**STATISTICAL ANALYSIS PLAN (SAP)**

# Phase IIa Trial Evaluating the Safety of Intratumoral Injection of NanoPac in Subjects with Locally Advanced Pancreatic Adenocarcinoma

| | | | |
|---|---|---|---|
| **Protocol Number:** | NANOPAC-2016-05 | **Study Phase** | IIa |
| **Trial Design:** | Open-label, Dose Escalation Study including both a Dose-Escalation Phase (Single Dose) and a Second Phase (Two Doses) | | |
| **Medication/dosage:** | NanoPac® (sterile nanoparticulate paclitaxel) Powder for Suspension ("NanoPac") at concentrations of 6, 10, and 15 mg/mL administered into the tumor within the pancreas via endoscopic ultrasound-guided fine needle injection | | |
| **Population** | Up to 65 subjects with locally advanced pancreatic adenocarcinoma | | |
| **Study/Treatment duration:** | Up to 48 months | | |
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**Version:** Final

**Date:** 2023-04-03

## SIGNATURE APPROVAL PAGE

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| | |
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| Date of Final Protocol (including all amendments) | 25-Mar-2020 (version 7.0)<br>07-Aug-2019 (version 6.0)<br>09-Nov-2018 (Version 5.0)<br>26-MAR-2018 (Version 4.0)<br>08-JAN-2018 (Version 3.0)<br>23-FEB-2017 (Version 2.1) |

**Date of Final Plan: 03-Apr-2023**

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

**Digital Signatures**

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**Date of Final Plan: 03-Apr-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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# LIST OF ABBREVIATIONS

## 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 |
| BMI | Body Mass Index |
| BLQ | Below the Limit of Quantitation |
| CA19-9 | Cancer Antigen 19-9 or Carbohydrate Antigen 19-9 |
| CEA | Carcinoembryonic Antigen |
| 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. |
| DLT | Dose-Limiting Toxicities |
| DMP | Data Management Plan - details of how data are managed throughout the trial |
| DSMB | Data Safety Monitoring Board |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |

| **Abbreviation** | **Definition** |
|---|---|
| Alimentiv | Alimentiv Inc., company contracted to perform the data management, statistical programming and analysis functions |
| LLOQ | Lower Limit of Quantitation |
| MedDRA | Medical Dictionary for Regulatory Activities (coding for AEs) |
| | – |
| PK | Pharmacokinetics |
| PT | Preferred Term (from MedDRA coding dictionary) |
| 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 |
| WHO | World Health Organization |
| WHODD | World Health Organization Drug Dictionary |

# 1 BACKGROUND

In this open-label, dose rising, Phase Iia trial, subjects with locally advanced pancreatic adenocarcinoma will receive intratumoral (ITU) NanoPac (sterile nanoparticulate paclitaxel) via endoscopic ultrasound-guided direct injection. Prior to study entry, subjects will complete at least one course of standard of care (SOC) IV chemotherapy and hematologic recovery will be confirmed before NanoPac is administered. Subjects enrolling to the second and third phases will have initiated their SOC IV chemotherapy.

Subjects will be enrolled in sequential cohorts of NanoPac 6, 10, and 15 mg/mL at up to 20% of the calculated tumor volume (with a maximum injection volume of 5 mL per subject). Each cohort will have three subjects, with cohorts enrolled sequentially starting at the lowest concentration. Following Data Safety Monitoring Board (DSMB) review of the cohort data, the next cohort may begin enrolling, an additional three subjects at the current dose may be enrolled, or if the first dose does not provide adequate safety and tolerability the study may be halted. 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 be the dose used in the second phase of the study which will enroll 22 additional subjects who will receive two injections of NanoPac at the same dose, one month apart. In the third phase of the study, up to 30 subjects will receive up to four injections of NanoPac at the same dose, one month apart. Subjects will be followed for three months after the first NanoPac injection for safety, overall survival (OS), progression-free survival (PFS), CA-19-9 levels, carcinoembryonic antigen (CEA) levels, reduction in pain, and tumor response to therapy (as shown by imaging). A follow-up visit may be conducted at six months, as applicable. Subjects in the second phase of the study, following their one-month follow-up, will receive a second injection; subjects in the second phase will have a follow-up phone call a month after the 6 month follow-up visit, which will be 6 months following the second injection. Subjects in the third phase of the study, receiving 4 injections, will be followed to nine months after first injection (six months following last injection).

