Statistical Analysis Plan

Protocol #:	NANOPAC-2020-01
Protocol Title:	***Phase 2 Trial Evaluating the Safety and Tolerability of Intratumoral Injections of NanoPac® with Standard of Care Therapy in Subjects with Lung Cancer***
Project Code:	NA09NAJ
Study Phase:	2
Trial Design:	Open-label, single arm, safety/tolerability focus
Study Drugs:	NanoPac (Sterile Nanoparticulate Paclitaxel) Powder for Suspension at 15 mg/mL concentration in intratumoral injection of up to 20% of the total calculated tumor and lymph node volume
Patients:	18
Treatment Period:	12 weeks (plus 40 weeks follow-up)
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Date:	November 13, 2023
Status:	Final

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Date of Final Protocol:	07-Jul-2021 v4.0
Amendments:	20-Mar-2020 v2.0 13-Nov-2020 v3.0 07-Jul-2021 v4.0
Date of Final Plan	13-Nov-2023

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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Date of Final Protocol:	07-Jul-2021 v4.0
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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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President and CEO
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Contents

List of Abbreviations and Definition of Terms

Abbreviation or Term	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
APR	Analysis Programming Requirements - detailed programming specifications required to convert the CRF data into analysis/presentation data sets.
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CT	Computerized Tomography
DLT	Dose Limiting Toxicity
DMP	Data Management Plan
EBUS-TBNI	Endobronchial Ultrasound-Guided Transbronchial Needle Injection
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
FCM	Flow Cytometry
IP	Intraperitoneal
ITU	Intratumoral
MedDRA	Medical Dictionary for Regulatory Activities (coding for AEs)
mIF	multiplex Immunofluorescense
NSCLC	Non-small Cell Lung Cancer
OS	Overall Survival
PCHG	Percentage of Change
PFS	Progression-Free Survival
PK	Pharmacokinetics
QOL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCLC	Small Cell Lung Cancer
SDLC	Systems Development Lifecycle
SOC	System Organ Class
SoC	Standard of Care
SOP	Standard Operating Procedure
SRC	Safety Review Committee
TEAEs	Treatment Emergent Adverse Events
VAS	Visual Analogue Scale
WHO	World Health Organization

Abbreviation or Term	Definition
WHODD	World Health Organization Drug Dictionary

Definition of Term(s)

Term	Definition
NanoPac	Sterile Nanoparticulate Paclitaxel. The investigational product.

1 Background

NANOPAC-2020-01 is a Phase 2, open-label trial in 18 subjects with lung cancer. Subjects will be given intratumoral (ITU) NanoPac injections via endobronchial ultrasound-guided transbronchial needle injection (EBUS-TBNI) directly into the lung cancer lesions and metastatic lymph nodes on up to three separate occasions 4 weeks apart.

This trial is designed to primarily evaluate the safety and tolerability of NanoPac injections, with secondary investigations of the pharmacokinetics of NanoPac, subject progression-free and overall survival, and lesion response to treatment.

There have not been previous clinical trials with NanoPac in the lung, but some previous clinical trials with NanoPac were have been completed.

- A Study in Prostate Cancer with direct injection of NanoPac into the prostate appears safe and tolerable.
- A Study in Peritoneal Malignancies with intraperitoneal (IP) NanoPac did not lead to increases in systemic toxicity over that usually associated with IV paclitaxel.
- A study in ovarian cancer with NanoPac direct instillation into the peritoneum just prior to surgical cytoreductive close shows, overall, a 66% progression-free survival (PFS) occurred at 12 months post-IP NanoPac, with further improvement noted at 18 months after treatment, supported by sustained reduction in cancer antigen 125 (CA-125) and lack of additional cancer-related symptoms 6 months or more after treatment.
- A Study in Pancreatic Mucinous Cystic Neoplasms shows that, there was no apparent association of the number, severity, or relationship of treatment emergent adverse events (TEAEs) with the dose/concentration or number of injections administered. Analysis of the response rate of subjects demonstrated that the majority of subjects demonstrated stabilization or improvement in calculated volume and/or longest diameter of the cyst.

