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BioMed Valley Discoveries

BVD-CNV2

Phase I safety study of intratumoral injection of *Clostridium novyi*-NT spores in patients with treatment-refractory solid tumor malignancies

Statistical Analysis Plan

209491

Version 2.0 [Final]
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Title:	**Statistical Analysis Plan - Phase I safety study of intratumoral injection of *Clostridium novyi*-NT spores in patients with treatment-refractory solid tumor malignancies**		
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SPONSOR / 3RD PARTY VENDOR Signatures

Signature below indicates that you have reviewed the document for clarity, completeness and consistency and approve it.

Signature:

Signature: PPD Date: 17-Mar-2017

Print Name: PPD Title: PPD

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
C. novyi-NT	*Clostridium novyi*-Non Toxic
CBC	Complete Blood Count
CR	Complete Response
CRP	C-Reactive Protein
CT	Computed tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group (performance status scale)
eCRF	Electronic Case report form
FAS	Full Analysis Set
HR	Heart Rate
IMP	Investigational Medicinal Product
IT	Intratumoral
IV	Intravenous
LDH	Lactate dehydrogenase
MCH	Mean Cell Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
msec	Millisecond
MTD	Maximum tolerated dose
MRI	Magnetic Resonance Imaging
N	Number of Observations
NCI	National Cancer Institute
NTEAE	Non-Treatment Emergent Adverse Event
PD	Progressive Disease
PR	PR interval of ECG
PT	Prothrombin time
PTT	Partial thromboplastin time

QRS	QRS interval of ECG
QTcB	QT interval corrected for heart rate of ECG using Bazett's formula
QTcF	QT interval corrected for heart rate of ECG using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RBC	Red Blood Cell
RR	Time duration between two consecutive R waves of the ECG.
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
SOFA	Sequential Organ Failure Assessment score
SpO_2	Oxygen saturation by pulse oximetry
WBC	White blood cell
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) is to provide details on the planned statistical methodology for analysis of the study data, and outlines the statistical programming specifications for the tables, listings and figures. It describes the data collected and the planned analysis to assess safety and efficacy as well as the anticipated data transformations and manipulations, and other details of the analyses not provided in the study protocol.

This SAP is based on BVD-CNV2_IT Protocol_A2 dated on 02Sep2014 and CRFv 5.0 dated on 17Jan2017 .

2 Study Objectives

- To determine the safety profile, dose limiting toxicities (DLT), and maximum tolerated dose (MTD) of *Clostridium novyi*–NT (*C. novyi*-NT) in humans with treatment-refractory solid tumor malignancies when administered as a single intratumoral (IT) injection.
- To document preliminary anti-tumor activity of both the injected tumor and an overall response after administering a single IT injection of *C. novyi*-NT in humans with treatment-refractory solid tumor malignancies. The evaluation of anti-tumor activity will include: 1) a response for the injected tumor and, 2) an overall response.
- To study the presence of circulating *C. novyi*-NT spores after administration as a single IT injection to humans with treatment-refractory solid tumor malignancies.
- To measure the host immune and inflammatory response to *C. novyi*-NT administered as a single IT injection in humans with treatment-refractory solid tumor malignancies.

3 Investigational Plan

3.1 General Considerations - Summary of Study Design

Patients who provide informed consent will be screened within 21 days prior to *C. novyi*-NT spore administration. Patients will report to the clinical site within 24 hours of Day 0 to reconfirm eligibility and for baseline assessments. Eligible patients will be admitted and enrolled sequentially into a dosing cohort as described in the section 3.6 of this SAP.

Spore dose administration will occur on Day 0, and patients will remain in-house for observation through Day 7 (a total of 8 days). Patients will return to the clinical site for follow-up visits at the following time points: Days 11, 14 (Week 2), 18, 21 (Week 3), 25, 28 (Week 4) and 2, 4, 8, and 12 months post-dose. Assessment of safety, efficacy, and

disposition of *C. novyi*-NT will be performed at scheduled time points throughout the study.

A standard "3+3" dose escalation will be used. The following definitions and rules will be employed:

- Toxicity Criteria will be those listed in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0, which is available at http://ctep.cancer.gov/reporting/ctc.html
- An adverse event (AE) of Grade 3 toxicity lasting three (3) days or longer or Grade 4 toxicity of any duration that is assessed to be at least possibly related to study agent will be considered a DLT. Signs and symptoms of *C. novyi*-NT infection which are associated with a Sequential Organ Failure Assessment (SOFA) score > 5 that require invasive intervention including percutaneous drainage of an abscess or that result in prolonged hospitalization (> 5 days) will also qualify as DLTs.
- DLT assessment period is defined as 4 weeks after dosing of the last patient in a cohort.
- Toxicity will be assessed from administration of study agent up to 8 weeks.
- The dose escalation rules, as outlined in Table 1, will be applied.
- Additional patients will be enrolled at the MTD to achieve a total of six patients at that dose level if fewer than six patients were treated previously at that dose.
- Doses will be increased in successive cohorts until the MTD is reached or until complete germination and tumor regression occurs, making higher doses unnecessary.
- The MTD (or dose at which complete germination and tumor regression occurs) will be the recommended dose for future Phase II *C. novyi*-NT IT administration studies.

