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STATISTICAL ANALYSIS PLAN

Protocol: ON-1003

A Phase 2, single-dose, open-label study to evaluate diagnostic performance and safety of Pegsitacianine, an intraoperative fluorescence imaging agent for the detection of peritoneal metastases, in patients undergoing cytoreductive surgery

SAP Version: Version 3

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DOCUMENT HISTORY

Revision History

Version Number /Date		Summary of Changes
SAP	**Protocol**	
Ver 1.0 05 OCT 21	Ver 1.0 23 JUN 21	Initial Approved
Ver 2.0 27 JAN 2022	Ver 2.0 18 JAN 2022	• Clarified exploratory objective of SBR effect on diagnostic accuracy • Added ITT population • Clarified sample size justification • Clarified definitions of Sensitivity, Specificity, PPV, NPV • Explained ROC analysis and sensitivity analysis for potential within-subject bias • Removed Child-Pugh score
Ver 3.0 24 JAN 2023	Ver 3.0 09 SEP 2022	• Changed date formatting from 2-digit year (YY) to 4-digit (YYYY). • Clarified presentation formatting of percentages and rates. • Changed comparison of camera type to use the Breslow Day test for homogenous odds ratios. • Removed Brian Madajewski as a signee. • Updated the efficacy population to be: all patients who receive >75% intended dose of pegsitacianine, had a minimum of one (1) image collected during their procedure, and had the opportunity for post-SOC evaluation of the peritoneal cavity. • Updated the sample size to 60 • Expanded methods to adjust for within-subject clustering • Added summaries of infusion related reactions

SIGNATURES OF APPROVAL

Study Title: A Phase 2, single-dose, open-label study to evaluate diagnostic performance and safety of Pegsitacianine, an intraoperative fluorescence imaging agent for the detection of peritoneal metastases, in patients undergoing cytoreductive surgery

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LIST OF ABBREVIATIONS

ABBREVIATION	TERM
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
ARE	antioxidant response element
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CC	Completeness of Cytoreduction Score
CFR	Code of Federal Regulations
CS	cytoreductive surgery
CSE	clinically significant event
CT	computed tomography
CV	Curriculum Vitae
DoH	Declaration of Helsinki
ECG	electrocardiogram
eCRF	electronic case report form
FDA	United States Food and Drug Administration
HIPEC	Hyperthermic intraperitoneal chemotherapy
HNSCC	head and neck squamous cell carcinoma
ICG	indocyanine green
ICH	International Conference on Harmonisation
IRB	institutional review board
IRR	infusion-related reaction
IV	intravenous
MFI	mean fluorescence imaging
MRI	magnetic resonance imaging
NIR	near-infrared
NSCLC	non-small cell lung carcinoma
NPV	negative predictive value
PC	peritoneal carcinomatosis
PEG	polyethylene glycol
PET	positron emission tomography
PK	pharmacokinetics

ABBREVIATION	TERM
PMMA	polymethylmethacrylate
PPV	positive predictive value
ROC	receiver operating characteristic
SAE	Serious adverse event
SBR	specimen to background ratio
SOC	Standard of care
SUSAR	suspected unexpected serious adverse reaction
SWI	sterile water for injection
TBR	tumor to background ratio

1. INTRODUCTION

This Statistical Analysis Plan covers the statistical analysis and reporting for the protocol ON-1003 dated 23JUN2021. A detailed list of tables, listings and figures (TLFs) will be supplied in a separate, version-controlled document.

In case of discrepancies between the SAP and the protocol, the SAP will overwrite the protocol with respect to analyses and reporting.

2. STUDY OBJECTIVES

2.1 Objectives and Endpoints

The main objective of this study is to investigate whether pegsitacianine can detect residual disease in the peritoneal cavity following standard of care (SOC) resection of peritoneal metastases using a [redacted] mg/kg dose administered [redacted] prior to surgery.