2 Objectives

2.1 Primary Objective

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

2.2 Secondary Objectives

a) To describe the PK of NanoPac when administered into the tumor(s) within the lung;
b) To evaluate effect on progression-free survival (PFS) and overall survival (OS) in this population; and

c) to assess changes in the treated lesion (and lymph nodes) via CT scan imaging.

2.3 Exploratory Objectives

a) To assess the changes in Eastern Cooperative Oncology Group (ECOG) Performance Status;
b) To assess the changes in pain (as measured by the visual analog scale [VAS]);
c) To assess the changes in QOL as measured by the validated EQ-5D QOL instrument, and
d) To assess the changes in immune markers in the blood by flow cytometry, and in the tissue by multiplex immunofluorescense (mIF).

3 Study Design

In this open-label, Phase 2, single arm trial, subjects with lung cancer will be receiving or plan to receive standard of care (SoC) treatment and will be enrolled after confirmation of adequate hematologic function.

Subjects will receive NanoPac via EBUS-TBNI to up to two lung lesions and up to five associated lymph nodes (at the Investigator's discretion).

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

The population in this trial consists of 18 subjects with primary or recurrent non-resectable non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC), with primary or recurrent measurable disease limited to the tracheal, hilar, mediastinal, and peribronchial structures (lung tumors and lymph nodes) accessible through EBUS-TBNI.

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

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

See the study schedule below for details of visit information.

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

1 History includes all events before initiation of NanoPac treatment.

2 ECOG Performance Status Scale attached as Appendix A.

3 PK Samples on Day 1, Week 4, and Week 8 will be drawn prior to injection and at 1, 2, and 4 hours post-dose. PK samples will also be obtained at each study visit thereafter. PK samples within the first 4 hours on Day 1 will allow for a 10-minute window around the samples.

4 Pain will be assessed with the visual analog scale.

5 Imaging with CT scan will occur during the screening period, prior to each NanoPac administration, and at Weeks 12, 18, 24, 38 and 52. Should the subject withdraw from the study at any time, a CT scan will be conducted as part of the end of study procedures. Additional imaging may be performed at the Investigator's discretion as per institutional standard of care and all resulting images will be collected for the subject's record.

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

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

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

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

3.1 Primary Outcomes

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

3.2 Secondary Outcomes

- Concentration of paclitaxel in the systemic circulation post-injection, as determined by PK analysis. Additionally, presence of paclitaxel in tissue biopsy samples obtained prior to each NanoPac injection;
- PFS (as assessed using RECIST v1.1) and OS to Week 52. Week 24 PFS and OS are a point of focus;

- Changes in all tumor and lymph node dimensions and volume, as determined by CT scan imaging, at Weeks 12, 24, 38, and 52 compared to baseline. Any changes in characteristics of tumors/nodes as determined by CT scan.

3.3 Exploratory Outcomes

- Change in Eastern Cooperative Oncology Group (ECOG) Performance Status at Weeks 12 and 24 from baseline;
- Changes in pain as measured by visual analog scale (VAS) at post-baseline visits up to Week 24 compared to baseline;
- Changes in Quality of Life (QOL) as measured by the EQ-5D Quality of Life Scale at Weeks 4, 8, 12, 18, 24, 38, and 52, compared to baseline;
- Immune markers assessed in the blood by flow cytometry (FCM), and in the tissues via multiplexed immunofluorescense (mIF).

3.4 Pharmacokinetic/Pharmacodynamic/Pharmacoeconomic Outcome(s)

- Concentration of paclitaxel in the systemic circulation;
- Concentration of paclitaxel in tissue biopsy samples.

4 Data Management

4.1 Data Management

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 Alimentiv. 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.

External laboratory data (from PK analysis, flow cytometry, and mIF) will not be entered into EDC system. External data sets will be provided.

The data management processes are outlined in the project specific Data Management Plan (DMP); this and all related documentation are on file at Alimentiv Inc. and are identified by the project code NA09NAJ.

