STATISTICAL ANALYSIS PLAN

Study Title:	A PHASE 2 MULTICENTER, OPEN-LABEL STUDY OF THE CDK4/6 INHIBITOR SPH4336 IN SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC LIPOSARCOMAS
Phase:	2
Protocol No.:	SPH4336-US-01
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CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

Reviewed and Approved By:

28Oct2024

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Date

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the planned data summary and analysis of data from Protocol SPH4336-US-01. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

1.1. STUDY OVERVIEW

This is a multicenter, non-randomized, open-label Phase 2 study of SPH4336 in subjects with well-differentiated/dedifferentiated or dedifferentiated liposarcomas.

SPH4336 was administered orally once each day in successive 28-day cycles until demonstration of progressive disease or the development of unacceptable toxicity.

The study incorporated a safety lead-in for the initial 10 subjects. Safety data was evaluated by the Safety Review Committee (SRC) after 10 subjects (minimum 1 cycle completed) were accrued and the SRC recommended that the study could continue.

Tumor assessments according to RECIST v1.1 were performed at baseline and every 6 weeks (from C1D1) for 36 weeks, then every 12 weeks thereafter.

1.2. SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

Cycle	SCN	C1	C1	C1	C1	C2	C2	C3+	C3+	ET	SFU	LTFU
Day of cycle (± 2 days)	-28 to 0	1	2	15	16	1	15	1	15			
Informed consent	X											
Medical history	X											
Weight	X	X		X		X	X	X	X	X	X	
Physical exam	X											
Symptom-directed exam		X		X		X	X	X	X	X	X	
Vital signs	X	X		X		X	X	X	X	X	X	
ECOG Performance status	X	X				X		X		X	X	
Adverse events	X	X		X		X	X	X	X	X	X	
Concomitant medications	X	X		X		X	X	X	X	X	X	
12-lead ECG	X	X		X		X	X	X				
Hematology	X	X		X		X	X	X		X	X	
Chemistry	X	X		X		X	X	X		X	X	
Coagulation	X	X		X		X	X	X		X	X	
COVID-19, HIV, TB, HBV, HCV tests	X											
Serum pregnancy test	[X]											
Tumor assessment	X						X	[X]	[X]	[X]		
Tumor tissue collection	[X]			[X]								
PK samples		X	X	X	X	X						
SPH4336 compliance		X				X		X		X		
Disease status												X

Study assessments (biopsy, laboratory and clinic visits) may be performed ± 2 days of the recommended date. Laboratory assessments may be performed in advance of clinic visits.

Screening (SCN) is performed within 28 days of Cycle 1 Day 1 (C1D1). Screening evaluations may be repeated within 7 days of C1D1 if requested by the Medical Monitor (e.g., borderline eligibility or clinical instability)

End-of-Treatment (ET) visit is performed on day that decision is made to discontinue SPH4336 administration if the decision is made during a clinic visit. In subjects where the decision to discontinue SPH4336 administration is made outside of a clinic visit (e.g., based on scan results only available later), the ET visit may be combined with the SFU visit.

Safety Follow-Up (SFU) visit is performed 28 days ± 14 days after last dose of SPH4336.

ET and SFU visits may be combined if any of the following apply: 1) subject discontinued SPH4336 outside of a clinic visit, 2) subject had no Grade 2 or higher SPH4336-related toxicity at their last study visit or, 3) subject started a subsequent therapy.

Long-Term Follow-Up (LTFU) – Performed at 3-month intervals (±1 month) following last study visit (i.e., ET or SFU) on all subjects achieving at least stable disease and do not develop progressive disease while on treatment. LTFU of disease status will be performed until progression of disease, start of a new treatment, death or 12 months after last study visit, whichever is sooner. May be conducted via review of the medical record without the need for a clinic visit.

X - Required

[X] – Optional, or not performed on every visit (see notes below for specific assessments).

Informed consent – May be performed at any time prior to the start of screening procedures (i.e., outside of the 28-day screening window).

