A PHASE 2 MULTICENTER, OPEN-LABEL STUDY OF THE CDK4/6 INHIBITOR SPH4336 IN SUBJECTS WITH LOCALLY ADVANCED OR METASTATIC LIPOSARCOMAS

PROTOCOL NUMBER:	SPH4336-US-01
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SPONSOR:	Shanghai Pharma Biotherapeutics USA Inc. 3545 John Hopkins Court, Suite 160 San Diego, CA 92121
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VERSION HISTORY

Version	Version Date	Notes
1.0	15-Dec-2021	Original Protocol

STUDY CONTACT INFORMATION

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CLINICAL PROTOCOL APPROVAL FORM

Protocol Title: A Phase 2 Multicenter, Open-Label Study of the CDK4/6 Inhibitor SPH4336 in Subjects with Locally Advanced or Metastatic Liposarcomas

Study No: SPH4336-US-01

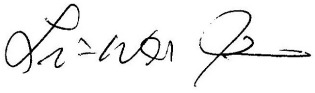
Protocol Version No: V2.0, Amendment 1.0

Protocol Version Date: July 26, 2022

This study protocol was subject to critical review and has been approved by the appropriate protocol review committee of the Sponsor. The information contained in this protocol is consistent with:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies: 45 CFR Part 46, 21 CFR Parts 11, 50, 54, 56, 312
- International Conference on Harmonization (ICH) GCP
- Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013)
- Applicable local legal and regulatory requirements.

The Investigator will be supplied with details of any significant or new findings, including adverse events, relating to treatment with the investigational product.

Name and Title	Approval	Signature	Date
Author: Kenneth W. Locke, Ph.D. - CSO	(Yes) No (circle one)		7/25/22
Clinical Operations: Li-Wei Jen- Sr Director, Clinical Operations	(Yes) No (circle one)		7/25/22

SPH4336-US-01 v2.0, Amendment 1.0

A Phase 2 Multicenter, Open-Label Study of the CDK4/6 Inhibitor SPH4336 in Subjects with Locally Advanced or Metastatic Liposarcomas

CONFIDENTIALITY AND INVESTIGATOR STATEMENT

The information contained in this protocol and all other information relevant to SPH4336 are the confidential and proprietary information of Shanghai Pharma Biotherapeutics USA Inc. (SPHBio), and except as may be required by federal, state or local laws or regulation, may not be disclosed to others without prior written permission of SPHBio.

I have read the protocol, including all appendices, and I agree that it contains all the necessary information for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the regulations stated in the Federal Code of Regulations for Good Clinical Practices and International Conference on Harmonization guidelines and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and any amendments, and access to all information provided by SPHBio or specified designees. I will discuss the material with them to ensure that they are fully informed about SPH4336 and the study.

_____

Principal Investigator Name (printed) Signature

_____ _____

Date Site Number

SPH4336-US-01 PROTOCOL SYNOPSIS

Title	A Phase 2 Multicenter, Open-Label Study of the CDK4/6 Inhibitor SPH4336 in Subjects with Locally Advanced or Metastatic Liposarcomas
Protocol No.	SPH4336-US-01
Phase	2
Sponsor	Shanghai Pharma Biotherapeutics USA Inc.
Study location	US
Investigational Product	SPH4336
Study Population	Subjects with locally advanced or metastatic CDK4-positive liposarcomas
Primary Objectives [Endpoints]	• Evaluate the efficacy of SPH4336 in subjects with CDK4-positive liposarcomas [PFS at 12 weeks]
Secondary Objectives [Endpoints]	• Evaluate the safety and tolerability profile of SPH4336 [AEs] • 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 • Evaluate tumor tissue biomarkers for activity (e.g., phospho-Rb, Ki-67) in the first 10 patients
Treatment Regimen	The dose will be 400 mg QD. SPH4336 tablets will be administered orally each day on a continuous schedule.

Study Design	The study is a multicenter, non-randomized, open-label Phase 2 study of SPH4336 with a safety lead-in in subjects with CDK4-positive liposarcomas. SPH4336 will be administered orally once each day in successive 28-day cycles until demonstration of progressive disease or the development of unacceptable toxicity. The study will incorporate a safety lead-in for the initial 10 subjects. Safety will be evaluated after 10 subjects (minimum 1 cycle completed) by a Safety Review Committee (SRC). The study will be stopped if unacceptable toxicity is observed in more than 2 subjects. Tumor assessments according to RECIST v1.1 will be performed at baseline and every 6 weeks (from C1D1) for 36 weeks, then every 12 weeks thereafter. PK samples will be collected in all subjects. Baseline (pretreatment) tumor tissue (archival or fresh) will be collected from all subjects to confirm histologically a liposarcoma with a dedifferentiated component and CDK4 positivity. Tumor tissue biomarkers (phospho-Rb, Ki-67) will be analyzed in the first 10 study subjects in baseline (pretreatment) and C1D15 tumor tissue samples. A SRC will oversee study safety and will meet at a frequency commensurate with accrual during the study (e.g., 10 subjects (safety lead-in) and 20 subjects, and as needed).
Pharmacokinetics	Single dose pharmacokinetic samples will be collected during Cycle 1 at the following timepoints: • Day 1: pre-dose and 1 h, 2 h, 4 h, 6 h post-dose • Day 2: 24 h post-dose Multiple dose pharmacokinetic samples will be collected during Cycle 1 at the following timepoints: • Day 15: pre-dose and 1 h, 2 h, 4 h, 6 h post-dose • Day 16: 24 h post-dose In addition, a single trough PK sample will be collected on the following days: • Cycle 2 Day 1 (pre-dose)
Correlative science	Baseline tumor biopsies (either fresh or archived) will be collected from all subjects to confirm histologically a liposarcoma with a dedifferentiated component and CDK4 positivity. Biomarkers (phospho-Rb, Ki-67) will also be analyzed in baseline tumor tissue and in biopsies collected on C1D15 in the first 10 study subjects.

Safety Review Committee (SRC)	The SRC will consist of the following individuals selected by the Sponsor: • At least one Investigator • The Sponsor Medical Officer or designee • The Medical Monitor Responsibilities of the SRC will include: • Review of all safety data • Evaluation of full safety data following the accrual of the initial 10 subjects (minimum 1 cycle completed) • Adjustment of the frequency of administration of SPH4336 (e.g., addition of administration breaks, changes to the dosing frequency), if appropriate based on developing PK and safety data The Safety Review Committee will meet at appropriate intervals (e.g., after first 10 subjects (safety lead-in) and 20 subjects) and as needed during the study.
Number of Subjects	Total: approximately 33 (29 evaluable)
Location	US
Number of Sites	5-10

Inclusion Criteria	• Informed consent
	• ≥ 18 years of age
	• ECOG performance status 0 or 1[1]
	• Histologically confirmed, locally advanced or metastatic sarcoma
	  o Dedifferentiated or well-differentiated/dedifferentiated liposarcomas
	• No more than 3 prior lines of therapy
	• Evidence of progression as evidenced by at least one of the following within the past 3 months:
	  o An increase of at least 20% in measurable tumors
	  o The appearance of new lesions
	  o Unequivocal progression of non-measurable lesions
	• Measurable disease per RECIST v1.1[2]
	• If residual treatment-related toxicity from prior therapy:
	  o All treatment-related toxicity resolved to Grade 1 or baseline (alopecia excepted)
	• ANC ≥ 1,500/μL
	• Platelets ≥ 100,000/μL
	• Hgb ≥ 9.0 g/dL (in the absence of pRBC transfusion over the prior 4 weeks)
	• Estimated glomerular filtration rate of ≥ 60 mL/min (based on the Cockcroft and Gault formula for individualized estimates of GFR[3])
	• Total bilirubin ≤ 1.5 x the Upper Limit of Normal (ULN) or ≤ 3 x ULN if known Gilbert's disease
	• AST and ALT ≤ 3 x ULN or ≤ 5 x ULN if malignant involvement of the liver
	• Sterile or willing to use effective contraception (approved hormonal contraceptive such as oral contraceptives, patches, implants, injections, rings or hormonally-impregnated intrauterine device (IUD), or an IUD in women of childbearing potential and a condom in men) during the study and for 3 months following the last dose of study drug
	• Availability of archived tumor tissue or willingness to undergo a baseline tumor biopsy, and in the first 10 study subjects, to determine baseline tumor biomarker levels and a willingness to undergo a second tumor biopsy at C1D15 to assess treatment-induced changes in tumor biomarker levels

