McDOUGALL SCIENTIFIC
INSIGHTS YOU CAN TRUST

Statistical Analysis Plan

Protocol #:	NANOPAC-2016-01
Protocol Title:	Phase II Study of Four Dose Levels of Intraperitoneal Nanopac® plus IV Carboplatin and Paclitaxel in Patients with Epithelial Ovarian Cancer Undergoing Cytoreductive Surgery
Project Code:	NA01NAE
Study Phase:	II
Trial Design:	3+3 dose finding phase followed by 1:1:1 randomized phase
Study Drugs:	Nanopac (Sterile Nanoparticulate Paclitaxel) 100, 200, 300, 400 mg/m^2
Subjects:	Dose finding phase: Approximately 16 subjects Efficacy phase: Approximately 45 subjects
Treatment Period:	Approximately 6 months of treatment, minimum 12 months of follow-up
Sponsor Contact:	Leanne Drummond US Biotest, Inc. 231 Bonetti Drive, Suite 240 805-595-1300 Leanne.drummond@usbiotest.com
Analysis Contact:	Blue Neustifter McDougall Scientific Ltd. 789 Don Mills Rd, Suite 802 Toronto, Ontario, M3C 1T5 416-673-9478 bneustifter@mcdougallscientific.com
Date:	January 29, 2020
Status:	Final v 1.0

Table of Contents

Signature Approval Page
1 of 2

Date of Final Protocol:	14-Jun-2016
Amendments:	V2 20-Oct-2016 V3 21-Feb-2017 V4 26-Jul-2017
Date of Final Plan	29-Jan-2020

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

Author:

Blue Neustifter
Senior Statistician, McDougall Scientific Ltd.

Date: dd-mmm-yyyy

Reviewed by:

Hong Chen, MSc., P.Stat
Chief Analytics Officer,
McDougall Scientific Ltd.

Date: dd-mmm-yyyy

Signature Approval Page
2 of 2

Date of Final Protocol:	14-Jun-2016
Amendments:	V2 20-Oct-2016 V3 21-Feb-2017 V4 26-Jul-2017
Date of Final Plan	29-Jan-2020

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

Reviewed by:

29 Jan 2020

Peter Mast
Clinical Project Manager
US Biotest

Date: dd-mmm-yyyy

Gere diZerega

Gere diZerega, MD
Vice President for Medical Affairs
NanOlogy, LLC

Date: dd-mmm-yyyy

1. List of Abbreviations Definition of Terms

Abbreviation or Term	Definition
AE	Adverse Event
APR	Analysis programming requirements
BLQ	Below the limit of quantification
CA-125	Cancer antigen 125
CV	Coefficient of Variation
DLT	Dose-limiting toxicity
DMP	Data management plan
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
IP	Intraperitoneal
MedDRA	Medical Dictionary for Regulatory Activities (coding for AEs)
MTD	Maximum tolerated dose
PFS	Progression free survival
PK	Pharmacokinetic
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SDLC	Systems development lifecycle
SMC	Safety Monitoring Committee
SOC	Standard of care
SOP	Standard operating procedure
TEAE	Treatment emergent adverse event

2. Background

NANOPAC-2016-01 is a two-part Phase II clinical trial of NanoPac suspension administered via intraperitoneal (IP) therapy in subjects with epithelial ovarian cancer considered appropriate for treatment with IV platinum and paclitaxel undergoing cytoreductive surgery. IP therapy is designed to expose cancer confined to the peritoneal cavity to higher concentrations of drug treatments for longer periods of time while reducing systemic toxicity.

NanoPac (previously Nanotax®) was previously subject to a Phase I dose-finding trial and did not show unexpected systemic toxicity up to doses of 275 mg/m^2 (the study maximum). Subjects receiving the active treatment in this study will receive the IP instillation of NanoPac at the time of their cytoreductive surgery and receive IV chemotherapy standard of care (SOC) post-surgery. Subjects randomized to control will receive IV chemotherapy SOC post-surgery.

