Asian Multinational Phase 2 Study of SP-02L (darinaparsin for injection) in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma

PROTOCOL

Protocol Number: SP-02L02

Local Sponsor : << XXXXXXXXXXX >>

Development Sponsor : Solasia Pharma K.K.
4F Sumitomo Fudosan Shiba-koen Tower,2-11-1,
Shiba-koen, Minato-ku, Tokyo 105-0011, Japan

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PROTOCOL SYNOPSIS

Title	Asian Multinational Phase 2 Study of SP-02L (darinaparsin for injection) in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma
Target Disease	Relapsed or refractory peripheral T-cell lymphoma (PTCL)
Study Phase	2
Objectives	[Primary Objective] To evaluate the efficacy of SP-02L monotherapy in patients with relapsed or refractory PTCL [Secondary Objectives] • To evaluate the safety of SP-02L monotherapy in patients with relapsed or refractory PTCL • To assess the pharmacokinetic (PK) profile of SP-02L at multiple doses in a subgroup of subjects
Study Design	This study is a phase 2 multinational, multicenter, single-arm, open-label, non-randomized study conducted in East Asia countries/regions. Subjects will receive SP-02L at 300 mg/m^2 once daily for 5 consecutive days followed by 16 days of rest per cycle of 21 days (3 weeks). SP-02L will be administered for 6 cycles to evaluate the efficacy and safety of SP-02L monotherapy by using various endpoints. If the subject wishes to continue investigational drug administration and the principal investigator judges that the continued administration of investigational drug is possible and necessary for the subject, the investigational drug administration can be continued beyond 6 cycles. Pharmacokinetics will be assessed in subjects enrolled in a part or all of the investigational sites in each of participating country or region at Cycle 1.
Endpoints	[Primary Endpoint] Tumor response (best overall response) according to the Revised Response Criteria for Malignant Lymphoma by an International Working Group to Standardize Response Criteria for Non-Hodgkin's Lymphomas in 2007 [Secondary Endpoints] • Progression-free survival (PFS), time to response (TTR), duration of response (DOR) and overall survival (OS) • Occurrence of adverse events (AEs) • Drug plasma concentration-time profile, PK parameters, and urinary excretion rates
Planned number of subjects	65 subjects The target number of subjects to be included in PK assessment is about 10 in each of participating country/region

Planned Study Duration	December 2015 to December 2021 (planned)
Eligibility Criteria	[Inclusion criteria] (1) Patients with ethnic background of each participating country/region; (2) Patients aged ≥ 20 years of age at the date of obtaining informed consent; (3) Patients with histopathologically confirmed diagnosis of one of the following: ・ Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS); ・ Angioimmunoblastic T-cell Lymphoma (AITL); ・ Anaplastic large cell lymphoma (ALCL), (ALK-positive/negative); The pathology specimens supporting the local diagnosis should be submitted for the central pathology review by the Pathological Review Committee. (4) Patients have a treatment history of at least one regimen with antitumor agents for the above diseases; (5) Patients have an enlarged lymph node or extranodal mass lesion that is measurable on computed tomography (CT); In this study, a measurable enlarged lymph node is defined as a lesion of > 1.5 cm in greatest transverse diameter regardless of short axis measurement or > 1.0 cm in short axis regardless of greatest transverse diameter, that is clearly measurable in 2 perpendicular dimensions. A measurable extranodal mass lesion is defined as a lesion of ≥ 1.0 cm in greatest transverse diameter (two times longer than the scan slice thickness). A nodular mass within the liver or spleen is defined as a space-occupying lesion of ≥ 1.0 cm in 2 perpendicular dimensions. (6) Patients with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0, 1, or 2; and (7) Patients with a life expectancy of at least 3 months (e.g. no acute exacerbation of their primary disease) as determined by the principal investigator or sub-investigator. [Exclusion Criteria] (1) Patient with inadequately maintained major organ functions as evidenced by the following laboratory test values taken at the screening visit. These laboratory test values should not be affected by blood transfusion or administration of hematopoietic growth factor agents, etc. Even though the patients who meet none of the following criteria, subject's condition should not show an obvious tendency toward worsening as determined by the principal investigator or sub-investigator: ・ Electrocardiogram (ECG): Fridericia-corrected QT interval (QTcF) ≥ 450 msec; ・ Hemoglobin: < 8.0 g/dL; ・ Neutrophil count: < 1,000/mm^3;