Exclusion Criteria	• Prior treatment with a CDK4/6-targeted agent • Patient's tumor known to be CDK4-negative • Anticancer therapy (e.g., chemotherapy, biologics, irradiation) within 14 days or 5 half-lives (whichever is greater) of screening • Major surgery within 28 days of screening • Requirement for systemic treatment with strong CYP3A4 inhibitors or inducers at study entry • Central nervous system metastases or leptomeningeal disease, unless appropriately treated and neurologically stable without steroids for ≥ 28 days • Other malignancy unless disease-free for ≥ 2 years and not expected to relapse or require treatment during study participation • Active systemic infection or severe localized infection • Known HIV-positive with CD4+ cell counts < 350 cells/uL or a history of an AIDS-defining opportunistic infection • Known hepatitis B virus (HBV) or hepatitis C virus (HCV) infection with viral load above the limit of quantification • Active COVID-19 infection • Major cardiac abnormalities (e.g., uncontrolled angina, unstable arrhythmias, myocardial infarction, NYHA Class ≥ 3 CHF) ≤ 6 months of C1D1 • Persistent (3 ECGs ≥ 5 mins apart) prolongation of the QTcF (Fridericia) > 470 msec[4] • [Females] Pregnant or nursing • Any other medical or psychiatric condition, or laboratory abnormality that would result in an unacceptable risk with study participation • Presence of active gastrointestinal disease or other condition expected to interfere significantly with absorption, distribution, metabolism or excretion of oral therapy (e.g., ulcerative disease, uncontrolled nausea, vomiting, chronic diarrhea, malabsorption syndrome)

Dose Holds/ Modifications	Subjects will have their dose of SPH4336 adjusted in response to SPH4336-related toxicity as follows:
	• Grade 1 or 2
	  ○ No dose hold required
	• Grade 3
	  ○ Hold dosing until toxicity has resolved to at least Grade 1 or baseline
	  ○ Reduce dose for second occurrence by at least 100 mg
	  ○ Permanently discontinue further SPH4336 administration for third occurrence
	• Grade 4 anemia or neutropenia
	  ○ Restart dosing only if recovery to ≤ Grade 1 occurs in ≤ 14 days, otherwise permanently discontinue
	  ○ If resumed, reduce dose by at least 100 mg
	• Grade 4 lymphopenia
	  ○ Hold dosing until toxicity has resolved to at least Grade 1 or baseline
	  ○ If resumed, reduce dose by at least 100 mg
	• All other Grade 4
	  ○ Permanently discontinue further SPH4336 administration

Sample size	The following assumptions were used to determine sample size: Based on historical data[19], PFS at 12 weeks of > 60% is considered promising and a PFS of < 35% is considered not promising.[19] 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.[23] 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.[23] A final sample size of 33 will be utilized to account for a non-evaluable rate of 15%.

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 to 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 Section 5.4 and will be provided in the laboratory manual.

LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CDK	Cyclin-Dependent Kinase
CFR	Code of Federal Regulations
CL/F	Formation Clearance
Cmax	Maximum Drug Concentration in Body After Dosing
CT	Computerized Tomography
CYP	Cytochrome P450
DLT	Dose-Limiting Toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic Case Report Form
EF2	Elongation Factor 2 gene
EMR	Electronic Medical Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
HCT	Hematocrit
HED	Human Equivalent Dose
hERG	Human Ether-À-Go-Go-Related Gene
HGB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HNSTD	Highest Non-Severely Toxic Dose
IC_{50}	Half-Maximal Inhibitory Concentration
ICF	Informed Consent Form

Abbreviation	Term
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
Kd	Kilodalton
MCH	Mean Cell Hemoglobin
MCV	Mean Cell Volume
MDM2	Mouse Double Minute 2 gene
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	No Observable Adverse Effect Level
NYHA	New York Heart Association
PD	Progressive Disease
PET-CT	Positron Emission Tomography
PFS	Progression-Free Survival
PHI	Protected Health Information
PI	Principal Investigator
PK	Pharmacokinetic
PO	By Mouth
PT	Prothrombin
PTT	Partial Thromboplastin Time
QD	Once Daily
QTc	Corrected QT Interval
QTcF	QT Interval corrected using Fridericia's formula
RB1	Retinoblastoma 1 gene
RBC	Red Blood Cells
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SRC	Safety Review Committee
SOC	Standard of Care

Abbreviation	Term
SPH3643	Free base of SPH4336
SRC	Safety Review Committee
$t_{1/2}$	Half-life
Tmax	Time to reach maximum (peak) plasma concentration
ULN	Upper Limit of Normal
Vss/F	Apparent volume of distribution at steady state
WBC	White Blood Cells

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1 BACKGROUND

1.1 Liposarcoma

Liposarcomas are rare tumors (~2000 new cases expected in 2021 in the US) derived from fat tissue. Liposarcomas are a subset of soft tissue sarcomas and make up about 20% of all soft tissue sarcomas.[5] Liposarcomas can present in any location, but are more commonly found in the extremities and retroperitoneum. The incidence of liposarcomas appears to be increasing for high-risk subgroups (males) and in the retroperitoneal location.[6] Risk factors for soft tissue sarcomas include prior radiation and certain familial cancer syndromes (e.g., neurofibromatosis, Li-Fraumeni syndrome). Oncogenes considered to be involved in liposarcoma include MDM2, CDK4 and HMGA2.[7] Five-year survival for subjects with liposarcoma varies by subtype (95% for well-differentiated vs. 57% for dedifferentiated tumors) and location (90% for extremity vs. 64% for retroperitoneal location).[6]

Liposarcomas are classified into 3 main groups (Table 2):

- Well-differentiated (WDLS) and dedifferentiated liposarcomas (DDLS)
- Myxoid/round-cell liposarcoma (MLS)
- Pleiomorphic liposarcoma (PLS)

Well-differentiated/dedifferentiated liposarcomas (WDLS/DDLS) account for the majority of liposarcomas. WDLS/DDLS is considered a biphasic disease. The WD component is slow growing and complete resection often results in long-term survival and cure. The DD component, which often arises in the setting of a preexisting WDLS, can be rapidly growing, aggressive, and metastatic. Both WDLS and DDLS are relatively resistant to chemotherapy.[5]

Genetic changes are common in liposarcoma and include amplification of 12q13-15 which harbors a number of cancer-related genes including MDM2, CDK4, HMG2A, TSPAN31. MDM2 amplification is a diagnostic marker of WDLS/DDLS, but is not pathognomonic for the disease as it is also seen in other sarcomas.[7] Amplification of cyclin-dependent kinase 4 (CDK4) is present in >90% of WDLS/DDLS. The level of CDK4 amplification in WDLS/DDLS is about 10x that seen in in normal fat tissue. Certain genes within the 12q13-15 amplicon have been associated with DDLS such as YEATS4, CPM and amplifications of 1p32 and 6p23.[5]

MLSs are considered more sensitive to chemotherapy and irradiation compared to WDLS/DDLS. A number of poor prognostic signs have been identified in MLS including the presence of a round cell component, the tumor site, a high proliferative fraction (as noted with MIB-1 labeling), and TP53 missense mutations.[5] The t(12;16)(q13;p11) translocation is considered pathognomonic for MLS.