# 2 OBJECTIVES

## 2.1 Primary Objective

The primary objective of this study is to evaluate the safety and tolerability of NanoPac injected directly into pancreatic cancer by endoscopic ultrasound-guided (EUS-guided) injection.

## 2.2 Secondary Objectives

The secondary objectives are: (a) to describe the pharmacokinetics (PK) of NanoPac when administered into the tumor within the pancreas; (b) to determine whether any of the NanoPac cohorts (6, 10, or 15 mg/mL) show signs of preliminary efficacy; and (c) to determine if two to four injections of NanoPac (one month apart at the determined dose for this cohort) shows signs of preliminary efficacy

# 3 STUDY DESIGN AND ENDPOINTS

## 3.1 Study Design

In this open-label, dose rising, Phase Iia trial, subjects with locally advanced pancreatic adenocarcinoma will have completed at least one course of chemotherapy as part of SOC. Once there is sufficient hematologic recover, subjects will receive ITU NanoPac via endoscopic ultrasound-guided direct injection.

Subjects will be enrolled in sequential, escalating cohorts of NanoPac at concentrations of 6, 10, or 15 mg/mL injected directly into the tumor within the pancreas at up to 20% tumor volume (with a maximum of 5 mL volume being administered to any subject).

The study will include a dose escalation phase and a second phase. Subjects in the second phase will have initiated their SOC IV chemotherapy and will receive two injections of NanoPac at the highest acceptable dose found in the dose escalation phase, one month apart. Subjects in the third phase will have initiated their SOC IV chemotherapy or have it scheduled to begin, but may receive the first NanoPac injection prior to IV chemotherapy is started.

Dose Escalation of Cohorts

Cohorts will be enrolled sequentially starting at the lowest dose (6 mg/mL). Each cohort will have a planned minimum of three subjects. All data from the first three subjects in a cohort will be reviewed and evaluated by the Data Safety Monitoring Board (DSMB) to determine whether the dose received is considered safe and tolerable, and to determine if dose escalation may occur. The DSMB will review the data on the three subjects once they have completed the two-week follow-up visit and will assess safety and tolerability based on the DSMB Charter, which will include reference to dose-limiting toxicities (DLTs). 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); or (c) return to the previous (lower) dose cohort and expand by three subjects (more than one DLT).

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 a

DLT, that cohort may be taken into the Second Phase. If greater than one subject in a six subject cohort experiences a DLT, the previous dose may be taken into the Second Phase.

Second Phase of Study

Once the dose deemed appropriate for expansion and further evaluation has been determined by the DSMB, an additional 22 subjects will be enrolled to the study and this cohort of subjects will receive two NanoPac injections to their lesion one month apart.

Third Phase of Study

Up to 30 additional subjects will be enrolled to receive up to four NanoPac injections to their lesion, 1 month apart.

## 3.2 Primary Endpoint

The primary endpoint will be safety and tolerability, as assessed by adverse events (AE), changes in vital signs, laboratory results, and physical examination at one month following NanoPac injection.

## 3.3 Secondary Endpoints

The secondary endpoints will be:

- Concentration of paclitaxel in the systemic circulation post-injection (as determined by PK analysis);
- Tumor response (RECIST as per Eisenhauer et al. 2009);
- Reduction in pain (as measured by the visual analog scale [VAS]);
- Change in tumor marker CA19-9;
- Change in tumor marker CEA.