Medical history – Includes all cancer-related history over a subject's lifetime and non-cancer related history limited to the 2 years prior to C1D1.

Symptom-directed exam – Limited physical exam performed in response to symptoms reported by the subject.

Vital signs – Performed once on visit days. Vital signs include heart rate (per minute), respiratory rate (per minute), blood pressure (mmHg), temperature (degrees Fahrenheit).

Concomitant medications – Recorded from 28 days prior to C1D1 to the time of the ET or SFU visit, except for medications administered as cancer treatment, for which lifetime history will be recorded.

12-lead ECG –ECGs performed as close as possible to each PK draw. ECGs should be performed in triplicate (at least 5 minutes apart) if the QTcF on the initial ECG is greater than 470 msecs. Additional ECGs may be collected if clinically indicated. On days without a PK draw, ECGs are performed once.

Hematology – [Blood] Complete blood count with differential to include WBC, RBC, HGB, HCT, platelets, MCV, MCH and differential

Chemistry – [Blood] Sodium, potassium, chloride, blood urea nitrogen, creatinine, glucose, calcium, AST, ALT, total, direct and indirect bilirubin, alkaline phosphatase, total protein, albumin

Coagulation – [Blood] PT, activated PTT (aPTT) and INR

Serum pregnancy test – [Blood] Only required for females of child-bearing potential

Tumor assessment – Performed at baseline and every 6 weeks (from C1D1) for 36 weeks, then every 12 weeks thereafter. Disease assessments may be performed less frequently if appropriate (e.g., subjects with complete responses) and approved by the Medical Monitor. Disease assessment should be performed using CT with contrast or MRI (if medically necessary).

PK sample(s) – [Blood] Collected in Cycle 1 Day 1: pre-dose and 1 h, 2 h, 4 h, 6 h post-dose, Day 2: 24 h post-dose and Day 15: pre-dose and 1 h, 2 h, 4 h, 6 h post-dose, Day 16: 24 h post-dose and in Cycle 2 (Day 1).

Tumor Tissue – Availability of archived tumor tissue or performance of a tumor biopsy during screening for confirmation of histologically of a liposarcoma with a dedifferentiated component and of CDK4 positivity, if not already known, in all subjects and for baseline tumor biomarker (phospho-Rb, Ki-67) determination in the first 10 subjects. A fresh biopsy will be collected on Cycle 1 Day 15 in the first 10 subjects to determine treatment-related changes in tumor biomarkers. Collection details are summarized in Protocol Section 5.4 and will be provided in the laboratory manual.

1.3. GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
BLQ	Below the Limit of Quantification
BOR	Best Overall Response
CDK	Cyclin-Dependent Kinase
CI	Confidence Interval
COVID	Coronavirus Disease
CR	Complete Response
CRF	Case Report Form
CT	Computerized Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DOR	Duration of Response
DLT	Dose Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
ET	End-of-Treatment
HBV	Hepatitis B Virus
HCT	Hematocrit
HCV	Hepatitis C Virus
HGB	Hemoglobin
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
INR	International Normalized Ratio
KM	Kaplan-Meier
LLOQ	Lower limit of quantification
LTFU	Long-Term Follow-Up
MCH	Mean Cell Hemoglobin
MCV	Mean Cell Volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NE	Not Evaluable
ORR	Overall Response Rate
OS	Overall Survival
OTR	Objective Tumor Response

PD	Progressive Disease
PD	Pharmacodynamic
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response
PT	Prothrombin Time
PT	Preferred Term
PTT	Partial Thromboplastin Time
QTcF	QT Interval corrected using Fridericia's formula
RBC	Red blood cells
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCN	Screening
SD	Standard Deviation
SD	Stable Disease
SFU	Safety Follow-Up
SOC	System Organ Classification
SRC	Safety Review Committee
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Events
TTR	Time to Response
WBC	White blood cells
WHO	World Health Organization
WHODD	WHO Drug Dictionary

2. OBJECTIVES

Primary Objective:

The objective of this study was to evaluate the efficacy (PFS at Week 12) of SPH4336 in subjects with well-differentiated/dedifferentiated (WDLS/DDLS) or dedifferentiated (DDLS) liposarcomas.