Table 1. Objectives and Endpoints

Objectives	**Endpoints**
Primary Objective	**Primary Endpoint**
The primary objective of this study is to determine if administration of pegsitacianine ([redacted] mg/kg) results in the detection of metastatic disease left behind following standard of care surgical resection of peritoneal metastases.	Rate of detection of disease left behind following SOC resection of peritoneal metastases as measured by rate of Clinically Significant Events (CSEs).
Secondary Objectives	**Secondary Endpoints**
Demonstrate reliable sensitivity, specificity, negative predictive values (NPPV), and positive predictive values (PPV) of the imaging agent at the level of the individual specimens.	Sensitivity, specificity. negative predictive values (NPV), and positive predictive values (PPV).

Demonstrate an acceptable safety profile.	Incidence of TEAEs and SAEs, abnormalities in lab values, vital signs, or ECG results.
Exploratory Objectives	**Exploratory Endpoints**
Assess the how the normalized SBR value affects the diagnostic accuracy of pegsitacianine in detection of metastatic disease vs. normal tissue.	ROC analysis across various specimen-to-background ratio fluorescence thresholds.
Effect of camera system on diagnostic results.	Diagnostic results across various camera systems.
Assess amount of fluorescence shown in various types of specimens.	Mean fluorescence intensity and Specimen-to-background ratio

3. STUDY DESCRIPTION

3.1 Study Design

This Phase 2 study will be an interventional, open-label, single arm trial where each patient is his/her own "intrapatient" control using two Groups. All patients will receive a single [redacted] mg/kg dose of pegsitacianine administered [redacted] prior to standard of care surgery.

Patients enrolled in Group 1 of the study will have a biopsy confirmed diagnosis of non-mucinous peritoneal carcinomatosis, defined as less than 50% mucin in the sample, with a suspected Peritoneal Carcinomatosis Index (PCI) greater than or equal to 10. Group 2 of the study will include patients with a suspected PCI greater than or equal to 10 and a biopsy confirmed diagnosis of mucinous peritoneal carcinomatosis, defined as > 50% mucin in the sample. A total of approximately 60 patients will be enrolled across both Groups. Enrollment will be open first to Group 1 with the opportunity to open Group 2 for enrollment at the discretion of the sponsor.

In both Groups 1 and 2, the surgeon will perform their SOC resection of visible metastases and image each resected specimen, and normal specimens on an area of normal tissue outside of the surgical field using the intraoperative NIR camera; no NIR imaging of the peritoneal cavity will be performed at this time. At the conclusion of SOC resection, the intraoperative NIR camera will be used to investigate the peritoneal cavity further for evidence of residual metastases highlighted by fluorescence using an approach similar to that performed for the calculation of the Peritoneal Carcinomatosis Index (i.e., 13 regions). Additional fluorescent specimens will also be imaged on an area of normal tissue within the surgical field prior to sending all surgical specimens to pathology for examination. The fluorescence status of each specimen will then be directly correlated to the histopathological outcomes of each specimen. This study design enables the calculation of pegsitacianine sensitivity, specificity, NPV, and PPV. Additionally, Completeness of Cytoreduction (CC) scores can be calculated following SOC resection and then adjusted following the additional resection of fluorescent metastases. The schedule of events for this study is presented in Appendix 1.

3.2 Study Treatment

Each patient will be administered a [redacted] mg/kg dose of pegsitacianine [redacted] The volume of drug and total dose will vary by patient and will depend on the patient's body weight.

4. SAMPLE SIZE AND POWER CALCULATION

The sample size for this study will be approximately 60 total subjects. This sample size is based on historical experience with similar pilot studies with the goal of informing power calculations for future studies. This study is not formally powered for hypothesis testing. A sample size of at least 40 total subjects (the originally planned sample size) will be sufficient for developing further understanding of the endpoints described herein. Sample size calculations account for non-evaluable and drop-out patients

5. ANALYSIS ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Clinically Significant Event Endpoints

The primary endpoint will include the identification of a clinically significant event (CSE) detected by pegsitacianine. CSEs will include increase in the Completeness of Cytoreduction

score following standard of care surgery, pegsitacianine detection of occult disease not otherwise known by the surgeon to exist, the detection of a positive surgical margin, and accurate identification of tumor negative SOC biopsies. A list of CSEs and their definitions is provided below.