## 3.4 Study Timeline and Schedule of Events

### 3.4.1 Schedule of Events Table – Dose Escalation Subjects

| | Screening[3, 8] | Day 1 (Injection) | 24 Hours Post-Injection | Week 2 | Week 4 (1 Month) | Week 8 (2 Months) | Week 12 (3 Months) | 6 Months (Final Study Visit) |
|---|---|---|---|---|---|---|---|---|
| **Informed Consent** | X | | | | | | | |
| **History[1]** | X | | | | | | | |
| **Concomitant therapy** | X | X | | X | X | X | X | X |
| **Physical Exam** | X | X | | X | X | X | X | X |
| **ECOG[2]** | X | X | | X | X | X | X | X |
| **Pain Assessment[6]** | X | X | | X | X | X | X | X |
| **Vital Signs** | X | X | | X | X | X | X | X |
| **Clinical Laboratory Tests (section 7.2.1)** | X | X | | X | X | X | X | X |
| **PK Samples[5]** | | X | X | X | X | X | X | X |
| **Imaging[7]** | X | | | | | | X | X |
| **NanoPac[4]** | | X | | | | | | |
| **Adverse Events** | | 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 During the interval after the conclusion of intravenous chemotherapy but prior to injection with NanoPac, subjects will visit the clinic for evaluation and hematologic assessment according to their institution's standard of care. NanoPac injection may be performed when platelets ≥ 75 x $10^9$/L and absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L.
4 Prophylactic antibiotics will be administered prior to NanoPac injection; NanoPac will be administered by endoscopic ultrasound-guided fine needle injection; subjects will be admitted to the hospital for overnight observation.
5 PK Samples on Day 1 will be drawn prior to injection and at 1, 2, 4, 6, and 24 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. The remaining samples within the first 24 hours will allow for a 30-minute window.
6 Pain will be assessed with the visual analog scale
7 Imaging with CT scan will occur within six weeks of NanoPac administration, at three months post-injection, and at end-of-study (six months after NanoPac injection). Should the subject withdraw from the study at any time, a 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 SOC and all resulting images will be collected for the subject's record.
8 Screening will occur up to four weeks prior to injection

### 3.4.2 Schedule of Events Table – Second Phase Subjects

| | Screening[3, 8] | Day 1 (Injection) | Week 2 | Week 4 (1 Month) | Week 6 | Week 8 (2 Months) | Week 12 (3 Months) | Week 24 (6 Months) | Week 28-30 (phone call) |
|---|---|---|---|---|---|---|---|---|---|
| **Informed Consent** | X | | | | | | | | |
| **History[1]** | X | | | | | | | | |
| **Concomitant therapy** | X | X | X | X | X | X | X | X | |
| **Physical Exam** | X | X | X | X | X | X | X | X | |
| **ECOG[2]** | X | X | X | X | X | X | X | X | |
| **Pain Assessment[6]** | X | X | X | X | X | X | X | X | |
| **Vital Signs** | X | X | X | X | X | X | X | X | |
| **Clinical Laboratory Tests (section 7.2.1)** | X | X | X | X | X | X | X | X | |
| **PK Samples[5]** | | X | X | X | X | X | X | X | |
| **Imaging[7]** | X | | | | | | X | X | |
| **NanoPac[4]** | | X | | X | | | | | |
| **Adverse Events** | | 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 NanoPac injection may be performed when platelets ≥ 75 x $10^9$/L and absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L.
4 Prophylactic antibiotics will be administered prior to NanoPac injection; NanoPac will be administered by endoscopic ultrasound-guided fine needle injection
5 PK Samples will be drawn prior to injection and at 1 and 2 hours post-dose, and at all other study visits. PK samples on the injection days will allow for a 10-minute window.
6 Pain will be assessed with the visual analog scale
7 Imaging with CT scan will occur during the Screening period (prior to NanoPac administration), and at three and six months post-first-injection. Should the subject withdraw from the study at any time, a 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 SOC and all resulting images will be collected for the subject's record.
8 Screening may occur up to four weeks prior to injection