Secondary Objectives:

The secondary objectives were as follows:

- To evaluate the safety and tolerability profile of SPH433 (AEs)
- To evaluate the pharmacokinetics of SPH4336 (non-compartmental PK)
- Median PFS, Best Overall Response, Duration of Response, Time to Response, Overall Survival and other efficacy assessments
- To evaluate various tumor tissue biomarkers (phospho-Rb, Ki-67) for activity in the first 10 patients enrolled

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. SAMPLE SIZE AND POWER

Based on historical data, Progression Free Survival (PFS) at 12 weeks of > 60% is considered promising and a PFS of < 35% is considered not promising. A sample size of 29 subjects provides at least 90% power with type I error rate of 0.1 to decide whether the PFS rate at 12 weeks is less than or equal to 0.35 or greater than or equal to 0.60. If the number of subjects who are progression-free at 12 weeks is 14 or more, the hypothesis that the PFS rate at 12 weeks is less than or equal to 35% is rejected. If the number of subjects who are progression-free at 12 weeks is less than 14, the hypothesis that the PFS rate at 12 weeks is greater than or equal to 60% is rejected. Sample size was calculated using a single-stage Phase 2 clinical trial design. A final sample size of 33 was intended to be utilized to account for a non-evaluable rate of 15%.

3.2. RANDOMIZATION AND MASKING

This is a non-randomized, open-label study.

3.3. HANDLING OF DATA

3.3.1. Strata and Covariates

No stratifications among subjects or the use of covariates is planned.

3.3.2. Examination of Subject Subsets

No subgroup analyses are planned.

3.3.3. Multiple Testing and Comparisons

No adjustments for multiplicity are planned.

3.3.4. Missing Data and Outliers

Every effort was made to obtain required data at each scheduled evaluation from all subjects. In situations where it was not possible to obtain all data, imputations of missing data may be necessary. These situations are described below. Unless otherwise specified, no imputation for missing data will be performed.

3.3.5. Imputation of Incomplete Dates

3.3.5.1. Imputation of Adverse Events and Prior/Concomitant Medications and Procedures

An incomplete date occurs when the exact date an event started or ended cannot be obtained from a subject. The database contains data fields for month, day, and year. A date is incomplete if at least one of these three fields is not known.

For many of the planned analyses, a complete date is necessary to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

For the purposes of handling partially reported start and stop dates for an event the following algorithm will be applied:

• Missing start day, but month and year present:

If the event occurs in the same month and year as the dosing of study drug, then the start day of the event will be assigned to the day of first dose of study drug.

Otherwise, the start day will be set to the first day of the month.

• Missing start day and month, but year present:

If an event occurs in the same year as study drug dosing, then the start date of the event will be assigned to Day 1.

Otherwise, the start day and month will be set to 01 January.

• Missing all components of a start date:

Assign the date of Day 1.

• Missing end day, but month and year present:

The day will be set to the last day of the month.

• Missing end day and month, but year present:

The end day and month will be set to the date of study completion/discontinuation. However, if the study completion/discontinuation year is greater than the year of the event, then the day and month will be set to 31 December.

• In the event of a completely missing end date (year not present and ongoing not checked), the end date will be imputed as the last day of dosing. If the imputed date is later than the date of study completion/discontinuation, then the date of study completion/discontinuation will be imputed for the date.

If any imputed date causes the end date to occur prior to the start date of the event, the start date of the event will be used for the imputation of the end date. If any imputed date causes the start date of the event to occur after the end date of the event, the end date of the event will be used for the imputation of the start date. In subject data listings, start and stop date of events will be displayed as reported on the eCRF (i.e., imputed values will not be listed).

