form by therapeutic drug class (ATC Level 2 code) and generic drug name (ATC Level 4 code) using the World Health Organization Drug Dictionary (WHODD).

Prior medications, i.e., started and stopped before direct injection, will be summarized and listed separately.

7.5.2 Concomitant Procedures

All concomitant procedures performed during the study will be listed.

Appendix A: ECOG Performance Scale

Patient performance status will be graded according to the Eastern Cooperative Oncology Group (ECOG) scale* as described below.

Grade	ECOG PERFORMANCE STATUS DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.