PLSs are rare and clinically aggressive with metastases observed in about 40% of subjects. PLSs are poorly responsive to chemotherapy and irradiation which is reflected in a disease-related mortality rate of about 50%. The genetic changes seen in PLS are complex and include deletion of 13q14.2-5 (containing Rb1), mutation or loss of TP53, and loss of NF1.[5]

Table 2: Clinical and Pathologic Features of the Four Principle Liposarcoma Subtypes*

Subtype	Well-differentiated	Dedifferentiated	Myxoid	Pleomorphic
Percent of liposarcoma	40-50	15-20	20-30	5-10
Age (years)	50-60	50-60	30-50 (also childhood/adolescence)	>50
Morphology	Pleomorphic mature adipocytes, variable numbers of lipoblasts	High-grade pleomorphic sarcoma on well-differentiated background	Round/oval mesenchymal cells plus signet ring lipoblasts within myxoid stroma	Variable pleomorphic lipoblasts on background of high-grade pleomorphic sarcoma
Typical sites	Extremities; retroperitoneum; paratesticular (rare); mediastinum (rare)	Retroperitoneum; extremities; paratesticular; mediastinum; head and neck	Thigh; other proximal extremities	Limbs
Recurrence	Local recurrence (retroperitoneum > extremities); Rare metastatic potential	Local recurrence in ~ 40%; Metastasis (lung) ~ 20%-30%	Local and/or metastatic (bone, soft tissue, serosa) ~ 40%	Local recurrence ~ 30%-50%; Metastasis (lung) ~ 30%-50%
Response to therapy	Poor	Poor	Generally sensitive to radiotherapy and chemotherapy	Variable chemosensitivity
Genomics	12q13-15 amplification	12q13-15 amplification plus other chromosomal abnormalities	t(12;16) with FUS-DDIT3 fusion	Complex, with multiple chromosomal abnormalities and higher mutation rate

**Adapted from Lee et al.*[5]*

Initial treatment for liposarcoma depends on the type, size and location of the tumor. If feasible, surgery is often attempted, but the option of surgery may be limited by tumor location, invasion of critical structures (e.g., adjacent organs or major blood vessels) or evidence of metastases. Adjuvant chemotherapy may be considered in subjects with locally invasive tumors or for tumors with high metastatic potential (e.g., MLS, PLS).[8] Nomograms have been developed that provide prognostic information to subjects undergoing surgery for liposarcoma.[9]

A number of chemotherapy drugs are used for soft tissue sarcomas (e.g., gemcitabine, docetaxel, dacarbazine), but doxorubicin and ifosfamide remain the most effective agents.[10,11] Systemic chemotherapy including an anthracycline has been reported to have only a modest response rate of 12% in soft tissue sarcomas with a median progression-free survival of 4.6 months and a median overall survival of 15.2 months.[12]

Trabectedin (Yondelis), and alkylating agent, was approved in 2015 for unresectable or metastatic liposarcoma or leiomyosarcoma in subjects who had received a prior anthracycline-containing regimen. Trabectedin was approved based on an improvement in progression-free

survival compared with dacarbazine (4.2 vs 1.5 months) despite no observed improvement in overall survival.[11,13]

Eribulin (Halaven), a microtubule polymerization inhibitor, was approved in 2016 for unresectable or metastatic liposarcoma in subjects who had received a prior anthracycline. The approval was based on a 7-month improvement in survival (15.6 months with eribulin vs. 8.4 months with dacarbazine). The improvement in OS was only statistically significant for advanced/metastatic DDLS and pleomorphic liposarcoma.[14]

1.2 Cyclin-Dependent Kinases 4 and 6 (CDK4/6)

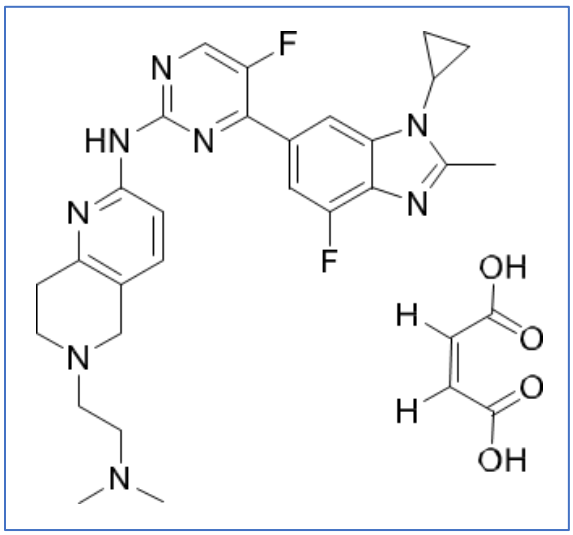
Cyclin-dependent kinases (CDKs), part of the serine/threonine protein kinase family, drive cell-cycle progression, control transcriptional processes, and regulate cell proliferation. CDK4/6 blocks the transition from the G1 to S phase of the cell cycle by blocking Rb phosphorylation and E2F release. Overexpression of the CDK4 protein leads to Rb (retinoblastoma) phosphorylation and progression in the cell cycle. Based on these effects, dysregulation of CDKs is considered to play a key role in tumorigenesis. CDK4/6 genes are widely expressed among various tumors, and high or moderate expression of CDK4/6 is commonly associated with poor survival. No CDK4/6 inhibitors are FDA-approved for the treatment of liposarcoma, however, several are approved for the treatment of post-menopausal hormone receptor-positive/human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer including palbociclib (2015), ribociclib (2017) and abemaciclib (2018).[15,16]

CDK4 is considered a potential target in WDLS/DDLS based on the amplification of CDK4 in >90% of these liposarcomas. Abemaciclib, a CDK 4/6 inhibitor, has been studied in a single-arm Phase 2 study in subjects with dedifferentiated liposarcomas where it demonstrated promising progression-free survival of 12 weeks in 76% of subjects. Median PFS was 30.4 weeks, and one subject had a partial response. Grade 3-4 toxicities included anemia (37%), neutropenia (20%), thrombocytopenia (17%) and diarrhea (7%).[17] Similar results were reported in WDLS/DDLS patients with palbociclib treated on two different intermittent dosing regimen.[18,19]

1.3 SPH4336

SPH4336 is a novel, highly selective CDK4/6 inhibitor currently being studied in a Phase 1 study in patients with solid tumors in China. The structure of SPH4336 is shown in Figure 1.

Figure 1: Chemical Structure of SPH4336



1.3.1 Preclinical Safety Pharmacology and Toxicology

The selectivity of SPH3643 (free base of SPH4336) against 30 kinases was compared with abemaciclib and palbociclib. SPH3643 showed better selectivity for CDK4/6 relative to activity against CDK7/9/1/2. SPH3643 had an IC_{50} greater than 300 nmol/L against a number of other kinases, except PKCa (73 nmol/L), FLT3 (75 nmol/L), and GSK3b (88 nmol/L) and supports the observation that SPH3643 is a highly selective inhibitor of CDK4/6.

After a single intravenous administration in rats, SPH3643 exhibited a moderate plasma $t_{1/2}$ (~5.5 h), high plasma clearance and apparent volume of distribution. After oral administration in rats, SPH3643 produced more than dose-proportional increases in exposure and $t_{1/2}$ (~7-19 h). Oral bioavailability was ~20% at higher doses with no apparent difference in the fed or fasted state. Multiple oral dosing resulted in accumulation in rats. After a single intravenous administration in cynomolgus monkeys, SPH3643 exhibited a long plasma $t_{1/2}$ (~11 h), high plasma clearance and apparent volume of distribution. Oral bioavailability was ~30% and no accumulation was observed with repeated oral dosing.

Plasma protein binding of SPH3643 in several species, including humans, was high and ranged from 87 to 97%. SPH3643 was highly metabolized and eliminated mainly by phase I metabolic reactions (demethylation, dehydrogenation, and oxidation), predominately by CYP3A4. SPH3643 had minimal inhibitory activity on most CYP450 isoforms and moderate inhibitory activity on CYP2B6. There was no indication of any induction of human CYP1A2, CYP2B6 or CYP3A4.

SPH3643 was generally well-tolerated in rats and monkeys with most drug-related findings being reversible. NOAELs of 30 and 10 mg/kg po were established for SPH3643 in the GLP 4-week rat and monkey toxicology studies, respectively. No significant differences in toxicity profile were noted between SPH3643 (free base) and SPH4336 (maleate salt) at a dose of 100 mg/kg po in a bridging GLP 4-week repeat-dose toxicity test in rats. Target organs were the

digestive (e.g., epithelial cell proliferation and macrophage infiltration in digestive tract), hepatic (e.g., liver enzyme elevations), hematologic (e.g., anemia) and immune systems (e.g., decreased bone marrow hematopoietic cells), consistent with the toxicities reported for other CDK4/6 inhibitors. Safety margins of approximately 0.5-fold to 3.6-fold (based on body surface area scaling) over a projected daily human dose of 400 mg SPH4336 given orally were established in these nonclinical studies.