3. Objectives

This trial of IP NanoPac suspension was planned to have two phases: a preliminary dose-finding phase, and an efficacy phase that follows the conclusion of the dose-finding phase. The study was put on hold in 2018 due to safety concern. Subsequently. a decision was reached in 2019 to not re-open enrollment, and so the final study did not include an efficacy phase and only included two doses in the dose-finding phase before study termination.

3.1. Primary Objective(s)

The primary objective of the dose-finding phase of this study is to determine the two best dose levels of IP NanoPac given at the time of surgery as determined by the occurrence of dose-limiting toxicity (DLT) events.

The primary objective of the efficacy phase of this study was to estimate the incidence of progression free survival (PFS) and time to progression for the first twelve months post-IV chemotherapy for the two doses of NanoPac determined in the dose-finding phase.

3.2. Secondary Objective(s)

Secondary objectives of this study are to:

- Determine the safety of IP NanoPac immediately following cytoreductive surgery
- Compare the duration of PFS between time-to-initial recurrence and time-to-recurrence following second cytoreductive surgery plus IP NanoPac in those subjects with recurrent cancer
- Determine plasma paclitaxel concentrations following IP administration of NanoPac
- Determine possible predictive factors for PFS to be used as stratification factors or covariates in subsequent studies

4. Study Design

NANOPAC-2016-01 is a Phase II trial with two stages planned, but with the second phase canceled due to early study termination. The first, dose-finding, phase has a design based on 3+3 designs common in oncology trials. Since the second phase is cancelled, this SAP will include only outcomes and data applicable to the first phase.

During the first phase of the study, eligible subjects will be enrolled in groups of 3 to dose-ascending cohorts of IP NanoPac at 100, 200, 300, or 400 mg/m^2 plus SOC chemotherapy (a target of six cycles of IV carboplatin and paclitaxel, total number subject to investigator discretion) following a standard 3+3 design. The first cohort of 3 will be assigned to 100 mg/m^2 IP NanoPac. For each cohort, if no Dose Limiting Toxicity (DLT) events (as defined in Section 6.1.1 of NANOPAC-2016-01 Protocol v. 4, dated 26-JUL-2017) occur, dose escalation will continue, and the following cohort will be assigned to a dose one level higher (e.g. from 100 mg/m^2 to 200 mg/m^2). If 2 or more DLTs occur in the first cohort of 3, dose escalation will stop and the prior dose level will be regarded as the Maximum Tolerated Dose (MTD). If exactly 1 DLT occurs in the first cohort at a dose, a further 3 subjects will be enrolled at the same dose level. If an additional 1 or more of the same DLT occurs in the second cohort, then dose escalation will stop and the prior dose level will be regarded as the MTD; otherwise, dose escalation will continue. This phase will continue until a MTD has been identified or until the top dose of 400 mg/m^2 is applied without violating the rules for escalation. A Safety Monitoring Committee (SMC) will review accumulating safety data for a maximum of four weeks per subject prior to dose escalation and approve dose escalation or addition of a second cohort to the current dose level.

4.1. Primary Outcomes

The primary objective of the dose-finding portion of the study is safety, with no quantitative outcomes defined. Adverse Events (AEs), especially DLT events, will be the primary outcome variable examined.

4.2. Secondary Outcomes

The dose-finding portion of the study has no further outcome variables.

4.3. Pharmacokinetic Outcomes

Plasma samples will be taken on Day 1 at 1, 2, 4, 8, and 24 hours post IP NanoPac instillation (as clinically feasible), weekly thereafter until IV chemotherapy begins, and prior to each cycle of post-surgery IV chemotherapy.

4.4. Safety Outcomes

Safety outcomes will be measured by summaries of AEs, laboratory assessments, and performance status on the Eastern Cooperative Oncology Group (ECOG) Performance Status scale.

5. Data Management

5.1. Data Management

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 clinical research staff 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 have 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, or the Sponsor delegate, and any Serious Adverse Events (SAEs) reconciled with the pharmacovigilance data base working with the Medical Monitor.