- Detection of Occult Disease or Positive Surgical Margins – identification of tumor-containing tissue due to pegsitacianine fluorescence, confirmed via histopathological analysis, that otherwise went undetected during pre-operative imaging (PET, MRI) or by the surgeon during SOC surgery.
    - This occurs when a sample that (1) exhibits fluorescence *in situ* and (2) is pathologically-confirmed as a tumor, is obtained by fluorescence during SOC surgery.
- Tumor Negative SOC Biopsies – during SOC surgery, the surgeon will collect tissue specimens that are suspicious for disease. If those samples do not demonstrate pegsitacianine fluorescence (e.g. do not exhibit fluorescence *ex situ)* and are found to be devoid of tumor pathologically, those specimens would be included as a tumor negative SOC biopsy.
    - This occurs when a sample that (1) exhibits no fluorescence *ex situ* and (2) is pathologically-confirmed as normal tissue, is classified as suspicious tissue during SOC surgery.
- Alteration to the Completeness of Cytoreduction (CC) Score – following the completion of the SOC surgery, the surgeon will document a CC score prior to fluorescence imaging using pegsitacianine. If the surgeon finds residual disease that results in the increase of the CC score, this will be considered a CSE.

A subject with any CSE will be considered a CSE responder.

5.1.2 Diagnostic Imaging Endpoints

Diagnostic performance of pegsitacianine will be assessed by calculating sensitivity, specificity, NPV and PPV of pegsitacianine in detecting tumor containing tissue. The *ex situ* fluorescence status (any fluorescence vs. no fluorescence) of collected SOC and pegsitacianine guided specimens, as well as lymph nodes, will be compared to histological analyses of the collected specimens. Sensitivity and specificity for detecting tumor-containing tissue versus normal tissue

will be evaluated using tissue specimen fluorescence and the corresponding pathological outcomes.

True/false negative/positive definitions are as follows:

- False positive is defined as fluorescence was observed on the sample but the sample was not found to have tumor via pathology.
- False negative is defined as no fluorescence was observed on the sample but the sample was found to have tumor via pathology.
- True positive is defined as fluorescence was observed on the sample and the sample was found to have tumor via pathology
- True negative is defined as no fluorescence was observed on the sample and the sample was found not to have tumor via pathology.

Pegsitacianine sensitivity and PPV will be calculated using the following equations:

$$\boldsymbol{Sensitivity} = \frac{\#\ of\ True\ Positive\ Specimens}{\#\ of\ True\ Positive\ Specimens + \#\ of\ False\ Negative\ Specimens}$$

$$\boldsymbol{PPV} = \frac{\#\ of\ True\ Positive\ Specimens}{\#\ of\ True\ Positive\ Specimens + \#\ of\ False\ Positive\ Specimens}$$

Specificity values and negative predictive values (NPV) calculated by the equation below:

$$\boldsymbol{Specificity} = \frac{\#of\ True\ Negative\ Specimens}{\#\ of\ True\ Negative\ Specimens + \#\ ofFalse\ Positive\ Specimens}$$

$$\boldsymbol{NPV} = \frac{\#\ of\ True\ Negative\ Specimens}{\#\ of\ True\ Negative\ Specimens + \#\ of\ False\ Negative\ Specimens}$$

5.1.3 Fluorescence Endpoints

Specimen-to-background (SBR) ratios will also be calculated using white light and NIR images of both SOC and pegsitacianine guided specimens. SBRs will be calculated using *ex situ* images of collected specimens. The equation for calculating SBR is listed below.

$$\boldsymbol{SBR} = \frac{Mean\ Fluorescence\ Intensity\ (Specimen)}{Mean\ Fluorescence\ Intensity\ (Normal\ Tissue)}$$

Note, Tumor-to-background (TBR) ratios are equivalent to SBR, but only relevant for specimens with tumors.