All programming will be performed in SAS EG 8.2.

4.2 Coding

AEs and medical history will be coded in MedDRA version 23.1 and signed off by US Biotest, Inc. The coding will be reviewed and signed off prior to database lock. All concomitant medications will be coded using the WHO Drug Dictionary (WHODD) Version March 1, 2020.

4.3 Pharmacokinetics (PK) Data

PK Data will be provided to Alimentiv in Excel data sheets to be transferred into the SAS system for summary and listings. Analyses will be performed by an external expert and will be reported separately.

4.4 Flow Cytometry and Immunohistochemistry

Analysis of whole blood FCM and biopsy mIF will be performed by NeoGenomics Laboratories, Inc. The results will be provided to Alimentiv in Excel data sheets to be transferred into the SAS system for listings.

4.5 Missing Data

Given that the primary objective of this study is to evaluate the safety and tolerability, there will not be any missing data imputation or sensitivity analyses.

In addition, since the primary objective of this study is to evaluate the safety and tolerability, for all possible intercurrent events (e.g. not completing the full course of treatment (i.e. three injections), use of alternative medication, stopping treatment due to an AE, or death), analyses of the outcomes will follow a treatment policy strategy: that means, any data collected, whether from prior to or after the intercurrent event, will be summarized without modification due to any intercurrent events.

5 Change to Analysis as Outlined in the Protocol

Section 10.4.11 of the protocol specifies that PK parameters (AUC, Cmax, Tmax) will be calculated based on plasma concentration data for the first 24 hours. The protocol specifies PK plasma draws prior to injection and at 1, 2 and 4 hours post-injection; these are not sufficient to calculate AUC, Cmax, and Tmax, within an acceptable degree of accuracy and so PK parameters are not included in the SAP.

6 Statistical Methods

6.1 Calculated Outcomes

The following are key outcomes derived from data captured in the EDC. Complete documentation of the calculations and data manipulation required to go from EDC to the analysis database are contained in the companion document - the study Analysis Programming Requirements (APR).

Age: It is defined as informed consent year – birthdate year, if consent date was on or after birthday, or as informed consent year – birthdate year – 1, if consent date was before birthday.

Study day: Study day is defined as date of event (or assessment) - first NanoPac injection date + 1, if the date is on or after the first NanoPac injection; it is defined as date of event (or assessment) - first injection date, if the date is before the first NanoPac injection.

(The study day of first NanoPac injection day is 1, i.e., Day 1.)

Baseline: The baseline value of a measurement is defined as the last non-missing measurement prior to NanoPac injection on Day 1.

Change from Baseline: Value collected at time point (Visit) – Baseline value.

Time on Treatment (days): Date of last NanoPac injection – Date of first NanoPac injection + 1. (That is the study day of the last NanoPac injection.)

Time in Trial (days): Week 52 visit date or withdrawal date (whichever is smaller) – informed consent date + 1.

Body Mass Index (BMI): The ratio of weight (in kg) at the visit and square of the height (in meter) at the screening.

Treatment Emergent Adverse Event (TEAE): It is "No" if onset date/time of AE is before the date/time of first NanoPac injection, and "Yes" otherwise.

Cumulative Dose numbers: Dose numbers received just prior to the onset of AE.

AE of special interest (AESI): As described in protocol Section 8.4.4, events of interest in MedDRA preferred terms include

- Acute interstitial pneumonitis;
- Anaemia;
- Bronchial obstruction;
- Bronchitis;
- Bronchospasm;
- Chest discomfort;
- Cough (only *reported term* "Worsening cough" to be included);
- Dyspnoea;

- Febrile neutropenia;
- Haemoptysis;
- Hypoxia;
- Musculoskeletal chest pain;
- Pleural effusion;
- Pneumonia;
- Pneumonia pseudomonal;
- Pneumonitis;
- Collapse of lung (in low level term);
- Productive cough (only *reported terms* "Increased productive cough" and "Productive cough" to be included);
- Pulmonary embolism;
- Tachypnoea.