Table 1: Dose Escalation Decision Rules

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	The dose escalation will proceed. Three patients will be enrolled at the next dose level
1 out of 3	Three more patients will be enrolled at this dose level • If zero of three patients experience a DLT, then dose escalation will proceed to the next dose level. • If one or more patients suffer a DLT, then dose escalation will stop. This dose will be the maximally administered dose (i.e., the minimum intolerated dose). Three additional patients will be entered at the next lowest dose level (i.e., the MTD) if only three patients were treated previously at that dose.
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (i.e., the minimum intolerated dose). Three additional patients will be entered at the next lowest dose level (i.e., the MTD) if only three patients were treated previously at that

	dose.

Patients will be monitored for infectious complications or other treatment – emergent adverse events with the objective of deciding if and when to initiate antibiotics and/or additional interventions. Patients will be followed with serial imaging studies for therapeutic response. The first patient in a cohort will be observed for a minimum of 2 weeks before treating the next patient, while there will be no required minimum observation interval before subsequent patients in the same cohort can be dosed. Patients will be observed for a minimum 4-week interval between cohorts. The planned follow-up period for every patient who receives *C. novyi*-NT will be 1 year.

3.2 Study Endpoints

Safety

- Changes from the pre-study physical examination findings
- Vital signs measurements (blood pressure, heart rate, oral temperature, and respiratory rate, body weight)
- Oxygen saturation by pulse oximetry (SpO2)
- Sequential Organ Failure Assessment (SOFA) score
- Eastern Cooperative Oncology Group (ECOG) Performance Grade assessments
- Laboratory assessments (Complete Blood Count (CBC) with differential, serum chemistry, coagulation, C-reactive protein (CRP), cultures from blood, and when available, tumor biopsy and abscess samples) at baseline and throughout the study period and changes from baseline
- CT/MRI imaging as scheduled on Day 7 and unscheduled imaging to investigate the possibility of abscess formation or to explore the unexpected toxicity
- Adverse events and Serious AE (SAE) count and rate, including symptoms of infection
- Antibiotic use (name, route, initiation date, and whether based on temperature or investigator's judgment or as per mandated in the protocol)
- Use of concomitant medications throughout the study period
- Telephone contact and survival information

Efficacy

- Tumor size of the targeted injection lesion and other targeted metastatic lesions, measured by Computed Tomography (CT) scans or Magnetic Resonance Imaging (MRI) scans
- Response Evaluation Criteria in Solid Tumors (RECIST) assessment on the injection lesion
- Overall RECIST response

Pharmacodynamics

- Serum banking to assess immune response: C-Reactive Protein (CRP), whole blood and serum samples, pre-dose injected tumor sample, post-dose injected and non-injected tumor samples, abscess material, and selected cytokines as markers of systemic inflammation
- Blood cultures, abscess material, and post-dose injected and non-injected tumor samples (when available) for detection of presence or absence of *C. novyi*-NT.

3.3 Interim Analysis

No interim analysis is planned.

3.4 Study Population

The study population is patients with solid tumor malignancies that are refractory to standard therapy or without available standard therapy. Men and women of all races and ethnic groups are eligible for this trial. Eligible patients must meet all the inclusion criteria and none of the exclusion criteria as stated in the protocol.

3.5 Sample size

Three to six (3 to 6) patients per cohort will be enrolled until the MTD is reached or until complete germination and tumor regression occurs.

3.6 Treatment Assignment

Patients will receive treatment with *C. novyi*-NT at a dose corresponding to their assigned cohort, starting with Cohort 1. The initial planned dosing groups are summarized Table 2 below. Based on initial patient tolerability findings and reported toxicities experienced during the study, higher dosing groups will be incorporated. *C. novyi*-NT spores will be administered as an IT injection into the target lesion. Patients will be given IV hydration after dosing.

Table 2: *C.* novyi-NT spores Planned Dose Levels

Cohort	Number of Patients	Dose ($\times 10^4$ spores)
1	3 to 6	1
2	3 to 6	3
3	3 to 6	10
4	3 to 6	30
5	3 to 6	100
6	3 to 6	300

3.7 Blinding

Not applicable. Patients will be enrolled sequentially into a given dosing cohort.

3.8 Eligibility Evaluation and Baseline Characteristics

3.8.1 Informed Consent

Each patient's informed consent will be taken at screening.

Separate consent will be requested to obtain/retain (for genetic and/or not genetic testing) of blood, serum, abscess material, archived tumor tissue and biopsy samples (when available). In addition, a separate consent for photograph collection from injected tumor and the storage for future use of information/data resulting from analysis of patient's samples will be requested.

3.8.2 Inclusion/Exclusion

Patient eligibility will be assessed at screening.

3.8.3 Blood Type

At Day -1 to Day 0 pre-dose patient blood type will be recorded.

3.8.4 Pregnancy Test

In female patients, with childbearing potential, serum pregnancy testing will be performed at screening and Day -1 to Day 0 pre-dose.

3.8.5 Demographics and Medical History

Medical history information will be collected at screening and Day -1 to Day 0 pre-dose.

Demographic information will be collected at screening.

The following demographic information will be recorded:
- Derived age at screening
- Sex (male or female)
- Race (American Indian or Alaska Native, White, Black, Asian, Native Hawaiian or Other Pacific Islander, Other with specified)
- Ethnicity (Hispanic/Latino, Not Hispanic/Latino, Other with specified)

3.8.6 Brain MRI

A brain MRI will be conducted at screening to evaluate for metastatic disease.

3.8.7 Echocardiogram (ECHO)

An echocardiogram will be performed at screening.

3.8.8 12-Lead Electrocardiograms (ECG)

12-lead ECGs will be performed at screening and Day -1 to Day 0 pre-dose. Information collected will include date and actual time of assessment, whether ECG was normal, and the recorded values of Bazett (QTcB) msec, Fridericia (QTcF) msec, RR (msec), PR (msec), QRS (msec) and HR.

