Concordia Laboratories Inc.

Statistical Analysis Plan

Study code: CLI-PHO1701

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A MULTICENTER, PROSPECTIVE, OPEN-LABEL, NON-RANDOMIZED SINGLE-ARM CLINICAL STUDY OF THE SAFETY AND TISSUE RESPONSE TO PHOTODYNAMIC THERAPY USING PORFIMER SODIUM FOR INJECTION AS TREATMENT FOR SOLID LUNG TUMOR PRIOR TO SURGICAL RESECTION

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomic-therapeutic-chemical
β-hCG	β human chorionic gonadotropin
BMI	Body mass index
CL	Confidence limit
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ITT	Intent-to-Treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
nm	nanometer
PDT	Photodynamic therapy
PHO	Photofrin®
RFA	Radiofrequency ablation
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all details and specifications for the analysis of the study CLI-PHO1701, "A Multicenter, Prospective, Open-Label, Non-Randomized Single-Arm Clinical Study of the Safety and Tissue Response to Photodynamic Therapy Using Porfimer Sodium for Injection as Treatment for Solid Lung Tumor Prior to Surgical Resection" as set forth in the clinical study protocol version 1 dated Mar 01, 2017.

2. STUDY DETAILS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to assess the safety of photodynamic therapy (PDT) in subjects with solid tumors in peripheral lung prior to surgical resection.

2.1.2 Secondary Objective

The secondary objective of this study is to assess the lung tumor and healthy tissue response to PDT.

2.2 Study Design

This is a prospective, multicenter, uncontrolled, non-randomized, open-label, clinical study with the primary objective to assess safety of PDT in subjects with peripherally located malignant tumors in lung parenchyma prior to surgical resection. A Time and Procedures Schedule for the overall conduct of the study is outlined in section 8.

The primary diagnosis will be performed as per standard of care no more than 60 days prior to consent signature. Upon signing consent, subjects will be assigned a unique participation number and will undergo screening evaluation conducted during the 30 days prior to enrollment. This phase will involve medical evaluations and thorough review of all reports that led to the primary diagnosis. Upon successful screening evaluations, subjects will be enrolled into the study.

Treatment Procedures will consist of one PDT-Photofrin® course performed through navigational bronchoscopy or peripheral ultrasound guided bronchoscopy. One course will consist of an intravenous (IV) injection of Photofrin® (PHO) 2 mg/kg over 3-5 minutes followed by one laser light application session. The end of injection will be Study Hour 0. Photodynamic laser therapy will be performed on Study Hour 40-50. Laser light (630 nm wavelength) will be applied at a dose of 200 J/cm of the diffuser length.

Ten to 15 days after PDT, subjects will undergo surgery as per standard of care. Macroscopic and microscopic examinations of the tumor and surrounding healthy lung tissue will be evaluated to determine the effect of PDT on the tumor and the healthy/non-tumor lung tissue. Macroscopic examinations will be performed at the local institution. Microscopic examinations will be performed by a central reader pathologist.

Follow-up assessments will include some or all the following procedures: physical exam; vital signs evaluation; body weight measurement; chest CT; chest X-ray; performance status; and clinical laboratory testing. All subjects will be asked general questions about the occurrence of adverse events, concurrent medical conditions, use of adjunctive therapy/procedure, and intake of concomitant medication.

Data will be analyzed to evaluate the safety of the modality up to 90 days post-surgery.

2.2.1 Schedule of visits

Pre-treatment assessments will be performed during the 30 days prior to enrolment. After enrolment, study visits will be as follows:

- Study Day 0 will be the day the subject is enrolled.
- Study Day 1 will be the day of the PHO injection. Study Hour 0 will be the time of the end of PHO injection.
- Study Day 3 will be the day of PDT. Study Hour 40-50 will be calculated from Study Hour 0.
- Study Day 5 will be the day of hospital discharge. Subjects will be discharged from the 48-hour hospital stay after the Chest X-ray and other safety evaluations indicating that the subject is stable and able to be discharged; otherwise, the subject's hospital stay may be extended to 72 hours or until the subject is stable for discharge
- Study Day 13 to Day 18 will be the time-period where the surgery will be performed post PDT.
- Study Day 20 to Day 25 (±2 days) will be the 7-day post-surgery visit.
- Study Day 43 to Day 48 (±3 days) will be the 30-day post-surgery visit.
- Study Day 103 to Day 108 (±7 days) will be the 90-day post-surgery last study visit.