1.3.2 Preclinical Efficacy

Studies of SPH3643 in a variety of xenograft models across a spectrum of CDK4-positive tumors (breast, colon, ovarian, lung, glioma, leukemia, liver, liposarcoma) demonstrated antitumor activity that was better or comparable with abemaciclib and palbociclib.[20]

1.4 Prior Clinical Experience

SPH4336 is currently under investigation as monotherapy in a Phase 1 dose escalation trial in China (Study SPH4336-101) for subjects with advanced solid tumors. Interim safety reports from the initial dose cohorts (50, 100, 200, 300, 400, 600 mg) show SPH4336 to be generally well-tolerated with no DLTs and adverse events typical of CDK4/6 inhibitors (e.g., anemia, leukopenia, lymphopenia, neutropenia, transaminitis, diarrhea).

1.5 Rationale for the Study

SPH4336 is considered appropriate for study in humans based on the following:

- CDK4 is a validated target in human tumors with several CDK4/6 inhibitors approved for the treatment of various solid tumors;
- CDK4 is considered a potential target in WDLS/DDLS based on the amplification of CDK4 in > 90% of WDLS/DDLS tumors;
- SPH4336 is a highly selective inhibitor of CDK4/6 with pharmacologic properties (e.g., increased exposure) that may result in an improved therapeutic index compared to currently available CDK4/6 inhibitors;
- Preclinical studies have demonstrated a safety profile of SPH3643 and SPH4336 consistent with other CDK4/6 inhibitors;
- Xenograft models have demonstrated antitumor activity of SPH3643 and SPH4336 at exposures that should be achievable in the clinic; and,
- Interim PK and safety data from an ongoing Phase 1 trial of SPH4336 in China support a dose of 400 mg in liposarcoma patients.

1.6 Dose of SPH4336

SPH4336 is under evaluation in China in an ongoing Phase 1, open-label, dose-escalation clinical study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of SPH4336 tablet monotherapy in patients with advanced solid tumors (Study SPH4336-101). Interim PK data from the first 6 dose cohorts (50, 100, 200, 300, 400, 600 mg) show that QD oral dosing of SPH4336 generally produced dose-related increases in exposure with increasing dose,

although plasma concentrations appear to plateau at the 400 mg dose. Accumulation was observed with repeated dosing, reaching steady-state within approximately 2 weeks of daily dosing. The ratio of C_{trough} 400 mg QD (at steady-state)/IC_{50} CDK4 SPH3643, adjusted for PPB (Plasma Protein Binding) *in vitro* was approximately 6.6. A similar ratio was observed for abemaciclib (Verzenio®) at its approved dose of 200 mg BID. This suggests that significant inhibition of CDK4 is achieved at trough concentrations following multiple doses of ≥ 400 mg SPH4336.

Safety data from the first 6 dose cohorts (50, 100, 200, 300, 400, 600 mg) as of a June 15, 2022 data cutoff from the ongoing Phase 1 study showed that SPH4336 was well tolerated. The safety profile was generally consistent with the safety profile of other CDK4/6 inhibitors. Treatment Emergent Adverse Events (TEAEs) included gastrointestinal events (e.g., nausea, diarrhea), hepatic events (e.g., liver enzyme elevations), constitutional symptoms (e.g., fatigue) and decreased blood cell counts (e.g., leukopenia, lymphopenia, neutropenia, anemia). There appears to be no correlation between exposure (C_{max}, AUC) and incidence or severity of adverse events. A total of 6 Grade 3 AEs (from 21 patients in the first 6 cohorts) were considered related to SPH4336, including anemia (50 mg cohort), lymphopenia (200 and 300 mg cohorts), leukopenia and neutropenia (400 mg cohort, 2 patients), and diarrhea (600 mg cohort). Both patients in the 400 mg cohort entered the study with borderline blood cell counts. While experiencing leukopenia and neutropenia with no clinical symptoms, both patients underwent brief dose interruptions and dose reduction. One patient ultimately discontinued the study treatment despite recovery to Grade 2. There were two Serious Adverse Events (SAEs) reported; both were considered not related to the study drug by the Investigator. One patient in 200 mg cohort who experienced disease progression withdrew from the study and died 29 days after the last dose of SPH4336 (reported as a Grade 5 non-study drug-related SAE). The other patient in the 300 mg cohort experienced intestinal obstruction shortly after enrollment. This patient was hospitalized and treated with supportive care, and the patient later resumed trial participation and received SPH4336 treatment (reported as a Grade 3 non-study drug-related SAE). Although the data are limited, the safety profile of 400 mg SPH4336 is comparable to or better than that of the 3 FDA-approved CDK4/6 inhibitors (abemaciclib (Verzenio®), palbociclib (Ibrance®) and ribociclib (Kisqali®)) at their approved dose.

Taken together, the interim PK and clinical safety data from the ongoing Phase 1 study along with the nonclinical safety package, support a dose of 400 mg QD in this Phase 2 study in liposarcoma patients. Clinical benefit/efficacy is best addressed in this Phase 2 study in a patient population (dedifferentiated and well-differentiated/dedifferentiated liposarcomas) expressing the drug target (CDK4).

1.7 Potential Risks and Benefits

1.7.1 Potential Risks

With limited human experience, the potential risks associated with SPH4336 are based on animal data and the safety profile of other CDK4/6 inhibitors. These risks include:

- GI Toxicity (e.g., nausea, diarrhea)
- Hepatic toxicity (e.g., transaminase elevations)

- Constitutional symptoms (e.g., fatigue)
- Hematologic toxicity (e.g., called leukopenia, lymphopenia, neutropenia, anemia, thrombocytopenia)

In addition, given the limited clinical experience with SPH4336, there may be risks that are not currently known.

1.7.2 Potential Benefits

Information gained from the study may help other people with locally advanced or metastatic liposarcoma in the future. SPH4336 may benefit subjects by reducing tumor volume and/or slowing tumor growth. A significant extension of Progression-Free Survival (PFS), as seen with other drugs acting through the same mechanism, may be observed. In subjects with symptoms related to the presence of a tumor, SPH4336 may result in a reduction in symptoms.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

- To evaluate the efficacy of SPH4336 in subjects with CDK4-positive liposarcomas

2.1.2 Secondary Objectives

- To evaluate the safety profile of SPH4336
- To evaluate the pharmacokinetics of SPH4336
- To evaluate other tumor responses
- To evaluate various tumor tissue biomarkers for activity

2.2 Endpoints

2.2.1 Primary Endpoint

- Progression-Free Survival (PFS) as assessed by the Investigator at 12 weeks

2.2.2 Secondary Endpoints

- Type, incidence, severity (as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v5.0), seriousness and relationship to study medications of AEs and any laboratory abnormalities
- Pharmacokinetics include plasma concentration-time profiles and C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $t_{1/2}$, CL/F, Vss/F, Accumulation Ratio for C_{max}, AUC, as appropriate
- Median PFS, Best Overall Response (BOR), Time to Response (TTR), Duration of Response (DOR), Overall Survival (OS), and other efficacy assessments
- Tumor tissue biomarkers (e.g., phospho-Rb, Ki-67) in the first 10 patients

3 SUBJECT POPULATION

3.1 Inclusion Criteria

- Informed consent
- ≥ 18 years of age
- ECOG performance status 0 or 1[1]
- Histologically confirmed, locally advanced or metastatic sarcoma
  - Dedifferentiated or well-differentiated/dedifferentiated liposarcomas
- No more than 3 prior lines of treatment
- Evidence of progression as evidenced by at least one of the following within the past 3 months:
  - An increase of at least 20% in measurable tumors
  - The appearance of new lesions
  - Unequivocal progression of non-measurable lesions
- Measurable disease per RECIST v1.1[2]
- If residual treatment-related toxicity from prior therapy:
  - All treatment-related toxicity resolved to Grade 1 or baseline (alopecia excepted)
- ANC ≥ 1,500/μL
- Platelets ≥ 100,000/μL
- Hgb ≥ 9.0 g/dL (in the absence of pRBC transfusion over the prior 4 weeks)
- Estimated glomerular filtration rate of ≥ 60 mL/min (based on the Cockcroft and Gault formula for individualized estimates of GFR[3])
- Total bilirubin ≤ 1.5 x the Upper Limit of Normal (ULN) or ≤ 3 x ULN if known Gilbert's disease
- AST and ALT ≤ 3 x ULN or ≤ 5 x ULN if malignant involvement of the liver
- Sterile or willing to use effective contraception (approved hormonal contraceptive such as oral contraceptives, patches, implants, injections, rings or hormonally-impregnated intrauterine device (IUD), or an IUD in women of childbearing potential and a condom in men) during the study and for 3 months following the last dose of study drug
- Availability of archived tumor tissue or willingness to undergo a baseline tumor biopsy, and in the first 10 study subjects, to determine baseline tumor biomarker levels and a willingness to undergo a second tumor biopsy at C1D15 to assess treatment-induced changes in tumor biomarker levels