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 NA01NAE.

5.2. Coding

The adverse experiences and medical history will be coded in MedDRA version 20.0 and signed off by the medical monitor. All concomitant medication will be coded using WHO Drug (version C Mar 2017) and reviewed and signed off prior to data base lock.

5.3. Missing Data

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

6. Change to Analysis as Outlined in the Protocol

A mid-study change clarified that subjects may receive more than six cycles of post-surgery IV chemotherapy at investigator's discretion—SAP language has been altered to reflect this.

Due to study termination prior to the efficacy phase, the study outcomes and analyses outlined in the SAP were changed to reflect the data that will be available at database lock. Outcomes related to the efficacy phase of the study (including models for Progression Free Survival) have

been removed and remaining outcomes have been clarified to be descriptive, with no inference attempted.

7. Statistical Methods

7.1. Study Populations

7.1.1. Safety Population

The Safety population consists of all subjects enrolled in any phase of the study who received study medication or were assigned to SOC-alone and underwent their cytoreductive surgery. All safety tables will be presented for this population.

7.2. 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 EDC database to the analysis database are contained in the companion document - the study Analysis Programming Requirements (APR).

Baseline value: Baseline value for CA-125 is defined as the first CA-125 measurement taken prior to the second cycle of IV chemotherapy post-surgery.

For other values, baseline is defined as the last measurement prior IP instillation.

Change from Baseline: Value at time point – Baseline value

Time in trial (days): Date of last contact – Date of informed consent + 1

Study Day: Study Day is calculated based on the time of IP NanoPac instillation, with the date of instillation/surgery as Study Day 1.

Treatment emergent adverse event (TEAE): In the dose-finding phase, an adverse event is considered treatment emergent if it occurs on or after the date and time of the first application of IP NanoPac (i.e. surgery) and before the date and time of the start of the first IV therapy.

7.3. Analysis Methods

All calculations and analyses will be performed using SAS version 9.4 or higher resident on the Windows Server 2012R2 at McDougall Scientific Ltd. in Toronto Canada. The continuous data will be summarized with N, mean, standard deviation, median and range, while the categorical data will be presented as counts and percentages (or proportions) for the descriptive displays.

7.3.1. Efficacy Analyses

For the dose-finding portion of the study, there are no analyses of efficacy.

8. Results

8.1. Study Subjects

All data collected will be at a minimum listed.

8.1.1. Patient Disposition

All enrolled subjects that underwent their cytoreductive surgery will be summarized. All post-surgery early discontinuations will be summarized by the reason of discontinuation by stratification factors and treatment/dose.

Treatment exposure (time in trial) will be summarized by dose cohort.

8.1.2. Patient Characteristics

8.1.2.1. Baseline Characteristics

Demographic information (age, ethnicity, and race) and baseline vital signs (height, weight, temperature, heart rate, respiration, systolic and diastolic blood pressure) will be summarized for the Safety population by and dose. Subjects who select more than one race category will be grouped into a single race category denoted as multi-racial. Tables will also include summaries of the highest historical CA-125 measurement from the ovarian cancer history at screening.

8.1.2.2. Medical History, Ovarian Cancer History, and Physical Examination

A listing of the abnormal medical history will be presented by subject including year of onset/ended and current ongoing (Yes or No) status. The medical history terms will be tabulated by SOC (System Organ Class) and PT (Preferred Term) for each of the treatments.

All results from the screening ovarian cancer history will be listed; highest historical CA-125 measurement will also be summarized in the demographic tables (Section 8.1.2.1).

A listing of Abnormal results from physical examinations (including gynecological, if applicable) are recorded as Medical History at screening and adverse experiences post-treatment.

8.2. Pharmacokinetic Outcomes

Plasma samples will be taken on Day 1 at 1, 2, 4, 8, and 24 hours post-IP instillation of NanoPac if clinically feasible, and weekly thereafter until IV chemotherapy begins for subjects that receive IP NanoPac. Additionally, IP NanoPac subjects will have PK samples taken prior to each cycle of IV chemotherapy.