5.2 Safety Endpoints

- TEAE incidence, severity, and relationship to study drug
- Physical examination results
- Vital signs results
- ECG results
- Clinical laboratory values (CMP, hemoglobin, and CBC with differentials)

6. ANALYSIS POPULATIONS

6.1 The Safety Population

All patients who receive at least one dose (either partial or full) of pegsitacianine.

6.2 The Intent-to-Treat Population

Identical to the Safety Population

6.3 The Efficacy Population

All patients who receive >75% intended dose of pegsitacianine, had a minimum of one (1) image collected during their procedure, and had the opportunity for post-SOC evaluation of the peritoneal cavity.

7. ANALYTICAL PLAN AND STATISTICAL METHODS

7.1 General Considerations

All computations for statistical analyses will be performed using SAS® software, Version 9.4 or later. All SAS programs used in the production of statistical summary outputs will be validated with independent programming prior to finalization. In addition, all program outputs will be independently reviewed. The validation process will be used to confirm that all data manipulations and calculations were accurately done. Once validation is complete, a senior

statistical reviewer will perform a final review of the documents to ensure the accuracy and consistency with this plan and consistency within tables. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

If necessary, the statistical analytical plan and statistical methods section may be updated before the database lock. Any changes in statistical methods that may have an impact on the primary conclusions drawn from this clinical trial will be described in an amendment to the protocol. All other changes in the statistical plan will be described in the clinical study report (CSR). An explanation will be provided for deviations from the planned analysis.

7.2 Reporting Conventions

The following conventions will be applied to all data presentations and analyses:

- Continuous variables will generally be summarized by the number of patients with missing and non-missing values, mean, standard deviation, median, Q1 (quartile 1), Q3 (quartile 3), minimum, and maximum.
- Categorical variables will be summarized by the number and percentage of patients within each category. If not specified otherwise, the number of patients with non-missing values will be the denominator for percentage calculations. The number of patients with missing values will be presented.
- Confidence intervals will be reported as two sided at the 95% level.
- All mean and median values will be formatted to one more decimal place than the measured value.
- Standard deviation values will be formatted to two more decimal places than the measured value.
- Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- For non-efficacy values the number and percent of responses will be presented in the form XX (XX %), where the percentage is in parentheses. Percentages will be rounded to

the nearest percent. In the case of a frequency of zero, the frequency and percentage will be presented as 0 rather than 0 (0%).

- Date variables will be formatted as DDMMMYYYY for presentation

All the analyses will be run displaying Group (Group 1 vs. Group 2). All rates will be summarized using counts and percentages.

7.3 Definition of Baseline

Baseline is defined as the measurement closest to, but prior to, the administration of study drug. No reassignment of visits will be conducted.

7.4 Handling of Dropouts and Missing, Unused and Spurious Data

All data will be analyzed.

No imputation of missing data will be performed, and analyses will use the observed cases only.

Formal outlier testing will not be performed. Data identified as potential outliers after review will be reviewed to determine whether they are spurious.

Spurious data are data determined to be incorrect upon review of site documents. If data is deemed to be spurious, the spurious data and the reason for it being spurious will be documented by the Sponsor in a Note-to-file. Data identified as spurious will be treated as missing unless they can be definitively corrected. If spurious data is identified, sensitivity analysis may be performed to assess the potential impact of any missing data or outliers on trial results by including the spurious data.

7.4.1 Dates

Imputation of missing or partial dates is not expected, but if a complete date is required for calculations, the following algorithms will be applied:

- For the start date:
    - If year, month, and day are missing then use the minimum of the patient's first visit date or the consent date.
    - If either only month or month and day are missing then use January 1.