3.8.9 Prior Cancer History

Prior cancer history will be captured on the eCRF including information on:

- Diagnosis: date of initial diagnosis, histology, primary site at diagnosis, initial staging (tumor size, lymph nodes, metastatic), date of initial diagnosis of metastatic, current extent of disease.

- Diagnostic and therapeutic procedures: date of procedure, purpose of the procedure, and any findings.

- Prior Systemic Anticancer Therapy: regimen number, drug, intent, start and stop date, dose amount, unit, number of cycles, frequency of cycles, best response, reason for discontinuation, date of progression.

- Prior Cancer Radiotherapy: regimen number, location, field of treatment, intent, date of first and last fraction, total dose, and best response.

3.9 Safety Assessments

3.9.1 Adverse Events

An Adverse Event (AE) is any new untoward medical occurrence or worsening of a pre-existing medical condition in a clinical investigation subject administered an investigational medicinal product, even if it does not have a causal relationship with that product. Any unfavorable or unintended sign, symptom, or disease temporally associated with the use of the study agent, whether or not it is considered study agent-related will be considered an AE. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of the study agent.

Monitoring for AEs will occur from the time of informed consent until the patient completes the study. The post-dosing observation period will begin with an 8-day inpatient stay (Days 0 to 7). This inpatient stay can be extended and requires that at least 2 days elapse from the resolution of any signs of infection or serious AEs (SAEs) before discharge.

All Grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as AEs. A Grade 1 or 2 clinical laboratory abnormality should be reported as an AE only if it is considered clinically significant by the investigator.

All AEs, including observed or volunteered problems, complaints, or symptoms from the time of informed consent until 8 weeks post-dose are to be recorded, regardless of causality. After 8 weeks post-dose, only AEs with possible, probable, or definite relationship to the study agent will be reported with follow up as noted above for AEs within the first 8 weeks post treatment.

Adverse events will be evaluated against the baseline history and physical examination and intensity graded using the NCI CTCAE, Version 4.0, which can be accessed at http://ctep.cancer.gov/reporting/ctc.html.

All AEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved or stabilized, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the PI or local investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up.

A Serious Adverse Event (SAE) is any AE, occurring at any dose and regardless of causality that:
• Results in death.
• Is life-threatening. Life-threatening means that the patient is at immediate risk of death from the reaction as it occurs; it does not include a reaction which hypothetically might cause death had it occurred in a more severe form.
• Requires inpatient hospitalization or prolongation of pre-existing hospitalization except when an extended inpatient hospitalization is required to manage local tumor inflammation or abscessation in the injected tumor lesion site. This does not include scheduled admissions for study-related issues (e.g., inpatient IT injection of study agent).
• Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
• Is a congenital anomaly/birth defect.
• Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, may jeopardize the patient and may require an intervention (medical or surgical) to prevent one of the outcomes listed above as a definition of SAE (e.g., bronchospasms).

All SAEs will be recorded from signing of informed consent until 8 weeks after study agent administration. After 8 weeks post-dose, only SAEs with possible, probable, or definite relationship to the study agent will be reported.

3.9.2 Concomitant Medications

Prior and concomitant medication use will be recorded for the 4 weeks prior to screening until the final study visit. Antibiotic usage is prohibited during the 14 days prior to study

agent administration (Day 0). Details will include: drug, indication, dose, dose unit, frequency, route, start date and time, stop date and time, ongoing.

Initiation of antibiotic use post-dose will be recorded including name of medication, route, initiation date, and whether the use was based on temperature, investigator's judgment or as per mandated in protocol.

3.9.3 Laboratory Tests

Routine laboratory tests (CBC with differential, serum chemistry panel, CRP, at screening; Day 0; 1 hour and 12 hours post-dose; Days 1 to 7 (24 to 192 hours post-dose); at follow-up weeks 2 and 3 (±1 days) and 4 weeks to 12 months. Assessments taken Days 1 to 7 will be performed once daily beginning 24 hours post-dose. Follow-up assessments 4 weeks to 12 months will occur at 28 days and 2, 4, 8 and 12 months (±2 days) after dosing. Anerobic culture for *C. novyi*-NT) will be performed at above time points except at screening visit.

The results of the CT/MRI scans, tumor biopsy for cultures will be listed by dose level for each patient.

Laboratory tests for magnesium, phosphorous, uric acid and coagulation parameters prothrombin time (PT) and partial thromboplastin time (PTT) will be measured at screening; Day 0; 1 and 12 hours post-dose; Days 1 to 7; at follow-up weeks 2, 3, 4 and months 2, 4, 8 and 12. These laboratory tests will be measured once daily on Days 1 to 7. Laboratory results will be summarized using Systeme International (SI) units, as appropriate.

Table 3: Laboratory Evaluations

Category	Parameter
Hematology	Red Blood Cell (RBC),White Blood Cell (WBC) Hemoglobin Mean Corpuscular Volume (MCV), Mean Cell Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC) Platelet Count, Neutrophils, Lymphocytes, Monocytes Eosinophils, Basophils
Serum Chemistry	Glucose, Uric Acid*, BUN, Creatinine, Calcium, Sodium Potassium, Chloride, Magnesium*, Phosphorous*, CRP*, Total Protein Albumin, Bilirubin, Alkaline Phosphatase, Lactate Dehydrogenase (LDH), Aspartate Aminotransferase (AST) (SGOT), Alanine Aminotransferase (ALT) (SGPT)
Coagulation	Prothrombin time (PT), Partial thromboplastin time (PTT)

(*) parameters will be measured at specified time points.