3.3.5.2. Imputation of Missing Date of Initial Cancer Diagnosis

For any partial initial diagnosis dates, the following imputation rules will be applied:
• Missing day will be set to 01.
• If both month and day are missing, the date will be set to 01 January.

3.3.5.3. Imputation of Missing Date of Death

Partial death dates are not expected. However, for any partial death dates, the following imputation rules will be applied:
• Missing day will be set to 01.
• If both month and day are missing, the date will be set to 01 January.

3.3.6. Imputation of Missing Severity or Relationship for Adverse Events

Adverse events (AEs) with missing severity or relationship to study drug will not be imputed. Actual values will be presented in the data listings.

3.3.7. Data Handling Rules for Efficacy Data

Subjects were assigned to one of the following best overall response categories: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), or Not Evaluable (NE) by the investigator.

Per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, a subject response was classified as NE for a timepoint if no measurement is performed. If only a subset of lesion measurements are made at an assessment, the case will be considered NE unless the contribution of the individual missing lesion(s) is considered to not change the assigned time point response.

A subject will be considered to have a response if all the criteria for response have been met per RECIST v1.1.

3.3.8. Presentations by Study Visit

Visits will be presented according to the nominal visit obtained from the CRF or laboratory data. Unscheduled assessments will be included in the listings.

3.3.9. Definitions and Terminology

Age
The age of a subject is defined as the number of whole years between the subject's birth date and the date of informed consent.

Baseline Value
For purposes of analysis, the baseline value is defined as the last non-missing value obtained prior to administration of SPH4336. If the last non-missing collection of ECGs is collected in triplicate, the average will be used for the baseline value.

Day 1 (Baseline)
Day 1 is the earliest day that study drug is initiated.

Study Day
Study Day is defined relative to the day of first dose administration on Cycle 1, Day 1. Thus, the study day of an event is calculated as:

date of event – date of first dose + 1, if event is on or after Cycle 1 Day 1, OR
date of event – date of first dose, if event is before Cycle 1 Day 1

There is no Day 0.

Days on Study
Days on Study is the number of days from Day 1 to the date of study completion or early termination as recorded on the End of Study CRF.

Study Visit
Study Visit is the nominal visit as recorded on the CRF.

Change from Baseline
Change from baseline for a given endpoint is defined as the Study Day X value minus the Baseline Value.

Last Dose of Study Drug
Last Dose of study drug is defined as the last date that the subject received SPH4336 as determined by last date of dosing as recorded on the End of Treatment CRF.

Study Drug Exposure

Study drug exposure will be summarized by duration of exposure (days), total dose received (mg) and daily dose (mg) received.

Duration of exposure will be presented in days and is defined as the number of days from the date of First Dose to the date of Last Dose calculated as:

(the date of last dose– date of first dose + 1) and corrected for any days dose was held.

Total dose received (mg) will be calculated as the (sum of all tablets dispensed – sum of all tablets returned) x (100 mg) + (sum of all tablets dispensed – sum of all tablets returned) x (200 mg). If the number of tablets dispensed or returned is missing, it is assumed that the number of tablets returned was 0.

Daily dose received (mg) will be calculated as total dose received (mg) / duration of exposure in days for each subject.

Study Drug Treatment Compliance
Treatment compliance will be calculated as a percentage based on the total dose received (mg) divided by the adjusted planned administration (mg) (extent of exposure after adjusting for any dose modifications or holds).

Adjusted planned administration (mg) will be calculated based on the number of days of planned dose multiplied by 400 (mg). Number of days of planned dose will be defined as the cycle duration or days until end of treatment (whichever was smaller) for each planned dose per cycle minus the number of days dose held as reported on the Study Drug Administration CRF.

Adverse Event
An AE is any untoward medical event that occurs to a subject following signing of the study Informed Consent Form (ICF), whether or not the event is considered SPH4336-related. AEs will be recorded as those that occur following signing the ICF through the sooner of 28 days after the last dose of SPH4336 or until the start of additional anticancer therapy.