Local AE of interest: As described in protocol Section 8.4.4, local adverse events of interest in MedDRA preferred terms include:

- Acute interstitial pneumonitis;
- Bronchial obstruction;
- Bronchospasm;
- Cough;
- Haemoptysis;
- Pneumonia (only *reported terms* "Infection (pneumonia)" and "Pneumonia" to be included);
- Pneumonitis;
- Productive cough (only *reported terms* "Increased productive cough" and "Productive cough" to be included);
- Pulmonary embolism

Tumor Volume: For a tumor or a lymph node, its volume is defined as

- (1/6)*3.1416*(diameter 1)* (diameter 2)* (diameter 3) if 3 diameters are available;
- (1/6)*3.1416*(diameter 1)* (diameter 1)* (diameter 2) if only two diameters are available, and (by convention,) diameter 1 is longer than or equals to diameter 2;
- (1/6)*3.1416*(diameter 1)* (diameter 1)* (diameter 1) if only one diameter is available.

Response Evaluation of A Target Lesion Based on Longest Diameter (RECIST 1.1): Calculating the percentage of change (PCHG) from baseline in longest diameter of the lesion, the response is

- "Complete Response (CR)" if PCHG = -100;
- "Partial Response (PR)" if -100 < PCHG ≤ -30;
- "Stable Disease (SD)" if -30 < PCHG < 20;
- "Progressive Disease (PD)" If PCHG ≥ 20.

Response Evaluation of a Target Lesion Based on Volume (and based on RECIST 1.1), Calculating PCHG in the volume of the lesion, the response is defined as the same way as in PCHG for longest diameter.

Progression (Yes/No): Progression = “Yes” in the case of Progressive Disease (PD) and Progression = “No” in any case of Complete Response (CR), or Partial Response (PR) or Stable Disease (SD).

Progression-Free Survival (PFS): It is the time from the first injection date to the date of progression or death, which equals the study day the date of progression or death. Unless an exact date is noted, when progression occurs noted at a visit, the PFS is the study day of the last visit among progression-free visits. In the case of no progression recorded, PFS is right censored at the end of study date or the early withdraw date.

Overall Survival (OS): In the case of death, the time is defined as the study day of the date of death. Otherwise, it is right censored at the end of study date or the early withdraw date.

6.2 Analysis Population

Safety population: Safety population consists of all subjects who receive at least one NanoPac injection. Safety population is the analysis population for all outcomes.

Efficacy population: Efficacy population consists of all subjects in safety population with lung cancer.

Cohorts: Three cohorts will be defined according to the total numbers of doses patients received.

Additional sub-group analysis: The following three sub-group variables will be used in sub-group analyses:

- Category of Non-Small Cell Lung Cancer (NSCLC): Squamous Cell Carcinoma (SCC) SCC, or Adenocarcinoma (AC)
- Dichotomized the sum of numbers of tumors and of lymph nodes in the screening visit into two categories: 1 or 2 tumors/nodes and more than 2 tumors/nodes.
- Dichotomized the size of tumors injected at medium (50% to 50%, or as close as possible) and named as small tumor size and large tumor size. (Note that the size of a tumor is the longest diameter of the primary tumor.)

6.3 Analysis Methods

All calculations and analyses (including analyses for OS and PFS) will be performed using SAS EG 8.2. Continuous data will be summarized via mean, standard deviation, median, range, and 95% confidence intervals, while categorical data will be presented as counters and percentages/proportions.

No statistical inference will be made for any outcomes.

7 RESULTS

All data collected in the EDC will be at a minimum listed. The eligibility data will be provided in a separate listing(s).

Summaries will be conducted by the 3 cohorts. Additional sub-group analyses will be conducted with the 4 sub-group variables.

7.1 Study Subjects

All baseline data will be analyzed based on safety population.

7.1.1 Subject disposition

All enrolled and treated subjects will be accounted for. All early discontinuations will be summarized by primary reason for discontinuation. Days in treatment, days in trial, survival days, days from diagnosis to first injection, and days from first injection to death will also be summarized.