3. DATA ANALYSIS CONSIDERATIONS

3.1 Determination of Sample Size

This study is designed to assess the safety of PDT in subjects with solid lung tumors prior to surgical resection and to assess the lung tumor and healthy tissue response to PDT. The intent of this study is to enroll 10 subjects. This sample size has the following precision for estimation of rates of AE's of special interest (AESI). The following table shows historical AE rates for RFA ranging from <1 to ~50%.

AESI	Rate Observed with RFA
Pneumothorax	11-52%
Pleural effusion	6-19%
Hemorrhage	6-18%
Pulmonary artery pseudoaneurysm	0.2%
Needle tract seeding	0.3-0.7%
Cavitation	14%
Bronchopleural fistula	0.6%
Pneumonitis	0.4%

The sample size of N=10 has precision for estimation of AE rates for estimates ranging from <0.01 to ~0.5 as shown in the following list. Precision is measured by 1-sided 95% upper confidence limit (CL) on the estimated AE rate via exact binomial distribution. PDT is expected to have lower AE rates than RFA, so, for example, for a RFA historical rate of 0.27 (27%), if no such AE's are observed on PDT, then the TRUE underlying PDT rate is lower than 0.27 with 95% confidence since the upper 95% CL is 0.26 - indicated by "*" in the list below.

No. of AESIs	Rate	Upper 1-sided 95% confidence limit
0	0.00	0.26*
1	0.10	0.39
2	0.20	0.51
3	0.30	0.61
4	0.40	0.70
5	0.50	0.78

The study will be suspended and re-evaluated from a safety standpoint if 20% of the subjects experience a serious adverse event that is related to PDT.

4. PRIMARY AND SECONDARY ENDPOINTS

4.1 Primary Endpoints

The primary endpoints are safety assessments:

- incidence of adverse events and serious adverse events
- laboratory data
- physical examination
- vital signs
- concomitant medication

4.2 Secondary Endpoints

Secondary endpoints will include:

- Tumor destruction and cell death in area of the PDT (0.75 cm radius if the laser fiber is eccentrically placed, or 1.5 cm diameter if the laser fiber is centrally placed) as defined by cytological and pathological evaluation.
- Effect of PDT on the non-cancerous lung tissue surrounding the targeted tumor.

5. STATISTICAL METHODOLOGY

5.1 General Considerations

All statistical evaluations will be conducted using SAS® version 9.4 or higher (SAS® Institute, Cary, North Carolina). All tables, figures and listings will be produced in landscape format.

In general, all data will be listed by subject and visit/time point where appropriate. The total number of subjects under the stated population (N) will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum. In case of n<2, where n indicates the number of evaluable subjects at the particular time point, the standard deviation will be empty. The statistic "Missing" will also be presented as the number of missing entries/subjects, if any at that visit/timepoint, and presented as a summary statistic only when non-zero. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data, whereas the standard deviation will be presented to two more decimal places than the original data.

In summary tables of categorical variables, counts and percentages will be used. The count [n] indicates the actual number of subjects with a particular value of a variable or event, which should always be less than or equal to the total number of subjects with non-missing value of the variable or event [M]. Percentage will be obtained by: % = (n/M)*100. Unless otherwise stated, all percentages will be expressed to one decimal place.

In by-visit summary tables only scheduled visits/timepoints will be summarized. In listings all visits and timepoints with any data collected, including both scheduled and unscheduled ones and early termination visits, will be included.

The closest non-missing measurement (whether from scheduled or unscheduled visit) taken prior to the administration of the study drug (PHO) will be considered as the baseline value. The change from baseline values will be derived for each subject as the post-baseline evaluation minus the baseline evaluation.

Study days will be calculated as the number of days from the date of the study drug administration:

Study Day = (Target Date - Date of the study drug administration) + 1 if target date is greater than or equal to the date of the study drug administration or

Study Day = (Target Date – Date of the study drug administration) if target date is less than date of the study drug administration.

All dates will be displayed in DD/MMM/YYYY format.

5.2 Analysis Populations

The analysis populations defined in this study are as follows:

5.2.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) Population will be defined as all enrolled subjects.

5.2.2 Safety Population

The Safety Population will be defined as all enrolled subjects who received the Photofrin® injection.