- If only day is missing, impute the first day of the month.

- For the end date:
  - If year, month, and day are missing then use the patient's last visit date.
  - If either only month or month and day are missing then use December 31.
  - If only day is missing then use the last day of the month.
  - Do not expand the record past the patient's last visit.
  - The original missing or partial date, the imputed complete date, and the indicator variable that indicates which dates were imputed will be retained in the database.

7.5 Adjustment for Multiplicity

There are no planned adjustments for multiple endpoints or analyses.

7.6 Adjustment for Multiple Centers

Differences between study centers will be not be incorporated into the statistical analyses for this study. There are no plans to analyze data within centers.

7.7 Patient Disposition

The number of screened patients will be summarized.

The number of enrolled patients will be summarized, along with the number and percentage of enrolled patients in all of the analysis populations, patients completing the study, patients withdrawing from the study and their primary reason for withdrawal, and the number of deaths, by Group and overall.

Data listings of patient disposition, screening failures, and patient assignment to analysis groups will be created.

7.8 Protocol Deviations

Protocol deviations are defined as any variation from the protocol, such as enrollment of a patient who did not meet all inclusion and exclusion criteria or failure to perform the assessments

and procedures within the required time frame, that are identified by the clinical research associate monitoring the study.

The number and percentage of patients with at least one major protocol deviation and the categories of the major protocol deviations will be summarized for the Safety population.

All protocol deviations will be provided in a listing.

7.9 Patient Characteristics

Unless otherwise noted, all patient characteristics will use the Safety population.

7.9.1 Baseline and Demographic Characteristics

All baseline characteristics will be summarized by each Group and overall for the Safety population. The following parameters will be summarized:

- Age (years)
- Race
- Ethnicity
- Sex
- Child-bearing Potential (if female)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)
- Karnofsky Performance Rating

No hypothesis testing is planned for baseline characteristics, so the analysis will be purely descriptive.

Data listings of baseline characteristics and demographics including Karnofsky Score will be created.

7.9.2 Medical History

Medical history will be summarized for all non-cancer related medical events, previous cancers, and previous anti-cancer therapies. Medical conditions will be coded using Medical Dictionary of Regulatory Activities (MedDRA) 23.0 dictionary or higher and summarized by System Organ Class (SOC) and preferred term (PT) in the Safety population. A listing for the variables above will also be generated.

7.9.3 Prior and Concomitant Medications and Procedures/Treatments

Prior and concomitant medication (as well as concomitant procedures/treatments) will be summarized by Group and overall in the Safety population. Medications will be coded with the World Health Organization (WHO) Drug Dictionary (B3 2021-09-01 DDE). Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) Classification System level 2 and 4 codes (ATC2 and ATC4). Procedures/treatments will be coded using MedDRA 23.0 or higher and summarized by SOC and PT. A medication, procedure, or treatment will be considered to be concomitant if its end date is after the date of study drug administration. Medications with a missing end date will also be considered concomitant. A medication with an end date prior to the date of study drug administration will be considered prior medications.

Listings for prior and concomitant medications / procedures will be provided.

7.9.4 Administration and Exposure of Study Drug

Administration of study drug (planned dose level, total dose administered, total volume administered, infusion flow rate, infusion duration, subjects with infusion reactions, and subjects with dose interruptions) will be summarized using descriptive statistics. Infusion flow rate will be calculated as total volume administered÷infusion duration. A listing will also be generated.

7.9.5 Cytoreductive Surgery Details and Specimen Collection

Cytoreductive surgery details including the following will be summarized on a patient level using descriptive statistics in the Safety population:

- Duration of surgery
- Suspected PCI score and fluorescence imaging PCI score
- Method of localization

- Number of SOC suspicious nodules collected
- Number of SOC normal specimens collected
- Additional fluorescent areas collected
- Cytoreduction score
- Time spent imaging
- Camera system used

A listing will also be generated.