### 3.4.3 Schedule of Events Table – Third Phase Subjects

| | Screening[3, 8] | Day 1, Weeks 4 and 8 (Injection) | Weeks 2, 6, 10 | Week 12 (Injection) | Weeks 14, 16, 20 | Week 24 (6 Months) | 9 Months (Final Study Visit) |
|---|---|---|---|---|---|---|---|
| **Informed Consent** | X | | | | | | |
| **History[1]** | X | | | | | | |
| **Concomitant therapy** | X | X | X | X | X | X | X |
| **Physical Exam** | X | X | X | X | X | X | X |
| **ECOG[2]** | X | X | X | X | X | X | X |
| **Pain Assessment[6]** | X | X | X | X | X | X | X |
| **Vital Signs** | X | X | X | X | X | X | X |
| **Clinical Laboratory Tests (section 7.2.1)** | X | X | X | X | X | X | X |
| **PK Samples[5]** | | X | X | X | X | X | X |
| **Blood for FCM[9]** | | X | | X | | X | |
| **Imaging[7]** | X | | | X | | X | X |
| **NanoPac[4]** | | X | | X | | | |
| **Adverse Events** | | 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 NanoPac injection may be performed when platelets ≥ 75 x $10^9$/L and absolute neutrophil count (ANC) ≥ 1.5 x $10^9$/L.
4 Prophylactic antibiotics will be administered prior to NanoPac injection; NanoPac will be administered by EUS-guided fine needle injection
5 PK Samples on injection days will be drawn prior to injection and at 1 and 2 hours post-dose; PK samples will also be obtained at all other study visits. PK samples on injection days post-injection will allow for a 10-minute window around the samples.
6 Pain will be assessed with the visual analog scale pre-and post-injection on injection days.
7 Imaging with CT scan will occur at the time of Screening, prior to NanoPac administration, at three months post-first-injection but prior to final injection, at three months following final injection (at Week 24), and at end-of-study (9 months after first NanoPac injection). Should the subject withdraw from the study at any time, a 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 SOC and all resulting images will be collected for the subject's record.
8 Screening may occur up to 4 weeks prior to injection
9 Blood sample for flow cytometric analysis will be taken prior to each injection and again at the Week 24 visit.

# 4 DATA MANAGEMENT

## 4.1 Data Collection and Database Construction

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 Inc. (Alimentiv). All participants will be trained in the use of the application, and the training documented prior to each site being given access to the system.

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.

The data management processes are outlined in the project specific Data Management Plan (DMP). DMP and all related documentations are on file at Alimentiv and are identified by the project code NA03NAE.

All programming will be performed in SAS EG 8.3 Update 7.

## 4.2 Coding

Adverse Events and medical history will be coded in MedDRA version 20.0 and signed off by US Biotest, Inc. All concomitant medications will be coded using WHO Drug Dictionary version March 1, 2017. All coding will be reviewed and signed off by the Medical Monitor or designee prior to data base lock.

## 4.3 Pharmacokinetics (PK) Data

The PK analysis of plasma paclitaxel concentration will be performed by Covance Inc. The concentration data will be provided to Alimentiv in Excel data sheets to be read into SAS system for descriptive summaries.

For Dose Escalation Phase subjects, PK parameters AUC, Cmax, and Tmax within 24 hours of injection day will be calculated by Alimentiv using the plasma paclitaxel concentration data provided by Covance Inc.

## 4.4 Adverse Events of Special Interest

Following AEs are of special interest to the sponsor and will be analyzed separately:

> Vomiting, Peritonitis, Retroperitoneal bleeding, Abscess formation, Fistula formation, Gastrointestinal bleed, Neutropenia, Abdominal pain, Pancreatitis, Neutropenic fever, Sepsis, Thrombocytopenia, Anemia.

After all AEs are recorded in EDC, the sponsor will review the AE list and highlight all AEs of Interest. Alimentiv will conduct the analysis according to Sponsor's selection.