3.2 Exclusion Criteria

- Prior treatment with a CDK4/6-targeted agent
- Patient's tumor known to be CDK4 negative
- Anticancer therapy (e.g., chemotherapy, biologics, irradiation) within 14 days or 5 half-lives (whichever is greater) of screening

- Major surgery within 28 days of screening
- Requirement for systemic treatment with strong CYP3A4 inhibitors or inducers of CYP3A4 at study entry
- Central nervous system metastases or leptomeningeal disease, unless appropriately treated and neurologically stable without steroids for ≥ 28 days
- Other malignancy unless disease-free for ≥ 2 years and not expected to relapse or require treatment during study participation
- Active systemic infection or severe localized infection
- Known HIV-positive with CD4+ cell counts < 350 cells/uL or a history of an AIDS-defining opportunistic infection
- Known hepatitis B virus (HBV) or hepatitis C virus (HCV) infection with viral load above the limit of quantification
- Active COVID-19 infection
- Major cardiac abnormalities (e.g., uncontrolled angina, unstable arrhythmias, myocardial infarction, NYHA Class ≥ 3 CHF) ≤ 6 months of C1D1
- Persistent (3 ECGs ≥ 5 mins apart) prolongation of the QTcF (Fridericia) > 470 msec[4]
- [Females] Pregnant or nursing
- Any other medical or psychiatric condition, or laboratory abnormality that would result in an unacceptable risk with study participation
- Presence of active gastrointestinal disease or other condition expected to interfere significantly with absorption, distribution, metabolism or excretion of oral therapy (e.g., ulcerative disease, uncontrolled nausea, vomiting, chronic diarrhea, malabsorption syndrome)

4 STUDY DESIGN

This is a multicenter, non-randomized, open-label Phase 2 study of SPH4336 in subjects with CDK4-positive liposarcomas.

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

The study will incorporate a safety lead-in for the initial 10 subjects. Safety will be evaluated after 10 subjects (minimum 1 cycle completed) are accrued to allow a full assessment of safety by a Safety Review Committee (SRC). The study will be stopped if unacceptable toxicity is observed in more than 2 subjects based on SRC recommendation.

Tumor assessments according to RECIST v1.1.[22] will be performed at baseline and every 6 weeks (from C1D1) for 36 weeks, then every 12 weeks thereafter. PK samples will be collected in all subjects. Baseline (pretreatment) tumor tissue will be collected from all subjects to confirm histologically a liposarcoma with a dedifferentiated component and CDK4 positivity, and in the

first 10 study subjects, tumor tissue biomarkers (phospho-Rb, Ki-67) will be analyzed in baseline (pretreatment) and C1D15 tumor tissue samples.

A Safety Review Committee (SRC) will oversee study safety and will meet at a frequency commensurate with accrual during the study (e.g., after 10 subjects (safety lead-in) and 20 subjects, and as needed).

4.1 Safety Lead-In

The study will incorporate a safety lead-in for the initial 10 subjects. Safety will be evaluated after 10 subjects (minimum 1 cycle completed) are accrued to allow a full assessment of safety by a Safety Review Committee (SRC). The study will be stopped if unacceptable toxicity is observed in more than 2 subjects based on SRC recommendation.

4.2 Unacceptable Toxicity

To be considered as unacceptable toxicity, an AE must meet each of the following 2 criteria:

- Occur during the first 28 days of SPH4336 administration
- Not be incontrovertibly related to underlying disease

In addition, an AE must meet at least one of the following criteria:

- Any Grade 4 AE
- Any Grade 3 non-hematologic AE
- Any AE that results in permanent treatment discontinuation

The following are excluded from the definition of unacceptable toxicity:

- Grade 4 anemia or neutropenia that resolves within 14 days and which is not expected to recur based on a treatment modification (e.g., use of erythrocyte or neutrophil growth factors)
- Grade 4 lymphopenia
- Grade 3 headache, nausea, vomiting, diarrhea, fatigue, or pain if controlled within 72 hours
- Grade 3 electrolyte abnormalities that are asymptomatic and resolve to at least Grade 2 within 72 hours

The SRC will have the option of declaring other toxicities not listed above as unacceptable, if necessary, to ensure subject safety.

4.3 Concomitant Medications, Treatments, and Procedures

During their participation on this study, subjects may continue to use concomitant medications, treatments and procedures previously prescribed to treat non-cancer related conditions provided that, in the Investigator's judgment, they will not interfere with the study outcomes.

Use of proton pump inhibitors are prohibited during the study.

Although SPH4336 is mainly metabolized by CYP3A4, the impact of CYP3A4 inhibitors or inducers on SPH4336 PK has not been characterized in humans. Consequently, drugs, herbal medicines and substances that strongly inhibit or induce CYP3A4 will be prohibited during the study. Moderate inhibitors or inducers of CYP3A4 are to be used with caution. Examples of strong and moderate inhibitors and inducers of CYP3A4 include, but are not limited to:

- Strong inhibitors - boceprevir, cobicistat, danoprevir, ritonavir, elvitegravir, grapefruit juice, itraconazole, ketoconazole, lopinavir, paritaprevir and (ombitasvir and/or dasabuvir), posaconazole, saquinavir, tipranavir, telithromycin, troleandomycin, voriconazole;
- Moderate inhibitors - aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil;
- Strong inducers - apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort; and,
- Moderate inducers - bosentan, efavirenz, etravirine, phenobarbital, primidone.

4.4 Prophylactic Medications, Treatments, and Procedures

The use of prophylactic medications intended to reduce toxicity associated with SPH4336 will not be allowed initially.

The SRC may elect to institute the use of prophylactic medications (e.g., for prevention of nausea and vomiting secondary to study medication) during the study. The specific medications used will be in keeping with generally accepted standards of care and the institutional guidelines of the participating sites.

4.5 Rescue Medications, Treatments, and Procedures

The Investigator will determine the appropriateness and use of any medications, treatments or procedures required to treat study-related toxicities or complications (e.g., treatment of drug-induced nausea or vomiting, treatment of drug-induced myelosuppression or anemia). Any rescue medication, treatments or procedures will be consistent with accepted medical practice and institutional guidelines.

4.6 Prohibited Cancer Treatments

Other medications/therapies intended to treat the subjects' underlying cancer are prohibited during the study (investigational or approved).

4.7 Discontinuation of SPH4336 Administration

SPH4336 may no longer be administered to a subject in the event of any of the following:

- Clinically and/or radiologically significant progressive disease;

- Unacceptable adverse event(s) considered secondary to SPH4336 despite appropriate therapy;
- Withdrawal of consent for SPH4336 administration by the subject (subject may agree to continued follow-up for safety and long-term outcome endpoints);
- Noncompliance by the subject as determined by the Investigator with agreement from the Medical Monitor; or,
- Termination of study by the Sponsor.

4.8 Replacement of Subjects

Non-evaluable subjects who are unable to complete at least two tumor assessments to evaluate efficacy (PFS at 12 weeks) may be replaced to ensure the appropriate number of subjects are fully evaluable for efficacy.

4.9 Removal of Subjects from Study Follow-up

No additional follow-up of a subject will occur in the event of any of the following:

- Withdrawal of consent for follow-up by the subject;
- Subject is lost to follow-up; or,
- Termination of study by Sponsor.