3.9.4 Vital Signs

The following vital signs will be measured:

- Blood pressure (systolic and diastolic [mmHg])
- Heart rate (beats per minute)
- Oral Body Temperature (°C)
- Respiratory rate (breaths per minute)
- Body weight

Vital signs will be performed at screening; Day -1 to Day 0 pre-dose; at 15, 30, 45, 60, and 90 minutes post-dose; at 2, 3, 4, 8, 12, 16, 20 hours post-dose; Days 1 to 7 every 4 hours beginning 24 hours post-dose (i.e., at 24, 28, 32, 36, 40, 44, 48…192 hours); days 11, 14, 18, 21, 25 (±1 day); and 28 days (1 month) and 2, 4, 8 and 12 months (±2 days) post-dose.

Weight will be collected at Day -1 to Day 0 pre-dose, Days 7, 14, 21 and 28 and months 2, 4, 8 and 12 post-dose.

3.9.5 Oxygen Saturation by Pulse Oximetry (SpO2)

SpO2 will be performed at screening, Day-1 to Day 0 pre-dose and then continuous monitoring will begin on the day of dosing (Day 0) and continue Days 1 to 7.

3.9.6 Sequential Organ Failure Assessment (SOFA)

A SOFA score assessment will be performed Day -1 to Day 0 pre-dose, at 8 and 16 hours post-dose, and on Days 1 to 7 every 8 hours beginning 24 hours post-dose (i.e., at 24, 32, 40, 48…192 hours). SOFA score will be derived as part of the EDC Process.

3.9.7 Eastern Cooperative Oncology Group (ECOG)

ECOG performance scale status will be performed at screening, Day -1 to Day 0 pre-dose, once daily on Days 1 to 7, days 11, 14, 18, 21 and 25 (±1 day), and 28 days (1 month) and 2, 4, 8 and 12 months (±2 day) post-dose. Each patient's ECOG performance will be graded per the table below:

Table 3: ECOG Performance Status Scale

Grade	ECOG
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 self-care but unable to carry out any work

	activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

3.9.8 Physical Examinations

Physical examinations will be performed at screening; Day -1 to Day 0 pre-dose; once daily on Days 1 to 7; days 11, 14, 18, 21 and 25 (±1 day); and 28 days (1 month) and 2, 4, 8 and 12 Months (±2 day) post-dose.

3.9.9 Telephone Contact and Survival

Following the inpatient observation period and during the first 28 days post-treatment patients will receive daily phone interviews on the days when they are not scheduled for a clinic visit to evaluate and catalogue any changes in status. These phone interviews will consist of a review of symptoms of infection, temperature checks and compliance with antibiotic regimen.

After patient discontinuation, every effort will be made to collect survival information, including phone calls on a quarterly basis for 12 months to the patient, patient's relatives or primary oncologist.

3.10 Efficacy Assessments

Tumor response and progression will be evaluated using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1: http://www.eortc.be/recist/).

Objective response will be measured by serial CT or MRI scans of the injected tumor and site of metastatic involvement. Overall response, using CT/MRI scan results, will be based on observation of measurable and non-measurable disease as compared to baseline and nadir in target and non-target lesions per RECIST 1.1 at screening and at follow-up times 1 to 12 months post dose.

3.10.1 Tumor Response

3.10.2 Computed Tomography (CT) or MRI Scans

Objective responses will be measured by serial CT or MRI scans of the chest, abdomen, pelvis, and any other sites of metastatic involvement.

CT or MRI scans will be performed at screening, Day 7, and at follow-up times (28 days, and 2, 4, 8 and 12 months post-dose). However, Day 7 CT/MRI is not used for tumor response assessment. It is used for abscess assessment to see if the patient can be discharged.

3.10.3 Response Evaluation Criteria in Solid Tumors (RECIST)

Tumor evaluation per RECIST including targeted injection lesion response and overall response will be evaluated.

Target lesion measurements will be assessed at Screening, and at Months 1, 2, 4, 8, 12. The injection lesion response and overall response will be evaluated at Months 1, 2, 4, 8, and 12.

Target lesion measurements will record the lesion number, location code, description of lesion, evaluation, days after dose administration, date of evaluation, method of evaluation, and the lesions' longest diameter (cm). The tumor response will categorize the lesion response as one of the following: complete, partial, stable, progressive, or unknown.

3.11 Pharmacodynamics - Correlative Studies

Correlative samples will be collected and stored for up to 5 years. Archived tissue (optional) may be used for correlative studies. Serum samples will be collected for banking at screening; Day 0; 1 and 12 hours post-dose; Days 1 to 7; at follow-up weeks 2, 3, 4 and months 2, 4, 8 and 12. Whole blood samples will be collected for immunological assessments and *C. novyi*-NT detection. When performed, post-injection site abscess material samples will be collected and stored (for up to 5 years). Whole blood samples for banking will be taken on Day -1 to Day 0 pre-dose; Days 1 and 7; at weeks 2 and 3; and 28 days (1 month) and 2, 4, 8, and 12 months post-dose. Whole blood samples for immunological assessment will be taken as banking except no collection on day 1. These blood samples will be used to evaluate the following:

3.11.1 Anti-*C. novyi*-NT Immune and Inflammatory Response

The immune and systemic inflammatory responses during *C. novyi*-NT treatment will be evaluated by serial measurement of CRP, selected cytokines and analysis of selected immune cell populations in blood. C-reactive protein and certain cytokines (IL-6, IL-8, TNF-alpha, etc.) are markers of systemic inflammation. Patient whole blood and serum will be obtained as indicated and, when performed, pre-dose and post-dose tumor samples and abscess material will be collected.