# 5 CHANGE TO ANALYSIS AS OUTLINED IN THE PROTOCOL

According to Section 10.4.11 of the Protocol, an exploratory analysis is planned for PK parameters AUC， $C_{max}$, and $T_{max}$ within 24 hours of the injection:

> Pharmacokinetic (PK) parameters (i.e., AUC, Cmax, Tmax) will be calculated based on the plasma concentration data for the first 24 hours.

After the Protocol was updated to Version 7 (March 25th, 2020), all subjects of the Second Phase and Third Phase will have three PK samples drawn at injection day:

> PK samples will be drawn prior to NanoPac injection, and then 1- and 2-hours post-injection.

For subjects of the Second and the Third Phase, because of only three concentrations (one pre-dose and two post dose) the calculation and analysis of AUC, $C_{max}$, and $T_{max}$ are not applicable and will not be conducted. Their concentration data will still be summarized and listed.

# 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

As there are no formal inferential statistical analyses planned, the sample size estimates below are provided for informational purposes only to help with decision-making around the cohort size and the rarity of events that could be detected.

Since a purpose of the study is dose-finding, the incidence of DLTs would be an appropriate endpoint for the sample size consideration. If a particular adverse event is known to occur in only 5% of subjects, there is a 26.5% chance it will appear in a particular cohort of 6 subjects, and a 60.3% chance it will occur during the study of 18 subjects. If the event only occurs in 1% of patients, there is only a 6% chance it will appear in a given 6-subject cohort, and a 16.5% chance it will be observed in the entire escalation phase.

The rationale to expand Second Phase to 22 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. With 22 subjects the probability of detecting the 0.1 event rate is 90.2% as well as some probability of detecting much rarer events (19.8% probability of detecting an event with a base rate of 0.01, and 67.6% probability of detecting an event with a 0.05 base rate).

The additional of up to 30 subjects in the third phase and the total number of subjects (i.e. 65) across all three phases increases the probability of detection proportionally as can be seen in the table below. Calculations were performed in nQuery version 8.5.1.0, procedure POC2-1 “confidence interval for probability of observing a rare event”.

Probability of Observing a Rare Event

| | Rare Event Frequency | | |
|---|---|---|---|
| Sample Size | 0.1 | 0.05 | 0.01 |
| 12 | 71.8% | 46.0% | 11.4% |
| 22 | 90.2% | 67.6% | 19.8% |
| 30 | 95.8% | 78.5% | 26.0% |
| 65 | 99.9% | 96.4% | 48.0% |

The table assumes that each subject has an equal probability of having the adverse event, and so could be conservative, if there is any dose related effect; the actual dose given increases across the phases.

## 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

In order 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 value xx.
- All "> xx" lab results will be converted to 1.01 * xx. The adjustment is +1% of value 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 paclitaxel concentration in this study, all BLQ values will be set to LLOQ / 2.

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 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).

| Outcome | Calculation | Comment |
|---|---|---|
| Baseline value | Value reported prior to treatment injection | If multiple values collected prior to treatment initiation, non-missing value closest to the date/time of treatment injection is considered baseline |
| Change from Baseline | Value collected at time point (Visit) – Baseline value | |
| % Change from Baseline | = 100 * Change from Baseline / Baseline value | It will be calculated for tumor markers CEA and CA19-9 |
| Study Day | = the days from Day 1 (the First Injection Date) to the event date<br>= Date of Event – Date of Day 1 + 1, if the event occurs on or after Day 1,<br>= Date of Event – Date of Day 1, if the event occurs before Day 1 | |
| Time in Trial (days) | = Study completion/withdrawal date – date of informed consent date + 1 day | |