7.10 Efficacy Endpoint Analyses

Imaging will be assessed on the Efficacy population.

7.10.1 Primary Analyses

7.10.1.1 Analysis of Clinically Significant Events

The number and proportion of subjects with CSEs will be summarized by Group. CSE responders will be summarized, as well as each type of CSE. These summaries will include 95% 2-sided confidence intervals for the proportion of CSEs calculated via Clopper-Pearson method.

A listing of all CSEs by patient will be provided.

7.10.2 Secondary Analyses

7.10.2.1 Analysis of Diagnostic Imaging

The positive predictive value, negative predictive value, sensitivity, and specificity (biopsy level) will be calculated and summarized for each Group. The summary will include the true/false negatives/positive rate and number of specimens. Two-sided 95% confidence intervals will be calculated for each rate via Clopper-Pearson method.

A listing by subject and specimen showing the fluorescence status, pathology result, specimen type (SOC vs. fluorescence), suspicious vs. normal, fluorescence in *in situ* and *ex situ,* and fluorescence measures (MFI, SBR or TBR) will be provided.

7.10.3 Exploratory Analyses

7.10.3.1 Analysis of Fluorescence Intensity

A summary of MFI for the tumor (or suspected tumor), MFI for the normal background tissue, and TBR will be provided by Group and pathology result (tumor vs. no tumor). This summary will be at the specimen level, meaning each subject may have multiple specimens.

7.10.3.2 ROC Analysis

In this pilot study we are assuming that any fluorescence is indicative of tumor presence. To assess how the amount of observed fluorescence (e.g., the SBR or TBR) may affect the diagnostic accuracy of pegsitacianine, a receiver operating characteristic (ROC) analysis will be performed on all specimens using the observed thresholds of SBR and TBR. The corresponding ROC curve will be provided along with the area under the curve (AUC).

7.10.3.3 Adjustment for Clustering

There is potential for within-subject correlation to bias our estimates of pegsitacianine's diagnostic accuracy. To assess this issue, an ROC curve will be constructed from a mixed model that clusters specimens by the subject they originated from. We will compare the AUC of the mixed effects ROC curve to the standard ROC curve to assess if within-subject correlation is causing significant bias in our analyses. If it is determined that significant bias has been introduced, additional analyses on secondary endpoints may be performed to assess the diagnostic accuracy of pegsitacianine

The confidence intervals for diagnostic accuracy (e.g. the positive predictive value, negative predictive value, sensitivity, specificity, and true/false negative/positive rate) will also be constructed via a cluster-bootstrap to determine confidence intervals that account for the effects of within-subject clustering. Since the number of specimens each subject has is variable, in order to keep the same number of specimens in the bootstrapped sample, we will cluster initially by the number of specimens each subjects has, and then resampling will occur by first choosing a subject within that cluster and then resampling the same number of specimens they originally had.

7.10.3.4 Camera System Analysis

An analysis on diagnostic results by camera system will be performed. 2x2 incidence tables comparing the true/false negative/positive results will be constructed for each camera system, and compared via the Breslow-Day test to assess if there is any effect of camera system on diagnostic results (e.g. to test if the common odds-ratio of each incidence table is equivalent across camera types). A summary including the diagnostic true/false negative/positive numbers and rates for each camera system, sensitivity, specificity, and p-value of this analysis will be provided.

7.10.3.5 Other Exploratory Analyses

Relationships of sensitivity and specificity may be evaluated post-hoc with respect to additional covariates including, but not limited to, tumor size, tumor type, and tumor location.

7.11 Safety Endpoint Analyses

All the analyses in this section will be performed on the Safety population by Group. Patients will be analyzed according to the actual treatment they received.

Repeated or unscheduled results will not be included in the summary statistics but will be included in the individual data listings.