Treatment-emergent Adverse Event
A TEAE will be an AE that occurred during the study after the first dose of study drug. Treatment-emergent AEs will be recorded from the first administration of SPH4336 up to the sooner of 28 days after the last dose of SPH4336 or until the start of additional anti-cancer therapy. Additionally, it is assumed that an Adverse Event which was reported to have started on Day 1 occurred after the initiation of study drug.

Serious Adverse Event (SAE)
An SAE is any AE that results in any of the following outcomes:
- Death
- A life-threatening experience
- An inpatient hospitalization or prolongation of an existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- An event that is not listed above, but that requires intervention to prevent one of the outcomes listed above also is considered a SAE

The following will be excluded from the definition of an SAE:
- Elective hospitalizations that are not in response to an AE
- Hospitalizations that are of less than 24 hours duration
- Hospitalization related to disease progression

Concomitant Medications
Concomitant medications are those medications taken on or after the initiation of SPH4336 and will be determined programmatically based on medication start date. This definition includes medications started prior to the initiation of SPH4336, but continuing concomitantly with SPH4336.

Prior Medications
Prior medications are those medications taken and discontinued prior to the initiation of SPH4336 and will be determined programmatically based on medication start date and end date.

3.4. TIMING OF ANALYSES

The final analysis of the study will occur when accrual has ceased and no patients remain on study treatment or if the study is stopped for safety reasons or lack of study drug efficacy.

4. ANALYSIS POPULATIONS

The populations for analysis will include the Safety Analysis Population and Efficacy-Evaluable Population. A PK report describing the PK analysis will be included as an appendix in the clinical study report. An analysis of the biomarkers was not performed. Since the study ended prematurely because of futility, a limited analysis of efficacy will be performed.

4.1. SAFETY ANALYSIS POPULATION

The Safety Population will include all subjects who receive at least one dose of SPH4336.

4.2. EFFICACY-EVALUABLE POPULATION

The protocol defined the Efficacy-Evaluable Population is to include all subjects who received at least 1 dose of SPH4336 and met at least one of the following 2 criteria: have at least 2 post-baseline disease assessments (including at Week 12) and received study treatment for at least 12 weeks without disease progression; or experience disease progression while on study treatment.

5. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study, with no hypothesis testing performed for the primary and other selected efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (N), number of observations (n), mean, median, standard deviation (SD), interquartile range, minimum, and maximum for continuous data and frequencies and percentages for categorical data.

Data required for an abbreviated clinical study report will be included in the data listings. Unless otherwise noted, the data will be sorted first by subject number, date, and time (as applicable).

The statistical analyses will be conducted with the SAS® System version 9.4 or higher.

5.1. SUBJECT DISPOSITION

Subject disposition will be presented for the Safety Population in Tables and Listings. Summaries will include the reason(s) for discontinuation.

Subject disposition, protocol deviations and inclusion / exclusion criteria (for screened subjects) will be presented in data listings.

5.2. DEMOGRAPHIC CHARACTERISTICS

Demographic characteristics will be summarized based on the Safety Population. Demographic variables including age, sex, ethnicity and race will be summarized. Age at the time of informed consent, as collected on the eCRF, will be summarized using descriptive statistics. Sex, ethnicity and race will be summarized with the number and percentage of subjects in each parameter category. Demographic characteristics will be presented in a data listing.

5.3. BASELINE CHARACTERISTICS AND CANCER HISTORY

Baseline characteristics include weight (lb) and ECOG performance status score at baseline. Weight will be summarized using descriptive statistics. Frequency counts and percentages will be used to summarize subjects' ECOG performance status score and cancer history.
Baseline characteristics and cancer history data will be presented in data listings.

5.4. MEDICAL HISTORY

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 or later by preferred term (PT) and system organ classification (SOC). The number and percentage of subjects experiencing each medical history event will be summarized by SOC and PT for the Safety Population. A listing of medical history will also be provided.