	・ Platelet count: < 50,000/mm^3; ・ Aspartate aminotransferase (AST) and alanine aminotransferase (ALT): > 3 times ULN defined at the investigational site; or ・ Creatinine: > 1.5 times ULN defined at the investigational site; (2) Patients with a positive result for either hepatitis C virus antibody (HCV antibody) or hepatitis B virus (HBV) surface antigen (HBs antigen) test during the screening period. Alternatively, the patients with a negative result for HBs antigen; however, with a positive result for either HBV surface antibody (HBs antibody) or HBV core antibody (HBc antibody), and with an HBV deoxyribonucleic acid (DNA) level (HBV-DNA level) ≥ the detection sensitivity of the assay; (3) Patients who are known to be positive for human immunodeficiency virus antibody (HIV antibody) or human T-cell leukemia virus type I antibody (HTLV-1 antibody); (4) Patients who are known or suspected metastasis or invasion to the central nervous system, or lymphoma lesions in the central nervous system; (5) Patients who have a concurrent active malignancy other than PTCL with the disease- or treatment-free period of < 5 years, excluding skin basal cell carcinoma, skin squamous cell carcinoma and carcinoma in situ of the cervix that are judged to have been cured; (6) Patients who have concurrent or a past history of central nervous system disease (e.g. seizure, dementia, Parkinson's disease, Alzheimer's disease), cerebrovascular disorder (e.g. transient ischemic attack, cerebral infarction, cerebral hemorrhage), or psychiatric disorder (e.g. schizophrenia, depression, addiction); (7) Patients who concurrently have any of the following conditions: ・ Congenital long QT syndrome; ・ Poorly controlled cardiac arrhythmia; ・ Poorly controlled diabetes mellitus; ・ Infections requiring systemic administration of antibiotic, antifungal or antiviral drugs; ・ Acute hepatitis, chronic hepatitis, or liver cirrhosis; or ・ Serious acute or chronic organ dysfunction (e.g. cardiac, hepatic, renal, or respiratory failure); (8) Patients who have known or suspected hypersensitivity to arsenic; (9) Patients who have used agents containing darinaparsin; (10) Patients who have received anticancer chemotherapy (including continuous use of oral administration or injection of corticosteroids equivalent to > 10 mg/day of prednisolone, as anticancer therapy) or anticancer immunotherapy (excluding antibody therapy) within 3 weeks before the day of subject enrollment;

	(11) Patients who have received antibody therapy (including investigational drugs) within 12 weeks before the day of subject enrollment; (12) Patients who have received radiotherapy within 3 weeks before the day of subject enrollment; (13) Patients who have received autologous hematopoietic stem cell transplant within 12 weeks before the day of subject enrollment, or patients who have received allogeneic hematopoietic stem cell transplant; (14) Patients who underwent major surgery (e.g., surgery requiring systemic anesthesia, craniotomy, thoracotomy, or laparotomy) within 4 weeks before the day of subject enrollment; (15) Patients who are participating in other clinical trials or received any investigational drug or device within 4 weeks before the day of subject enrollment; (16) Patients who are unable to stay in the hospital for the period specified in the protocol; (17) Female patients who are breast-feeding, pregnancy or planned pregnancy; (18) Patients of reproductive potential who will not be able to use adequate contraceptive precautions during the treatment period and following 3 months after the last dosing of investigational drug; in the judgment of the principal investigator or sub-investigator; or (19) Patients with considerable concern for compliance with the protocol, in the judgment of the principal investigator or sub-investigator.
Dosage and dosing schedule of the investigational drug	Subjects will receive SP-02L at 300 mg/m^2 once daily for 5 consecutive days (Days 1-5) followed by 16 days of rest per cycle of 21 days (3 weeks). SP-02L will be administered for 6 cycles according to the protocol-specified criteria of postponement (skip) of administration, dose reduction and treatment discontinuation. If the subject wishes to continue investigational drug administration and the principal investigator judges that the continued administration of investigational drug is possible and necessary for the subject, the investigational drug administration can be continued beyond 6 cycles. Reconstituted and diluted SP-02L solution should be infused intravenously over 1 hour (± 10 minutes) on each dosing day. Because the injection site abnormalities have been frequently reported in subjects who received SP-02L infusion via a peripheral line in the previous clinical studies, the investigational drug is recommended to be administered through the central vein.