| Outcome | Calculation | Comment |
|---|---|---|
| Duration from Initial Diagnosis to Screening | = Date of Screening Visit – Date of Diagnosis + 1<br>= Date of Screening Visit – Scan Date of Target Lesion + 1 | |
| Disease Progression | = Yes, if the subject ‘s disease status is determined to be progressive disease by any imaging modality after treatment injection;<br>= No, otherwise | Disease status is assessed by investigator and recorded in EDC’s CT scan or additional imaging forms |
| Overall Survival (OS) | = the days from Day 1 (Injection Date) to the date of death if the subject died<br>= the days from Day 1 (Injection Date) to the end of study date or the early withdrawal date | Censor data will be included in Survival Analysis |
| Survival Time from Diagnosis | = the days from diagnosis to the date of death if the subject died | |
| Disease Progression as per RECIST | = Yes, if there is at least a 20% increase in the sum of the longest dimension of all target lesion(s), and with an absolute increase of at least 5 mm | |

| Outcome | Calculation | Comment |
|---|---|---|
| Progression-Free Survival (PFS) / Time to Disease Progression | = the days from Day 1 (Injection Date) to the date that the subject experienced disease progression and/or death<br>= the days from Day 1 (Injection Date) to the end of study date or the early withdrawal date, if the subject did not experience disease progression or death | Censor data will be included in Survival Analysis |
| Reduction in Pain | = Pain score on Day 1 before injection – Pain score post treatment | |
| Tumor Volume | = $1/6 * \pi * (d_1 * d_2 * d_3)$, if three tumor diameters $d_1$, $d_2$, and $d_3$ are recorded<br>= $1/6 * \pi * (d_1^2 * d_2)$, if only two tumor diameters $d_1$ and $d_2$ are recorded, where $d_1 \geq d_2$<br>= $1/6 * \pi * (d_1^3)$ if only one tumor diameter $d_1$ is recorded. | |
| $C_{max}$ | = the largest paclitaxel concentration value within 24 hours of each injection | It is only calculated for dose escalation subjects |
| $T_{max}$ | = the earliest time that paclitaxel concentration reaches $C_{max}$ | It is only calculated for dose escalation subjects |
| AUC | = Area under the concentration curve from hour-0 to hour-24 | It is only calculated for dose escalation subjects |

| Outcome | Calculation | Comment |
|---|---|---|
| Treatment Emergent Adverse Event (TEAE) | = No, if onset date/time of AE is before the date/time of NanoPac injection<br>= Yes, otherwise | According to conservative rule, all AEs that cannot be determined as started before NanoPac injection will be considered as TEAE |
| TEAE at 3-month Period | = Yes, if TEAE onset data/time is on or before the 3-month follow-up visit<br>= Yes, if the subject does not attend 3-month follow-up visit but TEAE onset date/time is within 3 months (91 days) after first injection<br>= No, otherwise | |
| TEAE at 6-month period | = Yes, if TEAE onset data/time is on or before the 6-month follow-up visit<br>= Yes, if the subject does not attend 6-month follow-up visit but TEAE onset date/time is within 6 months (183 days) after first injection<br>= No, otherwise | |

| Outcome | Calculation | Comment |
|---|---|---|
| TEAE within 4-week Post-Treatment | = No, if onset date of the TEAE is after the date of Week 4 Visit, for the subjects from Dose-escalation Phase and attended Week 4 Visit<br>= No, if onset date of the TEAE is after Day 28, for subjects from Dose-escalation Phase but did not attend Week 4 Visit<br>= No, if onset date of the TEAE is after the date of Week 8 Visit, for subjects from Second Phase and attended Week 8 Visit<br>= No, if onset date of the TEAE is beyond 28 days after the second injection, for subjects from Second Phase but did not attend Week 8 Visit<br>= No, if onset date of the TEAE is after the date of Week 16 Visit, for subjects from Third Phase and attended Week 16 Visit<br>= No, if onset date of the TEAE is beyond 28 days after the last injection, for subjects from Third Phase but did not attend Week 16 Visit<br>= Yes, otherwise | According to conservative rule, all TEAEs that cannot be determined as onset beyond 4 Weeks after last treatment are considered as onset within 4-week post treatment period |

## 6.5 Analysis Population

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

## 6.6 Interim Analysis/ Data Monitoring

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 dose escalation cohorts.