Sub-groups, date of informed consent, date of each treatment, date of end of study, days in treatment and days in study, reason for early discontinuation will be listed.

Date of (lung cancer) disease diagnosis, date of death, days from diagnosis to screening, to first injection, and to death will be listed.

7.1.2 Demographics and Baseline Characteristics

Demographics (age, sex, ethnicity, and race), baseline body measurements (height, weight, and calculated BMI), and vital signs (systolic and diastolic blood pressure, heart rate, and temperature) will be summarized and listed.

7.1.3 Lung Cancer History

Lung cancer history (including stage of lung cancer (if available); histological type (squamous, adenocarcinoma) and initial diagnosis date will be listed.

7.1.4 History of IV Chemotherapy/Radiotherapy/Targeted Therapy Regimens

History of IV Chemotherapy/Radiotherapy/Targeted Therapy Regimens (including number of cycles planned and number of cycles completed and frequency) will be listed.

7.1.5 Medical History

Medical history (other than lung cancer history and history of IV Chemotherapy/ Radiotherapy/ Targeted Therapy Regimens) will be listed and be summarized by MedDRA System Organ Class and by Preferred Term.

7.1.6 NanoPac Administration

NanoPac administration from all injection days, including injection date, time, calculated injection volume, actual volume (in mL) injected and total mg administered will be listed.

7.2 Primary Outcomes

All safety outcomes will be analyzed based on safety population.

7.2.1 Adverse Events

All AEs will be listed (which at least includes subject ID, cumulative dose to date, investigator term, Medical Dictionary for Regulatory Activities (MedDRA) coded term, date/study day (from initial treatment) for onset and cessation, severity (using the NCIC severity grading), relationship to study medication and relationship to IV chemo/other therapy. Deaths (including the cause of death if known), AESIs, DLTs and SAEs will be listed separately.

Only treatment emergent adverse events (TEAEs) will be summarized. Two sets of AE summaries will be provided: one for AEs up to 12 Weeks and the other for AEs after 12 weeks and up to 24 weeks. Summaries of AEs will include:

- Overall AE summary, including the number of AEs, serious AEs (SAEs), AEs leading to death, and AEs leading to early discontinuation of study;
- AEs by System Organ Class (SOC) and Preferred Term (PT);
- AEs by SOC, PT, and relationship to NanoPac treatment;
- AEs by SOC, PT, and severity;
- AEs by SOC, PT and by the number of injections received prior to AE;
- SAEs by SOC and PT;
- SAEs with relationship to NanoPac by SOC and PT;
- AEs leading to death by SOC and PT;
- AEs leading to early discontinuation of study by SOC and PT;
- AEs of special interest by SOC and PT.
- Local AEs by SOC and PT.

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

7.2.2 Laboratory Assessments

Panels and tests in each panel are as follows:

- Chemistry : sodium, potassium, chloride, carbon dioxide (CO2), calcium, phosphorus, glucose, blood urea nitrogen (BUN), creatinine, alkaline phosphatase, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total protein, albumin, and calculated creatinine clearance (calculated by stats);

- Hematology : Red blood cell count (RBC), hemoglobin (Hgb), hematocrit (Hct), white blood cell count (WBC) including differential, reticulocyte count, platelet count, and absolute neutrophil count (ANC);
- Urinalysis : specific gravity, hydrogen ion concentration (pH), RBC, WBC, protein, and glucose; and urine pregnancy test;
- Coagulation : Prothrombin time (PT), activated partial thromboplastin time (PTT), and international normalized ratio (INR);
- Serology : HIV, Hepatitis B and Hepatitis C.

Laboratory assessments of the panels and tests in each panel including raw assessments at each visit and change from baseline for post-baseline visits, will be summarized by visit and analyte. Normal/abnormal status and clinical significance (if abnormal) based on investigator determination will be summarized qualitatively in the same table.

The result for each non-missing lab analyte will be assigned to a low/normal/high classification based on the normal range if available. Shift tables will be provided for change from baseline low/normal/high classification to the value at each assessed visit.