Prohibited concomitant therapy	Throughout the study (from the day of obtaining the informed consent to the end of follow-up period), none of the medications or treatments listed below should be proscribed for any reason: • Anticancer chemotherapy or anticancer immunotherapy, other than the investigational drug; Continuous use of oral administration or injection of corticosteroids (equivalent to > 10 mg/day of prednisolone) is also prohibited. However, single or as-needed use for the treatment of fever or pretreatment for blood transfusion etc. is allowed. • Radiotherapy; • Hematopoietic stem cell transplants; • Cellular immunotherapy (e.g., cancer vaccine therapy); • Gene therapy; • Major surgery (e.g., surgery with general anesthesia, craniotomy/thoracotomy/laparotomy); • Any other investigational drugs, therapeutic drugs that are not approved by regulatory agency in each country or region (excluding drugs already approved for off-label use) and investigational device.
Study Procedures	See “Schedule of Study Procedures”
Statistical Procedures	Based on a central assessment at Efficacy and Safety Review Committee, the best overall responses for 6 cycles will be summarized to calculate the overall response rate (ORR) and 90% confidence interval (90% CI). Based on a local assessment at each investigational site, the best overall responses for 6 cycles and in the entire period will be summarized to calculate ORR and 90% CI. To assess the tumor response in each subject, the waterfall plot will be produced to show the rate of tumor shrinkage at best overall response. PFS, TTR, DOR and OS will be summarized overall and by histopathological subtype. PFS and OS will be analyzed by using Kaplan-Meier methods overall and by histopathological subtype. The occurrence of AEs will be summarized by system organ class and by preferred term according to the MedDRA, and by ethnic background and by severity. The occurrence of investigational-drug-related AEs, serious AEs or investigational-drug-related serious AEs will be also summarized in a similar way. In the PK analysis, drug concentration will be summarized overall and by ethnic background, and the graphs of mean drug concentration-time profiles will be provided. The PK parameters for each subject will be estimated using non-compartmental methods and summarized overall and by ethnic background. Urinary excretion rates will be calculated and summarized overall and by ethnic background.

Schedule of Study Procedures

	Screening Period	Treatment Period								Follow-up Period		Study Completion / Discontinuation
Day	−28 to −1	1	2	3	4	5	6	8	15	22 to 42		-
	IC									22		
Informed Consent (IC)	X											
Subject Background	X											
Primary Disease	X											
ECOG Performance Status	X											
Medical History	X	X*1										
Pregnancy Test	X	X*2										
Body Height	X											
Body Weight	X	X*2										
Subject Enrollment	X											
Hospitalization		C1	C1	C1	C1	C1	C1*3					
SP-02L Administration		X	X	X	X	X						
Time Window (day)	-	-	-	-	-	-	-	±2	+6	+7		
Physical Examination	X	X*2				C1*4		X	X	X		
Vital Sign and Arterial SaO_2 Measurement	X	X*2				C1*4		X	X	X		
ECG	X	X*5				C1*5		X		X		
Laboratory Test	X*6	X*2				C1*4		X	X	X		
Con. Med. Reporting	←	X	→									
Adverse Event Reporting		←	X	→								
Assessment of Lymphoma Lesions	X								X*7	X*7		
End of Study												X*8
The following procedures will be performed only at the investigational sites where a principal investigator's agreement to perform these procedures is made prior to the study start												
Blood Sampling for Plasma PK		C1*9	C1*9	C1*9	C1*9	C1*9	C1*9	C1*9	C1*9			
Urinary Collection for Urine PK		C1*9	C1*9			C1*9	C1*9					

C1: Only in Cycle 1

*1: Disease status of concurrent disease is identified prior to the start of SP-02L dosing on Day 1 in Cycle 1
*2: Prior to the start of SP-02L dosing
*3: Subjects for PK assessment are hospitalized until the completion of blood/urine collection on Day 6
*4: Within 60 minutes after the end of drip infusion. Physical Examination on Day 5 is given after the end of drip infusion.
*5: Prior to SP-02L dosing and within 60 minutes after the end of drip infusion
*6: Hepatitis virus test is performed in the screening period
*7: On any day during the period from Day 15 to Day 21 in Cycle 3 and 6, and in every 3±1 cycles from Cycle 7. On any day during the period of Day 15 to Day 42 in the last cycle and prior to the start of subsequent treatment.
*8: Following the day of study completion, survival surveillance will be continued for up to 2 years from the day of the 1st dosing of SP-02L in Cycle 1.
*9: See "Schedule for Blood and Urine Sample Collection for PK Assessment" (shown in the next page)