PK analysis will be performed and reported separately by a third party, and will not be described in this SAP.

8.3. Safety Outcomes

The safety profile will primarily be analysed by means of descriptive statistics and qualitative analysis. All summaries and listings in the section are based on the Safety population.

8.3.1. Adverse Experiences

The adverse experiences/events reported will be summarized by treatment group using both the counts of subjects and the number of reports, for each SOC and PT. The presentations will separate out and highlight any Serious Adverse Experiences (including deaths) and adverse events leading to discontinuation from the study.

The summaries will at a minimum be: 1) the number of subjects reporting for all events; 2) the number of reports for all events; 3) the number of subjects reporting treatment-related events (probable and possible relationship); 4) the number of reports of treatment-related events.

A by-subject listing of all adverse events will be provided.

8.3.2. Concomitant Medication

The concomitant medications will be listed by patient; the reason for the medication as well as the start and stop date/time will be presented. Concomitant medications will also be tabulated and summarized by anatomical system and therapeutic class for each treatment group.

8.3.3. Vital Signs

Vital signs (temperature, heart rate, respiration, systolic blood pressure, and diastolic blood pressure) and body measurements (weight and height) will be summarized as mean values with variance, including the change from baseline, by treatment dosage.

8.3.4. ECOG Performance Status

The Eastern Cooperative Oncology Group (ECOG) Performance Status scale is administered to subjects at screening and the end-of-treatment visit. The ECOG scale is a 6-point scale for describing a patient's ability to carry out activity post-disease. The scale ranges from 0 ("Fully active, able to carry on all pre-disease performance without restriction") to 5 ("Dead").

Screening and end-of-treatment results will be summarized as incidence of each rating by dose at each of the two assessments.

8.3.5. Laboratory Analytes

Haematology and biochemistry data will be presented as mean values with variability and change (absolute and relative) from baseline in each laboratory parameters.

Results for urinalysis visit will be summarized by dose cohort.

8.3.6. IV Chemotherapy

Drugs administered as part of SOC IV chemotherapy will be fully listed separately from concomitant medications by subject and IV cycle.

For each treatment, a summary of the number of subjects completing each IV chemotherapy cycle will be provided.

8.3.7. CA-125

Descriptive statistics of CA-125 will be provided by dose and assessment visit. Listings of CA-125 by subject and assessment will contain a flag indicating if measurement is twice that of baseline.

8.3.8. Cancer-Related Symptoms

Incidence of cancer-related symptoms will be provided by dose for the Safety population. Cancer-related symptoms will be determined by medical monitor.

Signature: Gere diZerega
Gere diZerega (Jan 29, 2020)
Email: gere.dizerega@usbiotest.com

NANOPAC-201601-SAP-final

Final Audit Report 2020-01-29

Created:	2020-01-29
By:	Peter Mast (peter.mast@usbiotest.com)
Status:	Signed
Transaction ID:	CBJCHBCAABAAOyQ8Dpt1Tn-86g4rZ25N918U9QMcPDPA

"NANOPAC-201601-SAP-final" History

Document created by Peter Mast (peter.mast@usbiotest.com)
2020-01-29 - 8:14:39 PM GMT- IP address: 74.82.134.51

Document emailed to Gere diZerega (gere.dizerega@usbiotest.com) for signature
2020-01-29 - 8:15:37 PM GMT

Email viewed by Gere diZerega (gere.dizerega@usbiotest.com)
2020-01-29 - 8:22:04 PM GMT- IP address: 74.82.134.51

Document e-signed by Gere diZerega (gere.dizerega@usbiotest.com)
Signature Date: 2020-01-29 - 8:24:38 PM GMT - Time Source: server- IP address: 74.82.134.51

Signed document emailed to Peter Mast (peter.mast@usbiotest.com) and Gere diZerega (gere.dizerega@usbiotest.com)
2020-01-29 - 8:24:38 PM GMT