5 STUDY ASSESSMENTS AND EVALUATIONS

5.1 Informed Consent

Written informed consent will be obtained prior to the performance of any study-related procedures.

5.2 Screen Failures

Subjects who have provided informed consent, but were subsequently found to be ineligible for study participation will be considered screen failures.

5.3 Pharmacokinetic Assessments

Single dose pharmacokinetic samples will be collected during Cycle 1 at the following timepoints:

- Day 1: pre-dose and 1 h, 2 h, 4 h, 6 h post-dose
- Day 2: 24 h post-dose

Multiple dose pharmacokinetic samples will be collected during Cycle 1 at the following timepoints:

- Day 15: pre-dose and 1 h, 2 h, 4 h, 6 h post-dose

- Day 16: 24 h post-dose

In addition, a single trough PK sample will be collected on the following days:

- Cycle 2 Day 1

The window for collection of PK samples with be ± 25% of the scheduled time.

PK analysis will be conducted as outlined in Section 10.9.

5.4 Tumor Tissue Assessments

Archived tumor tissue or tissue obtained from a tumor biopsy at baseline will be examined histologically to confirm a diagnosis of a dedifferentiated or well-differentiated/dedifferentiated liposarcoma. CDK4 positivity (at least 1+ per IHC or evidence of amplification on FISH[18]) will also be confirmed in baseline tumor tissue, if not already known. Baseline tumor biomarker (phospho-Rb, Ki-67) determinations will be performed in the first 10 study subjects. A fresh biopsy will be collected on Cycle 1 Day 15 in the first 10 subjects to determine treatment-related changes in those tumor biomarkers. Collection and processing of tumor tissue will be detailed in a laboratory manual. Briefly, tumor cores are obtained by needle (e.g., 2 mm) biopsy (5 cores or as specified by institutional policy). Tissue is fixed in formalin and embedded in paraffin for preparation of 4 μm thickness unstained slides. Slides will be distributed to the appropriate laboratories for analysis using validated assays.

5.5 PFS and Response Evaluations

Tumor assessments according to RECIST v1.1[22] will be performed at baseline and every 6 weeks (from C1D1) for 36 weeks, then every 12 weeks thereafter.

6 INVESTIGATIONAL PRODUCT

6.1 Dosage forms

SPH4336 will be provided as film-coated tablets containing 100 or 200 mg SPH4336 free base (30 tablets per soda-lime glass bottle with a high-density polyethylene cap and a sealing gasket for a medicinal glass bottle).

Excipients in the formulation include the following:

- povidone K30
- cellactose® 80
- croscarmellose sodium
- magnesium stearate
- a film coating premix (gastric soluble, Opadry®, model 85G630034-CN, orange)

6.2 Storage

SPH4336 tablets are stored in a secure location at ambient temperatures 20-25 °C (68-77 °F) with excursions permitted between 15-30°C (59-86°F).

6.3 Administration

SPH4336 tablets should be swallowed whole, without chewing or crushing the tablets. SPH4336 will be administered at least 1 hour before eating or 2 hours after eating. SPH4336 should be taken at a consistent time each day.

On scheduled PK collection days, patients will be instructed to only take SPH4336 when instructed in the clinic.

6.3.1 Missed doses

If a patient misses a dose of SPH4336, the patient should take the dose as soon as possible, but not less than 8 hours before the next dose is due. If the next dose is due in less than 8 hours, the patient should skip the missed dose and take the next scheduled dose.

6.3.2 Vomiting shortly after dosing

If a patient vomits shortly after taking SPH4336, the patient should not retake the dose, but should resume dosing with the next scheduled dose. If vomiting persists, the patient should contact the Investigator.

6.4 Accountability

SPH4336 compliance will be assessed at each visit where SPH4336 is dispensed. The study pharmacist or coordinator and clinical Investigator will maintain accurate records of receipt of all study drug, including dates of receipt. Study personnel will maintain accurate records regarding when and how much study drug is dispensed to and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At completion of the study, to satisfy regulatory requirements regarding study drug accountability, all study drug will be reconciled and retained or destroyed according to applicable state and federal regulations and International Conference on Harmonisation (ICH) guidelines.

6.5 Disposal

SPH4336 tablets must not be destroyed unless prior approval has been granted by the Sponsor or its representative. Disposal will be performed using institutional guidelines.

6.6 Dose Holds and Modifications

Subjects experiencing SPH4336-related toxicity may have SPH4336 held or reduced as outlined in Table 3.

Table 3: Dose Hold Secondary to SPH4336-related Toxicity

Toxicity (CTCAE Grading)	Dose Hold	Dose modification on resumption
1 or 2	No dose hold required	None
3	Hold dosing until toxicity has resolved to at least Grade 1 or baseline	First occurrence (of same AE): No dose reduction Second occurrence: Reduce dose by at least 100 mg Third occurrence: Permanently discontinue
4 anemia or neutropenia	Restart dosing only if recovery to ≤ Grade 1 occurs in ≤ 14 days, otherwise permanently discontinue	First occurrence (of same AE): Reduce by at least 100 mg Second occurrence: Permanently discontinue
4 lymphopenia	Hold dosing until toxicity has resolved to at least Grade 1 or baseline	First occurrence (of same AE): Reduce by at least 100 mg Second occurrence: Permanently discontinue
4 (non-hematologic)	N/A, permanently discontinue	N/A, permanently discontinue

6.6.1 Maximum duration of dose hold

Subjects are allowed to remain on study following a delay of up to 21 days due to SPH4336-related toxicity. Subjects who experience a delay of > 21 days due to SPH4336-related toxicity may be permanently discontinued from further SPH4336 administration.

6.6.2 Criteria for resumption of dosing

If a dose hold is implemented for SPH4336-related toxicity, in addition to the criteria listed in Table 3, subjects may restart study drugs only if the following conditions are met:

- No more than 21 days has passed since the last dose of SPH4336;
- The AE is not expected to recur (per the Investigator and Medical Monitor) at the same grade with resumption of SPH4336 based on an intervention such as the addition of a prophylactic treatment (e.g., prophylactic anti-emetics), or a reduction in the dose of SPH4336; and,
- Continued administration of SPH4336 is considered to be in the subject's best interest (per the Investigator).

6.6.3 Dose re-escalation

In subjects who undergo dose reduction, re-escalation may be considered if the following criteria are met:

- The toxicity responsible for the prior dose reduction is considered unlikely with return to the prior higher dose based on a change in subject status or treatment (e.g., successful medical management of underlying condition, uncertain relationship of prior toxicity to SPH4336); and,

- Approval of the Medical Monitor.

After dose reescalation, if the toxicity recurs and requires another dose reduction, the subject is not allowed to return to the higher dose level.

6.7 Overdose

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved SPH4336) must be communicated to Shanghai Pharma Biotherapeutics USA Inc. or a specified designee. Details of any signs or symptoms and their management should be recorded including details of any antidote(s) administered.

6.8 Discontinuation

SPH4336 may be discontinued in the event of any of the following:

- Clinically and or radiologically significant progressive disease;
- Unacceptable adverse event(s) considered secondary to SPH4336 despite appropriate therapy;
- Withdrawal of consent for SPH4336 administration by the subject (subject may agree to continue to be followed for safety and long-term outcome endpoints);
- Noncompliance by the subject as determined by the Investigator with agreement from the Medical Monitor and the Sponsor Medical Officer or designee; or,
- Termination of study by the Sponsor.

7 SAFETY

Safety assessments will consist of monitoring and recording AEs and Serious AEs (SAEs), measurement of protocol-specified hematology, chemistry, urinalysis, vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the SPH4336.

The Principal Investigator is responsible for recognizing and reporting AEs to the Sponsor or designee. It is the Sponsor's responsibility to ensure the reporting of relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible Institutional Review Board (IRB)/Ethics Committee (EC) according to the policies of that IRB/EC.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the safety reporting requirements.

7.1 Adverse Events

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.

Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms;
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation);
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy;
- Is clinically significant in the Investigator's judgment.
  (Note: For oncology trials, certain abnormal values may not qualify as adverse events).

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5xULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF. If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

Pre-existing conditions are not considered an AE unless the condition worsens by at least one grade following the start of SPH4336 administration.