Schedule for Blood and Urine Sample Collection for PK Assessment

Day	1						2	3	4
Time from the start of SP-02L infusion (hour)	0	1	2	4	6	8	0	0	0
Time from the end of SP-02L infusion (hour)	-	Just after the end of infusion	1	3	5	7	-	-	-
Time Window (minutes)	Before starting infusion -60	After the end of infusion +15	±15	±15	±30	±30	Before starting infusion -60	Before starting infusion -60	Before starting infusion -60
SP-02L Administration	**X**						**X**	**X**	**X**
Blood Sampling for Plasma PK	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Urine Collection for Urine PK	**X**[*1] [0-4 hours]			**X**[*2] [4-24 hours]					

Day	5						6	8	15
Time from the start of SP-02L dosing (hour)	0	1	2	4	6	8	(*3)	(*3)	-
Time from the end of SP-02L infusion (hour)	-	Just after the end of infusion	1	3	5	7	-	-	-
Time Window (minutes)	Before starting infusion -60	After the end of infusion +15	±15	±15	±30	±30	±60	±60	-
SP-02L Administration	**X**								
Blood Sampling for Plasma PK	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**[*4]
Urine Collection for Urine PK	**X**[*1] [0-4 hours]			**X**[*2] [4-24 hours]					

*1: For 4 hours from the start of SP-02L infusion (until 3 hours from the end of infusion), on Day 1 and Day 5
*2: For 20 hours from 4 hours after the start of SP-02L infusion, on Day 1 and Day 5
*3: At the same time of the start of SP-02L infusion on Day 5
*4: Window: Day 15 - 21

LIST OF AVVREVIATION

Abbreviation	Term
AITL	Angioimmunoblastic T-cell Lymphoma
ALCL	Anaplastic Large Cell Lymphoma
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BSA	Body Surface Area
CR	Complete Response
CRu	Complete Response/unconfirmed
CT	Computed Tomography
DOR	Duration of Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDG-PET	Fluorodeoxyglucose-Positron Emission Tomography
GCP	Good Clinical Practice
HBc antibody	Hepatitis B Virus Core antibody
HBs antibody	Hepatitis B Virus Surface antibody
HBs antigen	Hepatitis B Virus Surface antigen
HBV	Hepatitis B Virus
hCG	human Chorionic Gonadotropin
HCV antibody	Hepatitis C Virus antibody
HIV antibody	Human Immunodeficiency Virus antibody
HTLV-1 antibody	Human T-cell Leukemia Virus type I antibody
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPI	International Prognostic Index
IUD	Intra-uterine Device
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PIT	Prognostic Index for T-cell lymphoma
PR	Partial Response
PS	Performance Status
PTCL	Peripheral T-cell Lymphoma
PTCL-NOS	PTCL-not otherwise specified
QTcF	Fridericia corrected QT interval
RD	Relapsed Disease
SD	Stable Disease
TTR	Time to Response
WHO	World Health Organization