5.3 Coding Dictionaries Used

Adverse event and medical history verbatim terms provided by the investigator will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA, version 20.0). The resultant primary system organ class and preferred term will be used for AE summaries.

Prior and concomitant medication generic terms provided by the investigator will be coded according to WHO Drug Dictionary September-2016 B2 and classified by preferred terms and ATC classes. The highest available ATC class and preferred term will be used for prior and concomitant medication summaries and listings.

5.4 Analysis Methods

5.4.1 Study Subjects Disposition

Subject disposition will be summarized by presenting the number of subjects who were enrolled, were included into the ITT and safety populations, received PDT, underwent planned surgery, completed the study and prematurely discontinued with breakdown by the reason for early discontinuation. The analysis will be based on all enrolled subjects.

A listing will be presented to describe whether the subject completed the study, date of completion or early withdrawal, and the reason for early discontinuation, if applicable. A listing will also be provided to describe if the subject meets all inclusion/exclusion criteria. The reason for entry criteria violation, if any, will be presented.

5.4.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics such as age, sex, childbearing potential (for female subjects only), race, ethnicity, height (cm), weight (kg) and BMI (kg/m^2) as well as baseline ECOG status and skin phototype will be summarized. The analysis will be based on the Safety population and ITT population.

Descriptive statistics will be presented for age, height, weight, BMI. Frequency counts and percentage will be presented for sex, childbearing potential, race, ethnicity, ECOG status and skin phototype.

The demographic and baseline characteristic data will also be presented as a data listing.

5.4.3 Medical History

Medical history will be summarized by MedDRA system organ class and preferred term for the safety population.

Medical history details as collected on the CRF such as condition, MedDRA system organ class and preferred term, the date of onset, stop date and intensity of the condition will be presented in a by-subject data listing.

5.4.4 Primary Diagnosis and Oncology History

Primary diagnosis and oncology history findings collected at the CRF, such as whether the subject has primary or metastatic tumor, tumor size and whether it is completely resectable, location of primary tumor (for subjects with metastatic tumor), biopsy of cytology results will be summarized descriptively and listed.

5.4.5 Protocol Deviations

The study site will record all deviations occurred through the study on the CRF.

Protocol deviation frequencies will be summarized descriptively by deviation type.

All protocol deviations data collected on CRF will be presented as a by-subject data listing.

5.4.6 Photofrin® Injection

All details of Photofrin® injections collected on CRF will be listed.

5.4.7 Photodynamic therapy

All details of light application collected on CRF will be listed.

5.4.8 Surgery

All details of the planned surgery collected on CRF will be summarized descriptively and listed.

5.4.9 Tumor and Healthy Tissue Response Analysis

Macroscopic and microscopic examinations of the tumor and surrounding healthy lung tissue will be evaluated following the surgery. Findings collected on CRF will be summarized descriptively and listed.

5.4.10 ECOG Performance Status

ECOG performance status will be assessed at Screening, prior to PDT procedure, prior to surgery, at the Day 20-25, Day 43-48 and Study Exit visits. Number and percentage of subjects with each status will be presented by visit. All results will be listed.

5.4.11 Safety Analysis

All safety data will be listed and tabulated. The analysis will be performed on the Safety population.

Safety parameters include adverse events, laboratory data, physical examination findings, vital signs and concomitant medications.

5.4.11.1 Adverse Events

Adverse Events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA version 20.0) AE coding system for purpose of summarization.

Events collected at the "NCS Events" CRF page will be summarized together with Adverse Events, but excluded from analyses by CTCAE grade and relationship to study drug, since these data points are not captured for NCS events.

An AE will be defined as treatment-emergent (TEAE) if its date of onset is on or after the date of the study drug (PHO) administration.

An AE will be defined as treatment-related if its relationship to the study drug is recorded as "Reasonable Possibility" on the CRF.

An overall summary of number and percentage of subjects with at least one AE, TEAE, serious TEAE, treatment-related TEAE, serious treatment-related TEAE, TEAE leading to discontinuation and fatal TEAE will be presented.

A summary of the frequency (number and percentage of subjects) of TEAEs will be presented by system organ class and preferred term. One-sided 95% upper confidence limit will be computed for each AE percentage via exact (Clopper-Pearson) method for binomial proportion. Adverse events will also be analyzed by their CTCAE grade (1 to 5) and relationship to study drug (related or not related).