3.11.2 *C. novyi*-NT Detection in Circulation and/or abscess material/post-dose tumor sample

Aerobic blood cultures will be taken at screening and Day -1 to Day 0 pre-dose.

Anaerobic blood cultures and/or abscess material/post-dose tumor sample (when performed) will be assessed to determine the presence from circulation of *C. novyi*-NT.

Anaerobic blood cultures will be taken on Day -1 to Day 0 pre-dose; 1 and 12 hours post-dose; once daily on Days 1 to 7; and at follow-up weeks 2 and 3 and months 1, 2, 4, 8 and 12 post-dose.
Additional aerobic and anaerobic blood cultures may also be performed when clinically indicated.
Tumor biopsy (injected lesion) will be performed on Day -1 to Day 0 pre-dose and tumor biopsy (injected lesion and/or non-injected lesion) will be performed at month 1 (optional) and month 2 (required) post-dose for immunological assessment and tissue banking.

Abscess material post-dose will be collected for culture, immunological assessment and banking, when performed as part of the management of local tumor inflammation and abscessation.

4 STATISTICAL METHODS

4.1 General Considerations

4.1.1 Definition of Analysis Populations

Safety Population

The safety population will include all patients who received any amount of *C. novyi*-NT, the Investigational Medicinal Product (IMP). Patients will be included in the safety analysis according to the dose of IMP received.

Efficacy or Full Analysis Population

The efficacy data set or Full Analysis Set (FAS) will consist of all patients in the safety population who had both, a baseline tumor assessment and at least one post-baseline tumor assessment. Subjects will be included in the efficacy analysis according to the dose of IMP received.

4.1.2 Data Presentations

Data for all enrolled patients who received any amount of IMP will be presented in the data listings. Table summaries will only include those patients that received IMP.

For those listings or data summaries where baseline and change from baseline measurements will be presented, the last observed measurement prior to dosing on Day 0

will be considered the baseline measurement if collecting at both screening and Day -1 to Day 0 pre-dose.

All pre- and post-dose assessments including all unscheduled assessments will be included in the data listings. For pre-dose assessments, the last assessment (including unscheduled) taken for a time point will be used in the data summaries (summary tables, figures, and statistical analysis); for all post-dose time points, the original assessment for any given time point will be used in the data summaries (summary tables, figures, and statistical analysis).

Continuous data will be described using descriptive statistics: number of observations (N), mean, median, standard deviation (SD), minimum and maximum. Frequencies and percentages will be used for summarizing discrete (categorical) data. The denominator for all percentage, unless otherwise specified, will be the number of patients in a given cohort.

Data that are reported as missing will be excluded from all descriptive and non-descriptive data analysis. Observations that are spurious (extreme relative to the majority of the data) will not be altered or removed from any presentation of the data without agreement from the sponsor.

For data listings, all raw data will be reported/displayed exactly as provided. For summaries of quantitative data, the minimum and maximum value will be reported exactly as the raw data are reported; measures of central tendency (means, medians) will be reported to one more decimal place than the raw data; measures of variance (SD) will be reported to two more decimal places than the raw data.

Unless specified otherwise, data collected over time will be listed by cohort, dose level, patient number, and time point (where applicable). Unless specified otherwise, all tables and figures will be presented by dose level. The Summary of Tables, Figures and Listings in the attachment section might be updated later if needed. In this SAP, treatment will refer to any of the following planned categories of *C. novyi*-NT dose level:

- 1 (x 10^4 spores)
- 3 (x 10^4 spores)
- 10 (x 10^4 spores)
- 30 (x 10^4 spores)
- 100 (x 10^4 spores)
- 300 (x 10^4 spores)

4.1.3 Protocol Deviations

A protocol deviation is an unplanned excursion from the protocol that is not implemented or intended as a systematic change.

The separate document with detailed criteria and classification of protocol violations and minor deviations will be provided and finalized before database lock. Potential protocol violations will be identified and reviewed prior to database lock. Any modifications to the criteria will be documented after finalization. Every effort will be made to ensure that decisions will not be influenced by dose level to which the patient has been assigned.

Protocol violations will be listed for each dose level. All minor deviations will be listed.

4.1.4 Data Derivation

4.1.4.1 Imputation of missing or partial AE or concomitant medication dates

The following rules will apply in the situation of missing or partial AE or concomitant medication dates.

For partial start date:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the month is unknown, then:
  - If the year matches the year of the first dose date, then impute the month and day of the first dose date.
  - Otherwise, assign 'January'.
- If the day is unknown, then:
  - If the month and year match the month and year of the first dose date, then impute the day of the first dose date.
  - Otherwise, assign '01'.

For partial end date:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the month is unknown, then assign 'December'.
- If the day is unknown, then assign the last day of the month.

After implementing the rules above, to determine whether AEs (or medications) with missing start or stop dates are pretreatment or on/after treatment the following strategy will be used:

- If the start date and stop date are both missing, then the most conservative approach will be taken and the AE (or medication) is considered to be treatment-emergent (or concomitant).
- If the start date is missing but the stop date is not missing and is after the day of study dose administration, then the most conservative approach will be taken and the AE (or medication) is considered to be treatment-emergent (or concomitant).
- If the start date is missing but the stop date is not missing and is on or before The day of study dose and after the date of signed informed consent, then the AE (or medication) is considered to be pretreatment (or prior).