STUDY GLOSSARY

Abbreviation/Acronym/Term	Definition
SP-02	Drug Substance code of darinaparsin
SP-02L	Product code of darinaparsin for injection
Day 1	The first day of 5 consecutive days of investigational drug administration in each cycle; including the case that the planned dosing on the first day is skipped
the first screening visit	The day on which the subject signs the informed consent
Screening period	The period from the day of the first screening visit to the day before the first day of the investigational drug administration (Day 1 of Cycle 1)
Treatment period	The period from the first day of the investigational drug administration (Day 1 of Cycle 1) to the day before the first examination, observation and investigation scheduled during the follow-up period
End of follow-up period	The day on which the last (latest) examination, observation and investigation scheduled during the follow-up period is performed
Follow-up period	The period from the day of the first examination, observation and investigation scheduled during the follow-up period to the end of follow-up period
Study period	The period consists of “screening period”, “treatment period” and “follow-up period”
Measurable lymphoma lesions	• A measurable enlarged lymph node is defined as a lesion of > 1.5 cm in greatest transverse diameter regardless of short axis measurement or > 1.0 cm in short axis regardless of greatest transverse diameter that is clearly measurable in 2 perpendicular dimensions. • A measurable extranodal mass lesion is defined as a lesion of ≥ 1.0 cm in greatest transverse diameter (two times longer than the scan slice thickness). • A nodular mass within the liver or spleen is defined as a space-occupying lesion of ≥ 1.0 cm in 2 perpendicular dimensions.
Tumor response	“Complete Response (CR)” and “Partial Response (PR)”
Overall Response Rate	Proportion of subjects with “CR or PR” in the evaluable subject population
Progression-Free Survival (PFS)	Time from the first day of investigational drug administration (Day 1 of Cycle 1) to the date of "progressive disease" or "relapsed disease", or the date of "death", which occurs earlier

Abbreviation/Acronym/Term	Definition
Overall Survival (OS)	Time from the first day of investigational drug administration (Day 1 of Cycle 1) to the date of "death" from any cause
Time to Response (TTR)	Time from the first day of investigational drug administration (Day 1 of Cycle 1) to the first day of tumor response observed for patients who achieved a CR or PR
Duration of Response (DOR)	Time from the first day of tumor response observed for patients who achieved a CR or PR to the date of "progressive disease" or "relapsed disease", or the date of "death" which occurs earlier
Baseline	Results at the last time point of examination, observation and investigation before the start of the first administration of investigational drug in Cycle 1

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1. BACKGROUND AND RATIONALE

1.1. Target Disease

The peripheral T-cell lymphoma (PTCL) is a type of non-Hodgkin lymphomas, which is categorized into a heterogeneous group of mature T-cell and NK-cell neoplasms. It is categorized as aggressive lymphoma that progresses on a monthly basis from the perspectives of malignancy and activity/aggressiveness. In Asia, Mature T-cell and NK-cell neoplasms account for approximately 15% to 20% of all types of lymphoid neoplasm. The most common PTCL is classified as PTCL-not otherwise specified (PTCL-NOS) and accounts for about 30% of T-cell lymphomas. No clear evidence exists for the initial treatment of T-cell lymphomas; anthracycline-containing combination chemotherapy include CHOP (combination chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine and prednisolone) are commonly provided as regular medical care but are not considered to achieve sufficient treatment results. Moreover, no salvage therapy for patients with relapsed or refractory is established as the standard treatment, resulting in a poor prognosis. Therefore, the development of novel therapeutic agents with favorable tolerability and have different mechanisms of action from the existing antineoplastic agents is required so that they can be contained in a new combination chemotherapy that is aimed at improvement of treatment results.

1.2. Investigational Drug

See Investigator's Brochure (IB) for the detailed information on this investigational drug (SP-02L).

1.2.1. Origins and History of Discovery and Development

Darinaparsin (International Nonproprietary Name), the active ingredient of the investigational drug (Product code: SP-02L) (darinaparsin for injection), is an organic arsenic compound with antitumor activity. The development program of this product was started by ZIOPHARM Oncology, Inc. in the US (ZIOPHARM). Solasia Pharma K.K. (Solasia) has acquired a worldwide license to develop and commercialize darinaparsin from ZIOPHARM and has been conducting its clinical development with the target indication of PTCL.

Darinaparsin is the lead compound in a series of organic arsenics derivatives and this structure is one of the intermediate metabolites of the arsenic detoxification pathway in the body. Its place in the natural metabolic pathway is expected to result in lower toxicity and therefore a much wider therapeutic window.

1.2.2. Nonclinical Overview

The results of the previous nonclinical pharmacology studies indicated that darinaparsin had antitumor activity against hematologic cancers, and in vitro cell line screen suggests that this compound has cytotoxic activity against solid tumors as well. The mechanisms of action of darinaparsin include disruption of mitochondrial functions, increase in reactive oxygen

species (ROS), and effects on signal transduction. Darinaparsin induces cell cycle arrest and apoptosis and has potent anti-angiogenic activity.

In the preceding nonclinical studies, no finding that interfere with clinical use of darinaparsin have been extracted in the preceding nonclinical studies.