Adverse events will be captured starting at the time of informed consent. AEs occurring between the time of informed consent and the first dose of SPH4336 will only be captured if related to a study mandated procedure. AEs will continue to be captured until the sooner of 28 days after the last dose of SPH4336 or until a new anti-cancer treatment is started.

7.1.1 Intensity and Causality of Adverse Events

The event's **relationship to the study drug or treatment procedure** should be indicated according to the following definitions:

Related	The adverse event *is related* to the treatment or procedure. An adverse event (AE) is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug (i.e., there are facts, evidence, or arguments to suggest possible causation).
Not Related	The adverse event *is clearly not related* to the treatment or procedure.

The **frequency** of the event should be indicated according to the following definitions:

Single episode	This is the first and only experience/episode of the event in the trial.
Recurrent	The event has occurred before in the trial.
Continuous	The event is continuing.

The **intensity** grade of the event should be indicated according to the following definitions: All intensity of AEs will be assessed by the Investigator using NCI CTCAE v5.0.

The **outcome** should be indicated according to the following definitions:

Recovered without sequelae	Patient recovered completely from the AE.
Recovered with sequelae	Patient has recovered from the AE but displays other symptoms.
Ongoing	Patient continues to exhibit symptoms of the AE. The patient will be followed until the AE is resolved.
Death	Patient died (the date of death should be entered as the SAE resolution date).
Unknown	Outcome is unknown due to loss to follow-up.

7.1.2 Time Period for AE Reporting

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 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 anticancer therapy.

7.1.3 Reporting of Pregnancy

Pregnancy is neither an AE nor an SAE. However, all pregnancies occurring in subjects, or their partner, will be followed to assess for pregnancy-associated AEs or SAEs such as congenital anomaly. If, at any time between the first study drug dispensing and 7 days after the last dose of study drug, a pregnancy is suspected, the patient/partner will be instructed/requested to return to

the study center within 48 hours and undergo a serum pregnancy test, as confirmation of pregnancy. All confirmed pregnancies must be immediately reported using the appropriate form.

Upon confirmation of a subject pregnancy, no further investigational treatment will be administered. All pregnancies with study drug exposure will be followed until resolution (i.e., termination [voluntary or spontaneous] or birth).

7.2 Serious Adverse Events (SAEs)

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

7.2.1 Reporting of SAEs

The recording of SAEs (regardless of their relationship to study drug) will begin with the Screening visit (signing of ICF) until the Final Visit or Early Termination Visit. Any SAE, including death due to any cause, which occurs during the conduct of this study, regardless of relationship to study drug, must be reported within 24 hours of the Investigator's (or designee's) first awareness of the event.

An initial Serious Adverse Event Form (SAE form) should be completed and submitted per the SAE form instructions.

The Investigators should attempt to group signs and symptoms into a single term that constitutes a single unifying diagnosis and indicate the serious criteria that are applicable to the SAE (the list of serious criteria is also provided in the above section). The Investigator's opinion of the relationship of the SAE to study drug, the duration, intensity, frequency, actions taken with study drug, and the outcome of the SAE will be documented using the definitions/criteria in Section 7.2.

All serious adverse events are to be reported to the Institutional Review Board (IRB) by the Investigator.

7.2.2 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

SAEs that meet the criteria for a suspected unexpected serious adverse reactions (SUSARs) will be reported as an IND Safety Report to the appropriate regulatory authorities and participating investigators, in accordance with International Conference on Harmonization (ICH) guidelines and FDA regulations. A SUSAR that meets the seriousness criteria of life-threatening and/or results in death will be reported within seven (7) calendar days. A SUSAR that is not life-threatening or does not result in death will be submitted to the regulatory authorities within fifteen (15) calendar days.

Unexpected adverse reactions are adverse reactions, the nature, severity, consequences, or frequency of which are not consistent with the anticipated risks described in current relevant information (e.g., Investigator's Brochure) for the investigational product. The Investigator's Brochure serves as a primary document to provide safety reference information to determine whether an adverse reaction is expected or unexpected. Prior to submitting the appropriate IND safety report, the Sponsor will ensure that the event meets all three of the definitions for "suspected adverse reaction," "serious," and "unexpected."

8 EFFICACY

Tumor assessments according to RECIST v1.1.[22] will be performed at baseline and every 6 weeks (from C1D1) for 36 weeks, then every 12 weeks thereafter.

The Sponsor will have the option of collecting de-identified copies of all scans. The Sponsor may elect to conduct a central assessment of response prior to the completion of the study.

Other secondary efficacy endpoints (e.g., Median PFS, Best Overall Response, Time to Response, Duration of Response, Overall Survival) and tumor tissue biomarkers (in the first 10 patients) will also be assessed.

9 QUALITY ASSURANCE AND QUALITY CONTROL

9.1 Monitoring

Site monitoring shall be conducted to ensure that subject protection, study procedures, laboratory, study intervention administration, and data collection processes are of high quality and meet Sponsor, Good Clinical Practice (GCP)/ICH and, when appropriate, regulatory guidelines.

9.2 Audits and Inspections

The Investigator will permit study-related quality audits and inspections by the Sponsor or its representative(s), government regulatory authorities, and the IRB/EC of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The Investigator will ensure the capability for review of applicable study-related facilities. The Investigator will ensure that the auditor or inspector or any other compliance or

quality assurance reviewer is given access to all study-related documents and study-related facilities.

Participation as an Investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the IRB/EC, and the Sponsor or its representative(s).

9.3 Safety Review Committee (SRC)

A Safety Review Committee will govern the conduct of the study. The SRC will consist of the following individuals selected by the Sponsor:

- At least one Investigator
- The Sponsor Medical Officer or designee
- The Medical Monitor

Responsibilities of the SRC will include:

- Review of all safety data at the completion at appropriate intervals;
- Evaluation of safety data following the accrual of the initial 10 subjects (minimum 1 cycle completed); and,
- Adjusting the dose and/or schedule used in the study as appropriate based on accumulating safety data from the study.

Additional responsibilities may be asked of the SRC as appropriate to ensure subject safety.

The Safety Review Committee will meet as needed based on the rate of subject accrual (e.g., after 10 subjects (safety lead-in) and 20 subjects). SRC meetings may be conducted by teleconference or through email communications. Decisions made during the SRC meeting will be recorded in meeting minutes and will be part of the study documentation.

10 STATISTICAL CONSIDERATIONS

10.1 General Considerations

Data collected in this study will be presented using summary tables and subject data listings.

Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum.

Categorical variables will be summarized by frequencies and percentages.

An assessment of protocol violations, SPH4336 accountability, and other data that may impact the general conduct of the study will be presented.

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the SAP. In the event of differences between the protocol and the SAP, the SAP will

prevail. The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

10.2 Statistical Design

This is a multicenter, open-label, Phase 2 study of SPH4336 in subjects with advanced or metastatic liposarcoma.

10.3 Statistical Methods

A separate Statistical Analysis Plan (SAP) will be prepared, providing detailed methods for the analyses.

Any deviations from the planned analyses will be described and justified in the final integrated study report.

10.4 Study Subjects

10.4.1 Disposition of Subjects

The number and percentage of subjects screened and entered on study will be presented. Reasons for withdrawal will also be summarized.

10.4.2 Protocol Deviations

A summary of the number and percentage of subjects with protocol deviations by type of deviation will be provided.

10.4.3 Analysis Populations

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

The PK-Evaluable Population will include all subjects who have had at least one pre- and post-dose PK assessment performed.

The Efficacy-Evaluable Population will include all subjects who receive at least 1 dose of SPH4336 and meet at least one of the following 2 criteria:

- Have at least 2 post-baseline disease assessments (for PFS at 12 weeks); or,
- Experience clinical progression.

10.5 Demographics, Baseline Characteristics, and Concomitant Medications

Demographic data, medical history, concomitant disease, and concomitant medications will be summarized.

Baseline characteristics will be summarized for the safety population. Subjects who died or withdrew before treatment started or do not complete the required safety observations will be described and evaluated separately.

10.6 Treatment Compliance

Treatment administration will be summarized including dose administration, dose modifications or delays, cumulative dose, average dose, number of doses, and the duration of therapy.