All lab data (including urine pregnancy test at screening, Week 12 and Week 24.) will be listed. Clinically significant abnormal lab results will be listed separately.

7.2.3 Physical Examination

At each visit, the physical examination performance (yes/no), examination date, and change from previous visit status will be listed.

7.2.4 Vital Signs and Body Measurements

Vital Signs (systolic and diastolic blood pressure, heart rate, temperature, BMI) and weight will be summarized for each visit. Change from baseline values for all tests will be summarized at all post-baseline visits. BMI at each visit will be calculated based on weight at the visit and height at screening.

Vital signs measurements at all visits, including unscheduled visits, will be listed.

7.3 Secondary Outcomes

All efficacy outcomes will be analyzed based on efficacy population.

7.3.1 Paclitaxel Concentration and Presence

For paclitaxel concentration in systemic circulation data, at each scheduled timepoint, the data will be summarized; All concentration values with actual sample collection time will be listed; Mean and individual paclitaxel concentrations over time (in original scale and in logarithm transformation) will be graphed by all subjects and by sub-groups.

Presence or absence (absence defined as undetectable = less than lower limit of quantification) of paclitaxel in lung lesion tissues biopsies prior to each injection of NanoPac will be

summarized by injection. All data of presence or absence (and the data of actual measurement) of paclitaxel with actual sample collection time will be listed. Mean and individual paclitaxel concentrations over time (in original scale and in logarithm transformation) will be graphed for all subjects and by sub-groups.

7.3.2 Overall and Progression-Free Survival

Survival rates of OS and PFS will be summarized at Week 24 (end of primary study), Week 38 and Week 52 (end of follow-up) separately based on Kaplan-Meier estimation. Survival times of OS and PFS will be listed. Kaplan-Meier plots of OS and PFS will be created for all subjects and by sub-groups.

7.3.3 Tumor Measurement and Response

Tumor measurement and response will be summarized for the screening visit and Weeks 12, 24, 38, and 52:

- overall tumor response based on RECIST by tumor volume and longest diameter,
- tumor measurements and changes (actual and percentages) from baseline by tumor volume and longest diameter,
- total number of tumors, total number of nodes, total of all volumes of NanoPac calculated and total volume of NanoPac administered.

All variables in CT scan CRF, and the changes from baseline will be listed.

7.4 Exploratory Outcomes

All exploratory outcomes will be analyzed based on safety population.

7.4.1 Eastern Cooperative Oncology Group (ECOG) Scores

ECOG scales will be summarized at each scheduled assessment, and shift tables from baseline to each scheduled assessment will be created. All ECOG scale data will be listed.

7.4.2 Pain

VAS pain score and change from baseline will be summarized at all scheduled assessments. VAS pain score data will be listed.

7.4.3 Quality of Life

EQ-5D scores (Mobility, Self-Care, Usual Activities, Pain / Discomfort, and Anxiety/Depression) will be summarized in frequency. Total health score and change from baseline will be summarized. EQ-5D score data will be listed.

7.4.4 Flow Cytometry (FCM) and Multiplexed immunofluorescense (mIF).

FCM and mIF data will be provided by the Sponsor from the external labs. For FCM, test results (including fold change) will be listed. For mIF, test results for whole tissue, with tumor and outside tumor will be listed.

7.5 Others

All other outcomes will be analyzed based on safety population.

7.5.1 Concomitant Medication

Concomitant medications will be summarized by therapeutic drug class (ATC Level 2 code) and generic drug name (ATC Level 4 code) using the World Health Organization (WHO) Drug Dictionary (WHODD).

Concomitant medications will be listed by patient.

7.5.2 Concomitant Procedures

The concomitant procedures will be listed.

7.5.3 Concomitant IV Chemotherapy/Radiotherapy/Targeted Therapy Regimen

The concomitant therapy procedures (including therapy name, dose and frequency, cycles planned and completed, start and end date etc.) will be listed.

References

None.