5.5. PRIOR THERAPIES AND SURGERY

Prior systemic cancer treatment, prior radiation therapy, and prior cancer surgery will be listed. The following will be presented in summary tables:

- Number and % of subjects with any prior systemic cancer treatment
- Number and % of subjects with any prior radiation therapy
- Number and % of subjects with any prior cancer surgery

5.6. EXPOSURE AND COMPLIANCE

Exposure and compliance to SPH4336 will be summarized and listed for the Safety Population. Duration of exposure (days), total (mg) and daily dose (mg) received and treatment compliance (%) will be summarized using descriptive statistics as described in Section 3.3.9.

Study drug administration, drug accountability, exposure, and compliance information will be presented in data listings.

5.7. EFFICACY ANALYSIS

5.7.1. Primary Efficacy Endpoint

The primary efficacy endpoint was to be the number and percentage of Efficacy-Evaluable subjects who had Progression-Free Survival (PFS) at 12 weeks. PFS is defined as the time interval from the date of the first dose of the SPH4336 until the first date at which disease progression is documented as assessed by the Investigator or date of death due to any cause, whichever occurs first. Subjects who were alive and progression-free at the time of data analysis were to be censored at the time of their last tumor assessment. Progression was evaluated by the investigator according to RECIST v1.1.

5.7.2. Primary Efficacy Analysis

Limited efficacy analyses (tabulations) will be performed because this study ended prematurely due to futility (lack of efficacy). A by-patient listing of the objective responses evaluated by the investigators will be included in the report. The listing and table displaying duration of dosing will display the number of subjects who were dosed for 12 weeks or more without disease progression, and subjects who experienced disease progression at any time during the study, which were the criteria for inclusion in the Efficacy-Evaluable analysis dataset.

After 13 patients were enrolled in the study, too few Efficacy-Evaluable patients had reached 12 weeks of dosing without disease progression (2 of 10) to obtain a positive result for the primary study objective (see Section 3.1 Sample Size and Power). A futility analysis was performed, and it showed that the study would most likely not reach the threshold for a positive signal, even if additional patients were enrolled. A fourteenth patient was enrolled, but the study was closed (due to futility) before week 12.

Bayesian Evaluation of Futility

# Efficacy-Evaluable Patients	Stop Study if #Responses ≤
10	2
11	3
12	3
13	4
14	4
15	5
16	5
17	6
18	6
29	13

The analysis above was performed using available software (BOP2: Bayesian Optimal Phase II Design with Simple and Complex Endpoints (mdanderson.org)) and a simulation was conducted evaluating different sample sizes between current enrollment at the time of the evaluation (n=8) and full protocol enrollment (n=29).

5.7.3. Secondary Efficacy Endpoints

Secondary efficacy endpoints were to include:

- Median PFS
- Best Overall Response (BOR)
- Overall Response Rate (ORR)
- Duration of Response (DOR)
- Time to Response (TTR)
- Overall Survival (OS)

BOR will be tabulated, and overall response will be recorded in listings, but otherwise, analyses of secondary efficacy endpoints will not be performed because this study was prematurely ended due to a lack of efficacy.

5.8. SAFETY

Data from all subjects that receive at least one dose of SPH4336 (Safety Population) will be included in the safety analyses.

5.8.1. Adverse Events

Treatment emergent adverse events (TEAEs) will be coded by System Organ Class and preferred term using MedDRA version 23.0 or higher. The investigator grades the severity/intensity of each AE with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and categorizes the relatedness of the AE to SPH4336.

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Overall Summary of Treatment-Emergent Adverse Events;
- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term;
- Related Treatment-Emergent Adverse Events by CTCAE Grade, System Organ Class and Preferred Term;
- CTCAE Grade 3 or Higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term;
- Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term;
- Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term;
- Treatment-Emergent Adverse Events Leading to Discontinuation of SPH4336 by System Organ Class and Preferred Term;

Summaries of AEs will include the number and percentages of subjects with each preferred term and SOC unless specified otherwise. Missing onset dates will be imputed as previously outlined in Section 3.3.5.1 as required to determine treatment-emergent events.