10.7 Efficacy Analysis

Details of efficacy analyses will be outlined in the Statistical Analysis Plan (SAP). The progression-free survival (PFS) rate and overall response rate (ORR) will be summarized with frequencies and percentages, as appropriate. The duration of response for complete and partial response subjects will be summarized with descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) as well as categorically. PFS, Median PFS, Time to Response, Duration of Response and Overall Response Rate will be determined using RECIST v1.1.[22] Kaplan-Meier methodology will be used to summarize time to events.

Subjects will be classified according to their best overall tumor response (complete response, partial response, stable disease, or progressive disease). Frequencies, proportions, and exact 95% CI of subjects, when appropriate, stratified by their best overall tumor response will be calculated. Subjects with a best overall tumor response of complete or partial with a confirmed duration of at least 4 weeks (28 days) will be further classified as having an objective tumor response. A listing of subjects with an objective tumor response will be presented.

Duration of response will be calculated as the number of days from the first documentation of response (complete or partial) to the first documentation of disease progression or death, whichever comes first.

Time to response will be calculated as the number of days from the first dose of SPH4336 to the first documentation of response.

Subjects who are alive and progression-free at the time of data analysis will be censored at the time of their last tumor assessment.

Duration of stable disease will be calculated from Cycle 1 Day 1.

Based on historical data[19], PFS at 12 weeks of > 60% is considered promising and a PFS of < 35% is considered not promising.[19] 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.[23] 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.

Tumor tissue biomarkers (phospho-Rb, Ki-67) will be analyzed by immunohistochemistry in pretreatment and C1D15 tumor tissue samples; individual and mean change from baseline in the markers and % of subjects with biomarker reductions will be determined.

The methods for all efficacy statistical analyses will be defined in the SAP.

10.8 Safety Analyses

Data from all subjects that receive at least 1 dose of SPH4336 will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECOG performance status, body weight, ECGs, and concomitant medications and procedures will be tabulated and summarized.

AEs will be summarized overall and with separate summaries for serious AEs, AEs leading to discontinuation, AEs leading to death, and CTCAE v5.0 Grade 3 or higher AEs. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized using system organ class and preferred term for all subjects in the Safety Population.

Body weight and vital signs will be summarized descriptively (N, mean, standard deviation, median, minimum, and maximum). ECOG will be summarized categorically and descriptively.

Shift tables displaying subject counts and percentages classified by baseline grade and maximum grade on treatment will be provided for all laboratory data. A marked laboratory change is defined as a shift from a baseline Grade 0 to Grade 3 (non-hematologic) or Grade 4 or greater (hematologic) on treatment, or a shift from a baseline Grade 1 to Grade 4 or greater on treatment. The number and percentage of subjects with marked laboratory changes will be tabulated.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO Drug) and they will be listed and summarized by dose level.

10.9 Pharmacokinetic Analyses

Individual and mean (± standard deviation) plasma SPH4336 concentration-time data (and SPH4336, metabolites if appropriate) will be tabulated and plotted. SPH4336 PK parameters will be estimated from the plasma SPH4336 concentration-time data using a non-compartmental analysis method. Alternative methods may be considered. Estimated individual and mean (±SD) PK parameters will be tabulated and summarized. Other descriptive statistics may be reported for plasma SPH4336 concentration-time data and estimated PK parameters. Dose proportionality, SPH4336 accumulation, and attainment of steady state will be evaluated as data allow.

PK parameters evaluated will include plasma concentration-time profiles and C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $t_{1/2}$, CL/F, Vss/F, Accumulation Ratio for C_{max}, AUC, as appropriate. These parameters will be listed by individual subject and summarized by descriptive statistics (means, medians, ranges, standard deviations and coefficient of variation, as appropriate).

10.10 Interim Analyses

No formal interim analysis is planned.

10.11 Determination of Sample Size

Based on historical data[19], PFS at 12 weeks of > 60% is considered promising and a PFS of < 35% is considered not promising.[19] 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.[23] 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.[23] A final sample size of 33 will be utilized to account for a non-evaluable rate of 15%.

10.12 Final Analysis Time Point

The final analysis of the study will occur when the first of either of the following occurs:

- Accrual has ceased and no subjects remain on study
- Accrual has ceased and no subject has been on study for less than 12 months

11 ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

11.1 Ethical Standard

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in:

- United States Code of Federal Regulations (CFR) applicable to clinical studies: 45 CFR Part 46, 21 CFR Parts 11, 50, 54, 56, 312
- ICH E6
- Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013)
- Applicable local legal and regulatory requirements

11.2 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB registered with the OHRP.

Protocol amendments require review and approval by the applicable IRB prior to implementation.

Changes to the informed consent form will be submitted to the appropriate IRB for review.

At the time of any protocol amendment or change to the informed consent document, an assessment will be made regarding the need for re-consenting existing subjects.

11.3 Subject and Data Confidentiality

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the Sponsor. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Sponsor will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the Sponsor.

11.4 Research Use of Stored Human Samples, Specimens or Data

The Sponsor will be responsible for all stored samples generated during this study. Some samples will be stored with specific vendors as appropriate (e.g., pharmacokinetic samples). Samples and data will be stored using codes assigned by the clinical data system. Data will be kept in password-protected computers.

11.5 Future Use of Stored Specimens

Data collected for this study will be analyzed and stored by the Sponsor. After the study is completed, the de-identified, archived data will be maintained by the Sponsor and may be made available for use by other researchers including those outside of the study.

With the subject's approval and as approved by local IRBs, de-identified biological samples will be stored by the Sponsor with the same goal as the sharing of data with other researchers, some of whom may be outside of this study.

During the conduct of the study, an individual subject can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

11.6 Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the clinical database and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub investigator, all appropriate measures will be taken to safeguard and prevent access to this data by any unauthorized party.

11.7 Financial Information

The finances for this clinical study will be subject to a separate written agreement between the Sponsor and applicable parties.

12 DATA HANDLING AND RECORD KEEPING

12.1 Data Collection Responsibilities

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported by his or her site to the Sponsor.

This study will utilize a 21 CFR Part 11-compliant data capture system provided by the Sponsor or its representative for the purposes of data collection. Specific instructions on the system used for data collection will be provided to the study sites. Clinical data will be entered directly from the source documents.

12.2 Amendments to the Protocol

If an amendment to the protocol is required, the amendment will originate from and be documented by the Sponsor or its representative.

The amendment will be submitted to the FDA or other regulatory authorities by the Sponsor as applicable. IRB/EC approval will be obtained as applicable.

If an amendment to the protocol substantially alters the risk or benefit to the subjects, subject consent to continue participation in the study may be required.

12.3 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of SPH4336. These documents may be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

12.4 Data Collection

The study electronic CRF is the primary data collection instrument for the study. Case report forms will be completed in English.

In order to maintain confidentiality only study number, subject number and date of birth will identify the subject in the eCRF system. If the subject's name appears on any other document (e.g., laboratory report), it must be redacted on the copy of the document to be supplied to the Sponsor and replaced instead with the subject number. The Investigator will maintain a personal

subject identification list (subject numbers with corresponding subject identifiers) for subjects enrolled at his or her site to enable records to be identified and verified as authentic. Subject data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested by the eCRF system must be supported by and be consistent with the subject's source documentation. All missing data must be explained. For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The Investigator will electronically sign and date the subject eCRF indicating that the data in the eCRF is accurate. Each completed eCRF will be signed and dated by the Investigator once all data for that subject is final.

12.5 Disclosure and Publication Policy

The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication process. In general, authorship will be determined by the number of eligible subjects enrolled in the study by any given Investigator site and/or by the extent to which an individual Investigator may have contributed to the scientific design of the protocol. The Sponsor will have final say in determining authorship on any publication.

12.6 Data Handling for Subject Withdrawal or Termination

Data generated from subjects prior to withdrawal of consent or withdrawal from the study will be maintained and utilized in the final study analysis.

No data generated from subjects after their withdrawal from the study will be collected.

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14 APPENDICES

Table 4: ECOG Performance Status Criteria

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Source: European Society of Medical Oncology. Performance Scales: Karnofsky & ECOG Scores. Oncology//Pro. 2018.

Table 5: New York Heart Association (NYHA) Classification

Class	Functional Capacity	Objective Assessment
I	Subjects with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.