1.2.3. Clinical Overview

Six clinical studies have been conducted by ZIOPHARM in subjects with various hematologic malignancies, solid tumors, multiple myeloma and hepatocellular carcinoma, respectively. Two clinical studies have been conducted by Solasia in subjects with PTCL. Overview of these eight studies is shown in Table 1.

Table 1: Overview of Past Clinical Studies

Protocol No. * Cancer Type / Country	Phase	Dosage and dosing schedule	No. of Treated subjects
SGL1001: Hematologic malignancies / US	1	78-214 mg/m^2/day for 5 consecutive days followed by 23 days rest (1 cycle: 28 days)	11
SGL1002: Solid tumors / US	1	78-588 mg/m^2/day for 5 consecutive days followed by 23 days rest (1 cycle: 28 days)	40
SGL2001: Multiple myeloma / US, Canada	1	109-420 mg/m^2/day for 5 consecutive days followed by 23 days rest (1 cycle: 28 days)	17
	2	300 mg/m^2/day for 5 consecutive days followed by 23 days rest (1 cycle: 28 days)	14
SGL2001b: Multiple myeloma / US	2	420 mg/m^2/day twice weekly for 3 weeks followed by 1 week rest (1 cycle: 28 days)	17
SGL2003: Hematologic malignancies / US, India	2	300 mg/m^2/day for 5 consecutive days followed by 23 days rest (1 cycle: 28 days)	50
SGL2005: Hepatocellular carcinoma / US	2	420 mg/m^2/day twice weekly for 3 weeks followed by 1 week rest (1 cycle: 28 days)	15
SP-02L01 : PTCL / Japan	1	200 or 300 mg/m^2/day for 5 consecutive days followed by 16 or 23 days rest (1 cycle: 21 or 28 days)	17
SP-02L03 PTCL / Korea	1	300 mg/m^2/day for 5 consecutive days followed by 16 or 23 days rest (1 cycle: 21 or 28 days)	6

* Study numbers starting from “SGL” indicate studies conducted by ZIOPHARM Oncology, Inc.
Study numbers starting from “SP-02L” indicate studies conducted by Solasia Pharma K.K.

1.2.4. Known and Potential Risks

A total of 164 subjects received the investigational drug in 6 clinical studies conducted by ZIOPHARM. The integrated analysis includes all safety data collected and in the clinical data base as of March 31, 2012. Adverse events (AEs) occurring ≥ 5% of subjects across all studies that were reported by the investigator as being at least possibly related to investigational drug include nausea (20%), fatigue (18%), dizziness (9%), anemia (8%), vomiting (8%), headache (8%), confusional state (6%), diarrhea (5%), anorexia (5%), hypomagnesemia (5%), hyperglycemia (5%), and infusion site pain (5%). Of all Grade ≥ 3 AEs that were considered possibly related to investigational drug, those occurring in ≥ 2 subjects include fatigue (4%), hyperglycemia (4%), anemia (2%), febrile neutropenia (2%), neutropenia (2%), coordination abnormal (2%), confusional state (2%), infusion site pain (1%), hypoglycemia (1%), hypokalemia (1%), hypophosphatemia (1%), mental status changes (1%), and hypoxia (1%).

In two phase 1 studies conducted by Solasia Pharma K.K. respectively in Japan and Korea in subjects with PTCL (Study SP-02L01 and SP-02L03), 23 subjects received the investigational drug. A integrated analysis of these two clinical studies indicated that investigational-drug-related AEs, occurring in ≥ 2 subjects, included constipation (17%), nausea (17%), malaise (17%), pyrexia (17%), alanine aminotransferase increased (17%), aspartate aminotransferase increased (17%), activated partial thromboplastin time prolonged (17%), decreased appetite (13%), somnolence (13%), platelet count decreased (13%), herpes zoster (9%), lymphopenia (9%), hallucination (9%), white blood cell count decreased (9%), neutrophil count decreased (9%), C-reactive protein increased (9%), and blood alkaline phosphatase increased (9%). Grade ≥ 3 investigational-drug-related AEs occurred in 4 of 23 subjects (17%), and included neutrophil count decreased (9%, 2 subjects), platelet count decreased (9%, 2 subjects), diffuse large B-cell lymphoma (4%, 1 subject), anaemia (4%, 1 subject), febrile neutropenia (4%, 1 subject), lymphopenia (4%, 1 subject), nausea (4%, 1 subject), hepatic function abnormal (4%, 1 subject), lymphocyte count decreased (4%, 1 subject), white blood cell count decreased (4%, 1 subject), and activated partial thromboplastin time prolonged (4%, 1 subject).