- If the start date is not missing but the stop date is missing, then the most conservative approach will be taken and medication is considered to be concomitant while the AE is defined by start date.

4.1.4.2 Best overall response

The Best Overall Response is the best confirmed response (CR, PR, SD, PD, NE and unknown) recorded from the start of the study treatment until the disease progression/recurrence or death. Categories include Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) and Unknown (inevaluable).

- Complete Response (CR) upon confirmation at least 4 weeks of first CR before progression
- Partial Response (PR) upon confirmation at least 4 weeks of first PR before progression, but not qualifying for CR
- Stable Disease (SD) upon confirmation at least 8 weeks of first stable or better documented and before progression but not qualifying as CR or PR.
- Progressive Disease (PD) upon confirmation at least 16 weeks of first PD, not qualifying for CR, PR or SD
- Unknown: progression not documented within 16 weeks after the start of the study treatment and no other response category applies.

Best overall response will be derived as follows based on RECIST version 1.1:

Table 4: Best Overall Response Determination

Overall Response first time point	Overall Response subsequent time point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, Otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, Otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, Otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, Otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, Otherwise, NE
NE	NE	NE

CR= complete response, PR= partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
[a] if a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be charged to PR and the best response is PR.

Note: In the case of Stable Disease, measurements must have met the Stable Disease criteria at least once after study entry at a minimum duration of stable disease lasting 8 or more weeks.

4.1.4.3 Nadir

Nadir for injection lesion is defined as the smallest sum of the longest diameters of each injection lesion since start of treatment.

4.2 Patient and Treatment Information

4.2.1 Patient Disposition

The end of study status for each patient stating whether or not they completed the study protocol will be listed. The listing will also include the date of completion or premature discontinuation, the study day patient discontinued, the primary reason for discontinuation, and if applicable, the date and cause of death and whether an autopsy was performed or not.

The number of patients screened, enrolled, treated and the frequency and percentage of patients completing the study, patients withdrawing prematurely, and primary reason for withdrawal will be summarized by dose level.

4.2.2 Analysis Datasets

The number and percentage of subjects in each analysis set will be summarized by dose level. Whether or not each subject was included in each of the analysis data sets will be indicated in a listing.

4.2.3 Informed Consent and Enrollment

A listing will display the date and time the patient signed the informed consent and the date of enrollment. In addition, a listing for optional consents will be displayed for each patient.

- Tumor tissue biopsies (one month after treatment) collection
- Archived tumor tissue collection
- Photograph collection (from injected tumor)
- Storage for future use of samples of blood, and/or tissue for other tests (not genetic)
- Storage for future use of samples of blood, and/or tissue for other tests (genetic)
- Storage for future use of information/data resulting from analysis of patient's samples

4.2.4 Inclusion/Exclusion Review

Whether the patient met all inclusion criteria, none of the exclusion criteria, and any inclusion criteria not met or exclusion criteria met at screening will be listed.

4.2.5 Blood Type Results Pre-dose

Results of the assessment for patient blood type will be listed.

4.2.6 Pregnancy Tests

Whether a female patient is of childbearing potential and results of any pregnancy testing at Screening and Day 0 will be listed.

4.2.7 Demographics

The following demographic information collected at screening will be listed: sex, race, ethnicity, age, body weight, and height at screening.

Descriptive statistics will be calculated by dose level for the continuous variables age, body weight, and height. Frequencies and percentage of patients will be tabulated by dose level for the categorical variables collected at screening: ethnicity, race, and sex.

4.2.8 Medical History and Current Medical Conditions

All relevant medical history and current medical conditions collected at Screening and Day 0 until the start of the IMP will be listed for each patient.

Medical History conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 14.1. The MedDRA preferred term and system organ class of the medical history/condition will also be listed.

The number and percentage of subjects with medical history/current medical condition at the start of IMP administration will be summarized by dose level, system organ class, and preferred term at screening and day 0.

4.2.9 Prior Cancer History

A listing will present the diagnosis, date of initial diagnosis, histology, primary site at diagnosis, initial staging of the tumor size, lymph nodes, and metastasis, date of initial diagnosis of metastasis, and the current extent of disease.

Prior diagnostic and therapeutic procedures for cancer including the procedure, date, purpose, and findings will be presented in a listing.

Prior systemic anticancer therapies, including regiment number, drug, intent, dose, unit, date started and stopped, number of cycles, frequency of cycles, best response, reason for discontinuation, and date of progression will be presented in a listing.

A listing will contain prior cancer radiotherapies, including regimen number, location, radiotherapy field of treatment, intent, date of first and last fraction, total dose, and best response.

4.2.10 Brain MRI

Date of the brain MRI, indication of metastatic disease, and MRI findings and comments will be listed for each patient.

4.2.11 Echocardiogram (ECHO)

The date of the ECHO and whether or not the ECHO met the exclusion criteria will be listed.

4.2.12 Twelve-Lead Electrocardiograms (ECG)

Descriptive statistics will be calculated by dose level for the continuous variables QTcB, QTcF, PR, RR, QRS and HR at screening and Day -1 to Day 0 pre-dose.

Date and time of ECG, overall assessment, ECG abnormalities, and ECG parameters including QTcB, QTcF, RR, PR, QRS, and HR value taken at Screening and Day -1 to Day 0 pre-dose will be listed.