## 6.7 Analysis Methods

All calculations and analyses will be performed using SAS EG 8.3 Update 7 at Alimentiv Inc. in London, Canada. Continuous data will be summarized via PROC MEANS - mean, standard deviation, median, and range, while categorical data will be presented as counts and percentages (or proportions) via PROC FREQ for the descriptive displays.

All outcomes will be summarized by cohort (i.e., dose level), and visit, if applicable.

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 injection and visit structures of the three study phases, i.e., dose escalation, Second Phase, and Third Phase, all study completion/discontinuation, safety and efficacy data will be summarized separately by study phase. All other summaries, i.e., baseline data and medical history, will be presented by cohort, i.e., NanoPac dose level.

## 7.1 Study Subjects

### 7.1.1 Patient Disposition

All enrolled and treated subjects will be accounted for. All early discontinuations will be summarized by primary reason of discontinuation.

Time in trial will also be summarized.

### 7.1.2 Demographics and Baseline Characteristics

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

### 7.1.3 Medical and Surgical History

Medical history will be coded in MedDRA and presented in a by cohort table by System Organ Class (SOC) and Preferred Term (PT).

### 7.1.4 Pregnancy Test

Pregnancy test will be conducted at Screening Visit. The date of pregnancy test and test result will be listed.

### 7.1.5 NanoPac Administration

All NanoPac administration data, including administration date, time, dose level (mg/mL), study phase, tumor diameters measured by ultrasound, tumor volume, calculated NanoPac volume to be administrated (mL), actual volume (mL) and actual dose (mg) administrated, will be listed.

## 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. No statistical inference will be made for primary endpoint.

All Second Phase and Third Phase data will be summarized separately due to the different visit structures and the extra study treatment.

### 7.2.1 Adverse Events

Only treatment emergent adverse events (TEAEs) will be summarized. Three sets of TEAE summaries will be prepared for: All TEAEs, TEAEs onset within 4 weeks after treatment completion (i.e. Week 4 for dose escalation subjects, Week 8 for second phase subjects, and Week 16 for third phase subjects), TEAEs onset within the 3-month follow-up period, and TEAEs onset within the 6-month follow-up period. For each set, summaries will be provided by dose level cohort, and include:

- Brief summary of TEAEs - include the total number of TEAEs, serious TEAEs, and death
- TEAEs by MedDRA System Organ Class (SOC) and Preferred Term (PT)
- TEAEs by MedDRA SOC, PT, and severity
- TEAEs by MedDRA SOC, PT, and relationship to NanoPac treatment
- TEAEs by MedDRA SOC, PT, and outcome
- Serious TEAEs by MedDRA SOC, and PT

Adverse events of special interest will be presented, separately, by dose level cohort, SOC and PT.

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

All TEAEs will be listed by subject. Death and other serious TEAEs will be listed separately.

### 7.2.2 Laboratory Assessments

For biochemistry, hematology and coagulation, laboratory assessments with quantitative results, including assessments at each visit and change from baseline at post-baseline visits, will be summarized by treatment group, and visit for each test. For urinalysis, specific gravity and pH will be summarized.

Each no-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.

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, total bilirubin, direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), total protein, albumin, triglycerides, cholesterol, and uric acid.

Hematology: Red blood cell count (RBC), hemoglobin (Hgb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), white blood cell count (WBC) including differential, reticulocyte count, and platelet count.

Coagulation: Prothrombin time (PT) and activated partial thromboplastin time (PTT).

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. The date of physical examination will be provided in by-subject data listing.

### 7.2.4 Vital Signs

Height at screening visit and other vital signs (weight, BMI, systolic and diastolic blood pressure, heart rate, and temperature) at each visit will be summarized by treatment cohort.

Change of vital signs from baseline values will be summarized for all post-dose visits.