All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms. All adverse events that occurred prior to the initiation of study drug or more than 28 days after last dose of study drug will be excluded from the tables, but will be included in the listings. No imputation for missing severity or relationship will be applied for listings.

5.8.2. Clinical Laboratory Assessments

Results from both local laboratories and the central laboratory used in this study are included in all data displays.

All descriptive summaries of laboratory results will be presented in Système International (SI) units, as suggested by the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research *Position on Use of SI Units for Lab Tests* (Oct 2013). Descriptive

statistics of chemistry, hematology, and coagulation clinical laboratory results and their corresponding change from baseline will be presented at each visit where parameters were scheduled to be collected per the clinical study protocol.

Where applicable, hematology, chemistry and coagulation results for select parameters will be assigned a toxicity grade based on the U.S. Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (27 Nov 2017). If the quantitative criteria for grading are equivalent for two grades and the differentiation is described by clinical interventions, the clinical intervention component will not be considered and the highest CTCAE grade will be assigned. Similarly, death related to AE (i.e., Grade 5) cannot be determined with available laboratory-based data collection and, thus, will not be summarized as a category. Laboratory parameters that include multiple sets of criteria for each direction (e.g., separate criteria for potassium measures to assess hyperkalemia and hypokalemia) will be summarized separately to reflect each set of criteria.

Five-by-five contingency tables will be presented for lab tests where toxicity grading can be applied, to summarize the shift from the baseline grade to the worst post-baseline grade. Grades will be presented as none (Grade 0; i.e., measurements did not meet any CTCAE criteria for Grades 1 through 4), mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Summary results will include the count and percentage of subjects within each shift category. Hematology, chemistry and coagulation parameters will be presented in data listings.

5.8.3. Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary (WHODD) Global B3 March 2022 or later. Medications entered on the eCRF will be mapped to Anatomic Therapeutic Chemical (ATC) drug class and drug name.

Concomitant medications will be summarized. The number and percentage of subjects receiving any medication will be summarized, as will the number and percentage receiving any medication by ATC drug class and generic drug name. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class.

All medications will be listed.

5.8.1. Concomitant Procedures

Concomitant procedures will be coded using MedDRA Version 22.0 or later. Concomitant procedures will be summarized. The number and percentage of subjects receiving any procedures will be summarized, as will the number and percentage receiving any procedures by system organ class (SOC) and preferred term. Subjects reporting more than one procedure at each level of summarization (any procedure, SOC, and preferred term) will be counted only once. All procedures will be listed.

5.8.1. Electrocardiogram (ECG)

Descriptive statistics of heart rate/pulse (beats/min), RR interval (msec), PR interval (msec), QRS interval (msec), QT interval (msec) and QTcF (msec) interval and changes from baseline will be summarized, as well shift tables for overall interpretation. ECG parameters will be presented in data listings.

5.8.2. Vital Signs

Descriptive statistics for vital signs including heart rate (beats per minute), respiratory rate (breaths per minute), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), and temperature (Fahrenheit) values and changes from baseline will be summarized.

Vital signs parameters will be presented in data listings.

5.8.1. ECOG

The number and percentage of subjects with each ECOG performance status (0, 1, 2, 3, 4, 5) will be summarized categorically. Change from baseline for each post-baseline visit will also be summarized.

A listing of ECOG performance status results will be presented.

6. PROTOCOL DEVIATIONS

Subjects with protocol deviations will be presented in data listings.

7. CHANGES IN THE PLANNED ANALYSES

The study ended prematurely because of a lack of efficacy in study patients. Therefore, a formal analysis of efficacy will not be performed. Biomarker analysis was also not performed.

No other changes in the planned analysis are anticipated. Should any deviations from the analyses specified in the authorized statistical analysis plan arise, such deviations will be documented in the final clinical study report.