7.11.1 Adverse Events and Infusion Related Reactions

All adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). A TEAE is defined as an AE that occurs (or worsens) during or after study drug administration and through Day 28 after administration of study drug.

An overview of all AEs will be provided that will include:

- Number of AEs, TEAEs, non-serious TEAEs, and Serious Adverse Events (SAEs)
- Number of TEAEs and SAEs related to study drug
- Number of TEAEs related to study drug with CTCAE grade >= 3
- Number of AEs and study drug related SAEs resulting in:
    - Death

- Subject discontinuation
- Study drug discontinuation

TEAEs, treatment-related TEAEs, TEAEs by CTCAE grade, TEAEs that lead to discontinuation of study drug, SAEs, and SAEs that lead to discontinuation of study drug, will be summarized by system organ class (SOC) and preferred term (PT).

A listing of all AEs will also be generated.

Infusion related reactions (IRR) will be summarized, and a descriptive summary of the duration of IRR will be provided. A listing of all AEs, including a separate listing for IRR, will also be generated.

7.11.2 Laboratory Data

The clinical laboratory data will be summarized by scheduled time point, Group, and change from baseline. A listing will be provided where the values that are below the lower limit or above the upper limit of the reference range will be flagged. Those values or changes in values that are considered clinically significant by the investigator will also be flagged in the listing.

Repeated or unscheduled results will not be included in the by timepoint summaries but will be included when looking for extreme values and displayed in the individual data listings.

7.11.3 Vital Signs

Vital signs data will be summarized by time point, Group, and change from baseline. A listing will also be provided.

Repeated or unscheduled results will not be included in the summary statistics but will be included in the individual data listings.

7.11.4 Physical Exam

Physical examination results will be provided as a listing.

7.11.5 ECG

ECG results will be provided as a listing.

8. DEVIATIONS FROM ANALYSIS AS DESCRIBED IN THE PROTOCOL

No deviations from the protocol are planned.

9. APPENDIX 1: SCHEDULE OF EVENTS (GROUPS 1 AND 2)

	Screening	Treatment			
Evaluation	**Days –30 to –1**	**Day 0**	**Surgery [redacted] – [redacted]**	**Day 10**	**Day 28**
Informed consent & subject enrollment	X				
Inclusion/exclusion criteria	X	X			
Blood/Urine/Breath alcohol		X			
Pregnancy test (a)	X	X			X
Demographic data	X				
Medical history	X				
Physical examination	X			X	
Karnofsky Performance Status	X				
Height (b)	X	X			
Body weight (b)	X	X			
Vital signs (c)	X	X	X (d)	X	X
12-lead electrocardiogram		X (e)		X	
Concomitant medications	X	X	X	X	X
Study drug administration		X			
Adverse events review (f)		X	X	X	X
Serum chemistry	X	X	X	X	X
Hematology (g)	X	X	X	X	X
Surgery			X		
Intraoperative Imaging			X		
Pathology evaluation of surgical specimens			X (h)		

Footnotes

[a] For female subjects, a serum sample for a serum pregnancy test will be collected at screening and on Day 0 and Day 28.

[b] Body mass index will be calculated at Screening only.

[c] Vital sign measurements will include systolic and diastolic blood pressure, pulse, respiratory rate, and oral temperature (in degrees Celsius). Blood pressure and pulse will be measured after a resting period of at least 5 minutes in the supine position.

[d] Vitals are only to be collected if they are found to be abnormal at dosing

[e] 12-lead ECG is to be performed prior to study drug administration

[f] Patients will be assessed for AEs occurring from the time of dosing through Day 28 (±5 days)

[g] Hematology assessments will include hemoglobin, hematocrit, erythrocyte count (red blood cells), differential leukocytes, platelet count, and total leukocytes (white blood cells).

[h] Pathologic analysis of surgical specimens will take place from the conclusion of surgery and up to 10 days after