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

## 7.3 Secondary Outcomes

### 7.3.1 Plasma Paclitaxel Concentration

For subjects in the dose escalation phase, PK samples for paclitaxel concentration are collected on Day 1 prior to injection and at 1, 2, 4, 6, and 24 hours after NanoPac injection, as well as at all other study visits. Subjects in second phase and third phase of the study will provide PK samples at pre-injection, and at 1 and 2 hours post injection on both injection occasions (Day 1 and Week 4), and at all study visits.

For dose escalation subjects, PK parameters AUC, $C_{max}$, and $T_{max}$ calculated from injection day concentration data will be summarized by dose level cohort and scheduled time point.

All numeric paclitaxel concentration data above the Lower Limit of Quantitation (LLOQ), i.e. the detectable limit, will be tabulated by cohort using the arithmetic mean, standard deviation, coefficient of variation, median, and range. All BLQs (Below the Limit of Quantitation) will be presented as “BLQ” in the by-subject data listing.

For dose escalation phase subjects, graphs of Day 1 individual and mean paclitaxel concentration data will be generated.

For subjects of the second phase and third phase, paclitaxel concentration data of all injections (Day 1, Week 4, Week 8, and Week 12) will be graphed.

Pharmacokinetic (PK) parameters AUC and $C_{max}$ will be summarized using the arithmetic and geometric means, standard deviation, median, range, and % CV (coefficient of variation). $T_{max}$ will be summarized by the median and range of its values.

### 7.3.2 Tumor Responses

Tumor responses as per RECIST will be measured by CT scan or other imaging method within six weeks prior to the injection procedure, 3-month follow-up visit, and 6-month follow-up visit in all subjects, and 9 month follow-up visit in the third phase subjects. The size (longest diameter and calculated volume). The size of target lesion and change of size from baseline will be tabulated by dose level cohort. Disease status (complete response, partial response, stable disease, progressive disease, unevaluable) will be summarized using counts and frequencies by dose level cohort.

Disease progression (Yes/No) as defined in section 6.3 will be summarized using counts and frequencies. Survival analysis will be conducted for analysing the overall survival and the progression-free survival, and the Kaplan-Meier estimates of median, 25$^{th}$ and 75$^{th}$ percentiles of the survival time will be provided by dose level cohort. Overall survival and progression-free survival curves will be presented in Kaplan-Meier plots.

All CT scan and additional imaging data will be listed.

### 7.3.3 VAS Pain Assessment

Pain will be assessed using the visual analog scale (VAS) at all study visits, and will be conducted prior to and following the injection day(s) of NanoPac administration.

VAS pain assessment scores, including scores at visit and reduction in pain scores, will be summarized by dose level cohort.

### 7.3.4 Tumor Marker CA19-9

Serum CA19-9 levels will be obtained at Screening Visit, on the day of NanoPac administration prior to injection (Study Day 1), and at all other study visits.

CA19-9 concentration at visit, changes from baseline, and percent change from baseline will be summarized by dose level cohort and visit. Doubling of CA19-9 concentration, i.e. Percent Change ≥ 100% will be flagged in the data listing.

### 7.3.5 Tumor Marker CEA

Serum carcinoembryonic antigen (CEA) levels will be obtained at Screening Visit, on the day of NanoPac administration prior to injection (Study Day 1), and at all other study visits.

CEA concentration at visit, changes from baseline, and percent change from baseline will be summarized by dose level cohort and visit. Doubling of CEA concentration, i.e. Percent Change ≥ 100% will be flagged in the data listing.

## 7.4 Other Outcomes

### 7.4.1 Eastern Cooperative Oncology Group (ECOG)

Eastern cooperative oncology group (ECOG) performance status scale will be obtained at all study visits.

ECOG scale will be summarized as frequencies by treatment group and visit. The scale will also be summarized using a shift table from baseline to post-baseline visit.

### 7.4.2 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 (WHO) Drug Dictionary

(WHODD). The summaries will be provided for medications prior to and following the injection separately.

### 7.4.3 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.