A subject experiencing the same AE multiple times will be counted only once for that preferred term. Similarly, if a subject experiences multiple AEs (preferred terms) within the same system organ class, then that subject will be counted only once for that system organ class. When summarizing by CTCAE grade and relationship, only event with highest grade or relationship will be counted. All AEs will be presented in alphabetical order of SOC and preferred terms.

Skin photosensitivity is an adverse event of special interest (AESI). Skin photosensitivity will be summarized separately by SOC and preferred term as well as by SOC, preferred term and CTCAE grade.

All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim term given by the investigator, preferred term, system organ class, start date, stop date, CTCAE grade, outcome, action taken and drug relatedness. Separate listings will be created for Serious TEAEs, TEAEs leading to study drug discontinuation and skin photosensitivity events.

5.4.11.2 Clinical Laboratory Parameters

Samples will be obtained for the clinical laboratory tests at the following time points: Screening, Hospital Discharge (Day 5) and Study Exit visits.

The following tests will be performed:

- Chemistry: Glucose (random), Blood urea nitrogen, Sodium, Potassium, Chloride, Creatinine, Alkaline Phosphatase, Aspartate Aminotransferase, Alanine Aminotransferase, Total bilirubin, Albumin, Total protein.
- Hematology: Hemoglobin, Hematocrit, White blood cell, Red blood cell, Platelet count, Prothrombin time

Additionally, samples for Serum β-HCG pregnancy test will be collected from women of childbearing potential only at Screening, Day 43-48 visit and Study Exist visit.

Laboratory results for chemistry and hematology as well as changes from baseline will be summarized descriptively by visit. Only subjects with both non-missing baseline and time point values will be summarized at each time point.

Shifts among normal, low and high results (as determined by laboratory normal ranges) from baseline to last available post-baseline assessment will be summarized.

All individual subject clinical laboratory results will be presented in listings by subject and visit.

Results of the pregnancy test will be listed.

5.4.11.3 Physical Examination

Comprehensive physical examination will be performed at Screening and Study Exit Visits.

The physical examination will include assessment of the following systems: General Appearance, Skin, Head and Neck, Mouth, Lymph nodes, Thyroid, Abdomen, Musculoskeletal, Cardiovascular, Respiratory and Neurological. Each body system examined will be characterized as Normal or Abnormal.

Physical examination findings will be summarized by visit. The number and percentage of subjects with normal and abnormal findings will be presented for each body system. Additionally, a shift table comparing the Screening and Study Exit evaluations will be created.

All physical examination data will be provided in a listing.

5.4.11.4 Vital Signs

Vital signs (pulse, systolic and diastolic blood pressure, temperature, and respiration rate) will be collected at all visits. On Day 1, vital signs will be performed prior to Photofrin® injection and repeated at 15 and 30 minutes, 1, 2, 4, and 8 hours after injection. At other visits vital signs to be assessed once.

Actual values of vital signs and changes from baseline will be summarized using descriptive statistics by time point. Only subjects with both non-missing baseline and time point values will be summarized at each time point.

All vital signs data will be provided as a by-subject listing.

5.4.11.5 Prior and Concomitant Medications

Subjects may receive medication that is clinically indicated, such as pain prophylaxis, as per the investigator's clinical judgement. The brand name (or, if unknown, the generic name), dose, dose unit (or dosage form if compound), frequency, route of administration, duration of use (start date and, if applicable, stop date) and indication for all previous medications and concomitant medications must be documented in the concomitant medication record section of the case report form (CRF). Concomitant medications include intravenous fluids, herbal products, vitamins, and any over-the-counter medicines.

Prior medications are defined as those taken only before the date of informed consent, i.e. stopped before the date of informed consent. Concomitant medications are defined as any non-study medication taken during the course of the study i.e. on or after the date of informed

consent. Additionally, the medications will be considered concomitant if the stop date of the medication is missing (not available).

Prior and concomitant medications will be summarized by anatomical-therapeutic-chemical (ATC) classification (highest level available) and WHO Drug Dictionary preferred term.

Prior and concomitant medication information will be presented in a by-subject listing with ATC classification (highest level available) and WHO Drug Dictionary preferred term, start and stop date, dosage, route, frequency and indication.