8. REFERENCES

E. L. Kaplan & Paul Meier (1958) Nonparametric Estimation from Incomplete Observations, Journal of the American Statistical Association, 53:282, 457-481

9. PROPOSED TABLES, LISTINGS, AND FIGURES

Number	Title	Population
Tables		
14.1.1	Subject Disposition	Safety
14.1.2	Demographic Characteristics	Safety
14.1.3	Baseline Characteristics and Cancer History	Safety
14.1.4	Medical History	Safety
14.1.5	Prior Therapies and Surgery	Safety
14.1.6	Study Drug Exposure and Compliance	Safety
14.2.1	Best Overall Response	Efficacy
14.3.1.1	Overall Summary of Treatment-Emergent Adverse Events	Safety
14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.3	Related Treatment-Emergent Adverse Events by CTCAE Grade, System Organ Class and Preferred Term	Safety
14.3.1.4	CTCAE Grade 3 or Higher Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.5	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety
14.3.1.6	Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term	Safety
14.3.1.7	Treatment-Emergent Adverse Events Leading to Discontinuation of SPH4336 by System Organ Class and Preferred Term	Safety
14.3.2.1	Listing of Deaths	Safety
14.3.2.2	Listing of Serious Adverse Events	Safety
14.3.2.3	Listing of Grade 3 or Higher Adverse Events	Safety
14.3.2.4	Listing of Adverse Events Leading to Discontinuation of SPH4336	Safety
14.3.3.1	Hematology Results and Changes from Baseline	Safety
14.3.3.2	Shift in Hematology Laboratory Values in CTCAE Toxicity Grade to the Worst Abnormal Value	Safety
14.3.3.3	Chemistry Results and Changes from Baseline	Safety
14.3.3.4	Shift in Chemistry Laboratory Values in CTCAE Toxicity Grade to the Worst Abnormal Value	Safety
14.3.3.5	Coagulation Results and Changes from Baseline	Safety
14.3.3.6	Shift in Coagulation Laboratory Values in CTCAE Toxicity Grade to the Worst Abnormal Value	Safety

14.3.4.1	Concomitant Medications	Safety
14.3.4.2	Concomitant Procedures	Safety
14.3.5.1	Vital Signs Results and Changes from Baseline	Safety
14.3.5.2	12-Lead Electrocardiogram - Univariate Summary by Parameter and Visit	Safety
14.3.5.3	12-Lead Electrocardiogram Interpretation - – Shift from Baseline to Worst Post-Baseline Value	Safety
14.3.6	Summary of ECOG Performance Status	Safety
Listings		
16.2.1	Subject Disposition	Safety, Screened
16.2.2	Inclusion/Exclusion Criteria	Screened
16.2.3	Protocol Deviations	Safety
16.2.4.1	Demographic Characteristics	Safety
16.2.4.2	Medical History	Safety
16.2.4.3	Baseline Characteristics and Cancer History	Safety
16.2.4.4	Prior Systemic Cancer Treatment	Safety
16.2.4.5	Prior Radiation Therapy	Safety
16.2.4.6	Prior Cancer Surgery	Safety
16.2.4.7	Prior and Concomitant Medications	Safety
16.2.4.8	Concomitant Procedures	Safety
16.2.5.1	Study Drug Administration	Safety
16.2.5.2	Drug Accountability	Safety
16.2.5.3	Study Drug Exposure and Compliance	Safety
16.2.6.1	Overall Response	Safety
16.2.6.2	Target Lesion Assessment	Safety
16.2.6.3	Non-Target Lesion Assessment	Safety
16.2.6.4	New Lesion Assessment	Safety
16.2.7	Adverse Events	Safety
16.2.8.1.1	Hematology	Safety
16.2.8.1.2	Chemistry	Safety
16.2.8.1.3	Coagulation	Safety
16.2.8.2	Vital Signs	Safety
16.2.8.3	ECOG Performance Status	Safety
16.2.8.4	12-Lead Electrocardiogram	Safety
16.2.8.5	Physical Examination	Safety