4.2.13 Study Drug Administration

A listing will present dose level, cohort, patient number, anatomical site of injected tumor, whether the entire amount was given, estimated residual volume, the date and time of dose given, dose administered (units), total number of spores injected or administered, any problem with the injection, any pre-med given, whether the injection was performed using re-direction technique, how many re-directions, whether a needle was used or an alternate injection device, description of an alternate device was if used, needle gauge, needle size, syringe size, any radio guidance used for injection and any comments. Actual dose received will be summarized descriptively by dose level.

4.3 Efficacy Analysis

Results of the CT and/or MRI scans will be listed by dose level and time points for each patient.

Results of the injection lesion evaluation, the overall response assessment, and the best overall response assessment per RECIST will be listed by dose level and time points.

Summary table for individual patient data for injection lesion measurements will present descriptive statistics by dose level and time point for the lesions' longest diameter (cm),

including % reduction in injection lesions' longest diameter (cm) from baseline and nadir.

The overall lesion response will be summarized using the number and percentage of patients by dose level and time point within each of the categories: complete, partial, stable, progressive, or unknown.

The best overall lesion response will be summarized using the number and percentage of patients by dose level within each of the categories: complete, partial, stable, progressive, or unknown.

4.4 Pharmacodynamics Analysis

4.4.1 Anti-*C. novyi*-NT Immune and Inflammatory Response

All data collected to assess the immune and systemic inflammatory responses during *C. novyi*-NT treatment (CRP, IL-6, IL-8, TNF-alpha, etc.) will be the responsibility of BioMed Valley Discoveries.

4.4.2 *C. novyi*-NT Detection in Circulation and/or abscess material/post-dose tumor sample

Results from tumor biopsy assessments will be listed for each patient over time. Information presented will include the date and time of collection, days after IMP administration, anatomical location, and present the following for both anaerobic and aerobic culture: date and time of culture, days after IMP administration, culture results (positive/negative), whether bacteria was found (Yes/No), and if bacteria was found does the bacterial growth represent an infection or contamination.

Results will be summarized to show the number and percentage of patients.

Results from abscess material assessments will be listed for each patient over time. Information presented will include the type of material collected and volume, location (if other, specify non-injected lesion number or anatomical site), days after IMP administration, and present the following for both anaerobic and aerobic culture: date and time of culture, days after IMP administration, the culture result (presence or not), whether bacteria was found (Yes/No), and if bacteria was found does the bacterial growth represent an infection or contamination.

Blood culture and abscess results will be summarized to show the number and percentage of patients with presence of *C. novyi*-NT.

4.5 Safety Evaluation

4.5.1 Adverse Events (AEs)

Adverse Events will be mapped to the Medical Dictionary Regulatory Activities (MedDRA), Version 14.1 with the lowest level term that most accurately reflects the adverse event.

Adverse events will be categorized as:

- Treatment emergent adverse event (TEAE): A treatment-emergent adverse event is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.
- Non-treatment emergent adverse events (NTEAE): An AE that occurred before the first administration of IMP and did not worsen in severity or frequency after IMP exposure.

All adverse event data recorded on the eCRFs will be listed by dose level and patient. Included on the AE listing will be the adverse event, start date and time, outcome, stop date and time, CTCAE grade, relationship to study drug, action taken, whether the AE was serious, whether TEAE, whether or not a concomitant medication was taken, time of AE onset relative to IMP dosing and AE duration.

All serious adverse events will be listed. A listing of all AEs leading to treatment discontinuation will be presented. Details of death and hospitalization relating to serious adverse events will be listed.

As defined in the protocol, all adverse events will be assigned a CTCAE grade of 1 to 5.

Unless specified otherwise, all adverse event summaries will include the TEAEs only. In these summaries the count of AEs will be the number of patients reporting adverse events and not the number of events reported. If the same AE (preferred term) is reported several times for the same patient, it will only appear once for that specified dose level in the summary tables. For patients with multiple adverse events of the same preferred term and of different intensity, the highest intensity assessment will be used in summaries presented by intensity.

For purposes of the summary tables, AEs will be classified as either being related to IMP or not related. AEs related to IMP will include AEs classified as ‘Definite’, ’Probable’, or ‘Possible’. AEs not related to IMP will include AEs classified as ‘Not Related’ or ‘Unlikely'.

Frequency counts will be categorized and displayed by the MedDRA system organ class and preferred term.

An overview table will be presented by dose level and overall. This summary will present the number and percentage of patients, as well as number of events with treatment emergent: AEs; SAEs; AEs related to IMP; SAEs related to IMP; AEs leading to discontinuation of IMP; AEs by CTC Grade; and AEs with CTC Grade 3 or higher.

Other summary tables for adverse events will include:

- 1) Number and Percentage of Subjects with Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Dose Level
- 2) Number and Percentage of Subjects with Treatment Emergent Adverse Events 'Related to IMP' by System Organ Class, Preferred Term, and Dose Level
- 3) Number and Percentage of Subjects With Serious Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Dose Level
- 4) Number and Percentage of Subjects With Serious Treatment Emergent Adverse Events 'Related to IMP' by System Organ Class, Preferred Term, and Dose Level
- 5) Number and Percentage of Subjects with Treatment Emergent Adverse Events 'Related to IMP' by System Organ Class, Preferred Term, CTCAE Grade, and Dose Level
- 6) Number and Percentage of Subjects with Treatment Emergent Adverse Events 'Not Related to IMP' by System Organ Class, Preferred Term, CTCAE Grade, and Dose Level
- 7) Number and Percentage of Subjects with Treatment Emergent Adverse Events with Frequency >=2 Patients by Preferred Term
- 8) Number and Percentage of Subjects With Serious Treatment Emergent Adverse Events by Preferred Term

Above tables 1) – 4) present columns of Any grade and Grade >= 3 for each dose level, any grade includes missing grade; tables 5) and 6) present each available grade at each dose level; tables 7) and 8) present number of patients and number of events at each dose level by descending frequency of overall dose.