5.4.11.6 Adjunctive Therapy/Procedures

An adjunctive therapy/procedure is defined as any procedure or intervention (e.g., psychotherapy, surgery, dental work, acupuncture, physiotherapy, chiropracty, osteopathy) used to treat an illness.

The adjunctive therapy/procedure (type, duration of use [start date and, if applicable, stop date], and indication) received during 30 days prior to the date of the ICF signature and throughout the study will be recorded in the adjunctive therapy record of the CRF.

Frequency of adjunctive therapies will be summarized descriptively by therapy type. All information will be listed.

5.4.12 Chest X-ray

Chest X-ray will be performed at Screening, if not done up to 90 days prior to the visit, as well as at the Hospital Discharge and Day 20-25 visits. X-ray will be classified as normal or abnormal. Number and percentage of subjects with normal and abnormal findings will be presented by visit. All findings will be listed.

5.4.13 Other Assessments

12-lead ECG will be performed at screening if not done up to 30 days prior to the informed consent. Results will be listed.

Light challenge will be performed by subjects at home prior to Day 43-48 visit. Results will be listed.

Information on unanticipated events (physical risk, psychological risk, economic risk, social risk, other) will be collected throughout the study. Results will be listed.

CT scan will be performed prior to surgery and at the Day 43-48 and Study Exit visits. Findings will be listed.

6. CHANGES IN ANALYSIS FROM PROTOCOL

There are no changes from the protocol-specified analyses.

7. REFERENCES

1. Study protocol: "A Multicenter, Prospective, Open-Label, Non-Randomized Single-Arm Clinical Study of the Safety and Tissue Response to Photodynamic Therapy Using Porfimer Sodium for Injection as Treatment for Solid Lung Tumor Prior to Surgical Resection", version 1 dated Mar 1, 2017.

8. APPENDICES

Table 1 Study Schedule

Procedures/Examinations	STUDY TIME								
	S	E	Period I - PDT Course			Period II- Surgery	Period III - Follow-up		
	Days -30 to -1	Day 0	Injection Day 1	PDT Day 3 40-50 H	Hospital Discharge[g] Day 5	Day 13-18	Day 20-25 (±2 days)	Day 43-48 (±3 days)	Study Exit Day 103-108 (±7 days)
Informed Consent	X								
Eligibility criteria	X[a]		X						
Demography	X								
Medical and oncologic history and current medical conditions	X								
Skin phototype	X								
Vital signs[b]	X		X	X	X	X	X	X	X
Height	X								
Body weight	X		X						
Comprehensive physical examination	X								X
ECOG Status	X			X		X	X	X	X
Chest X-ray	X[c]				X		X		
12-lead ECG	X[d]								
CT scan and evaluation						X		X	X
Clinical labs[e]	X				X				X
Serum β-HCG[f]	X							X	X
Enrolment		X							
Photofrin® injection			X						
Instructions to subjects		X	X	X	X	X	X	X	X
PDT & 48-hour hospitalization				X					
Macro/microscopic tissue examination						X			
Light Challenge								X	
Record Adverse Events[h]	X		X	X	X	X	X	X	X
Medication/Therapy Assessment[i]	X		X	X	X	X	X	X	X

S=Screening; E=Enrolment; [a] Will include radiology/pathology reports confirming primary or metastatic solid tumor in peripheral lung and thoracic surgeon confirming the tumor resectability; [b] On Day 1, vital signs (pulse, blood pressure, temperature, and respiration rate) to be performed prior to Photofrin® injection and repeated at 15 and 30 minutes, 1, 2, 4, and 8 hours after injection. Afterwards, vital signs to be assessed once, prior to all other procedures being performed; [c] If not done up to 90 days prior to ICF signature; [d] If not done up to 30 days prior to ICF signature; [e] Clinical labs to include hematology and chemistry as specified in Appendix 13-4; [f] For females of childbearing potential only, who must agree to use acceptable contraceptive method for 90 days post Photofrin® injection; [g] Subject to be discharged from the 48-hour hospital stay after the Chest X-ray and other safety evaluations indicating that the subject is stable and able to be discharged; otherwise, the subject's hospital stay may be extended to 72 hours or until the subject is stable for discharge; [h] All AEs to be recorded from the time of ICF signature; [i] All medications and adjunctive therapies/procedures to be recorded 30 days prior to screening and throughout the study.