4.5.2 Clinical Laboratory

Routine hematology, chemistry and coagulation laboratory assessments will be provided in listings respectively. These listings also include the columns of normality/abnormality and change from baseline except the assessments in CRF. Laboratory values considered to be clinically significant will be listed.

Figures will be used to visualize the change from baseline values of all routine hematology, chemistry and coagulation laboratory assessments over time for each dose group. Figures considered will include plots of the mean over time for each dose level.

The number and percentage of abnormality with shift categories from normal at baseline to high and from normal at baseline to low for hematology, chemistry, and coagulation laboratory assessments.

Laboratory results will be summarized using Systeme International (SI) units.

4.5.3 Vital Signs

The observed and change from baseline values for blood pressure (systolic and diastolic), heart rate, respiratory rate, oral body temperature and weight will be listed by dose level, patient, and time point.

Figures will be used to visualize the change from baseline values of all vital sign parameters over time for each dose group. Figures considered will include plots of the mean over time for each dose level.

The number and percentage of abnormality with shift categories from normal at baseline to high and from normal at baseline to low for all vital sign parameters.

The number and percentage of patients who had fever at each temperature category will be provided over time for each dose. Temperature categories will be 38 - <=39°C, >39 - <=40 °C , >40 °C .

4.5.4 Oxygen Saturation by Pulse Oximetry (SpO2)

Hemoglobin-oxygen saturation (SpO2) is measured by pulse oximetry. The baseline measurement is defined as the last measurement prior to the first dose of study drug, including any repeated or unscheduled evaluations. Clinically significant changes in SPO2 at each post-treatment time point will be summarized by treatment group.

4.5.5 SOFA Scores

Results of the SOFA score assessment will be listed for each patient by dose level and time point. Descriptive statistics for the organ system (respiratory, renal, coagulation, liver, cardiovascular, and CNS (Glasgow Coma Scale)) SOFA scores will be provided by dose level and time point. The number and percentage of patients with each category of SOFA score (0, 1, 2, 3, 4) will be tabulated by dose level and time point.

4.5.6 ECOG Scores

Results of the ECOG performance scale assessment will be listed for each patient by dose level and time. The patient number and percentage for the ECOG grade will be provided by dose level and time.

4.5.7 Physical Examination

All comments/findings (pre and post-dose assessments) from the physical examinations will be listed.

4.5.8 Concomitant Medication

Medications will be coded using the appropriate WHO Drug Dictionary, Version March 2012.

Coding includes the Anatomical Therapeutic Chemical (ATC) Classification. Displays will use ATC class level 3 and preferred terms.

Medications will be categorized as:

Prior: medications that stop before study medication administration;
Concomitant: medications that stop on or after study medication administration.

All prior medications taken during the study before the first dose will be listed. Listing will include medication name and coded terminology, indication, dose (unit), frequency, route, start and end dates.

The number and percentage of patients treated with prior medications will be presented by dose level, also including an additional row of antibiotics during 14 days prior to study agent administration.

All concomitant medications taken during the study will be listed. Listing will include medication name and coded terminology, indication, dose (unit), frequency, route, start and end dates.

The antibiotics used (and times used) as well as the number and percentage of patients treated with antibiotics after IMP administration for management of study agent related toxicities will be presented by dose level and patient number.

The number and percentage of patients treated with concomitant medications will be presented by dose level.

4.5.9 Telephone Contact

All responses to the telephone contact will be listed by dose level and patient.

4.5.10 Diagnostic Procedures

Procedure name, date, interpretation and findings will be listed by dose level and patient.

4.5.11 Survival

Survival information will be listed by dose level and patient. This listing includes date of contact, how many days after IMP administration, how survival information was collected, who provided the information, the patient go on to receive anti-cancer therapy or not, status of patient, date of death and cause of death.

4.6 Reporting Output

The tables, listings, figures and any non-descriptive statistical analysis will be produced using SAS® Software (Version 9.2). The REPORT procedure will be used to produce all tables and listings; SAS/GRAPH will be used to produce all figures.

Listings will include all patients, unless otherwise specified and will be ordered by dose level, patient number, and time point (where applicable). In addition, all derived data used in a data summary or statistical analysis will be listed.

All tables, listings, and graphs will be produced to landscape orientation using Courier New 9pt font and will be incorporated into a MS Word document as a (RTF) rich text file.

5 Final Version Revision History

Date of Revision	Summary of change(s) From Version 0.1
16Mar2015	Updated from Protocol Amendment 2.0 and CRF 4.0
16Apr2015	Incorporating Medical Writer's Review comments to Version 0.2
08Jun2015	Incorporating Sponsor Comments to Version 0.3
21Jul2015	Incorporating Sponsor Comments to Version 1.0
27Feb2017	Added Cohort 6 information to Version 1.1
17Mar2017	Incorporating Sponsor Comments to Version 1.2

6 Attachment

6.1 Summary of Tables

Patient Disposition		
Table 14.1.1.1	Patient Disposition Summary	All subjects
Table 14.1.1.2	Analysis Populations	Safety
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Table 14.1.2	Summary of Demographics Data	Safety
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6.1.1 Medication and Treatment		
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Figure 14.2.2	Mean of Change from Baseline Value of Laboratory Chemistry Assessment Over Time by Dose Level	Safety
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