An extensive electrocardiogram (ECG) assessment in two clinical studies conducted respectively in Japan and Korea demonstrated that there was no drug-concentration-dependent nor treatment-duration-dependent change in Fridericia-corrected QT interval (QTcF) and there was no significant relationship between the plasma drug (arsenic) concentration of darinaparsin and a change in QTcF interval from time-matched baseline.

1.3. Study Rationale

1.3.1. Target Disease

In the phase 2 study (Study SGL2003) conducted by ZIOPHARM Oncology, Inc. in subjects with advanced hematologic malignancies who had failed at least 1 therapy and required treatment, darinaparsin was administered at 300 mg/m^2 once daily for 5 consecutive days followed by 23 days rest (1 cycle: 28 days) for up to 6 cycles or until unacceptable toxicity or disease progression occurs.

Out of a total of 50 subjects treated with the investigational drug, 29 were diagnosed with lymphomas (22 non-Hodgkin's, 7 Hodgkin's), 7 with acute myelogenous leukemia (AML), 5 with chronic myelogenous leukemia (CML), 5 with myelodysplastic syndromes (MDS), 2 with acute promyelocytic leukemia (APL), 1 with acute lymphoblastic leukemia (ALL), and 1 with chronic myelomonocytic leukemia (CMML). There were 7 subjects with peripheral T-cell lymphoma (PTCL) and 5 of them were judged evaluable. The tumor responses (best overall response) in the evaluable subjects with PTCL resulted in complete response (CR) in 1 subject and complete response/unconfirmed (CRu) in 1 subject.

Since the above phase 2 study (Study SGL2003) confirmed that the investigational drug had favorable tolerability as well as potential antitumor activity against relapsed or refractory PTCL, Solasia Pharma K.K. conducted phase 1 studies (Study SP-02L01 and SP-02L03) in Japan and Korea, respectively, in subjects with relapsed or refractory PTCL.

In phase 1 studies (Study SP-02L01 and SP-02L03) conducted in Japan and Korea, respectively, 200 or 300 mg/m^2 of the investigational drug was administered once daily for 5 consecutive days followed by 23 days rest (4-week cycle) or 16 days rest (3-week cycle). A total of 23 subjects, including 17 Japanese subjects in Japan phase I study (Study SP-02L01) and 6 Korean subjects in Korea phase 1 study (Study SP-02L03), received the investigational drug.

One subject who received 300 mg/m^2 of the investigational drug once daily for 5 consecutive days followed by 16 days rest (3-week cycle) in Japan phase 1 study (Study SP-02L01) had a report of hepatic function disorder (Grade 3) which was determined as a Dose-Limiting Toxicity (DLT). The maximum tolerated dose (MTD) was not identified in either of these studies. The integrated analysis was conducted for the efficacies (tumor responses) of the investigational drug in 14 subjects who completed at least 2 cycles and had a tumor response assessment. The best overall response in the efficacy analysis set were complete response (CR) in 1 subject, partial response (PR) in 3 subjects, stable disease (SD) in 6 subjects and progressive disease (PD) in 4 subjects. Five of 6 subjects with stable disease showed tumor shrinkage to some extent.

As described above, based on the previous clinical studies, no serious concern regarding safety of SP-02L was indicated, and preliminary tumor responses in patients with PTCL were confirmed, suggesting that the clinical development of SP-02L is positively significant for the treatment of this disease.

1.3.2. Study Design, Investigational Drug Dosage and Dosing Schedule

This is a multinational multi-center study, and East Asian countries and region where there is no significant difference in disease incidence and treatment algorisms of malignant lymphoma and also in clinical trial implementation environment has been established. The comparison among pharmacokinetics (PK) profiles of investigational drug in Japanese and Korean subjects in phase 1 studies in Japan and Korea (Study SP-02L01 and SP-02L03) and Caucasian subjects in phase 1 study for solid tumors in the US (Study SGL1002) showed that the mean plasma concentration-time profiles were overlapping and systemic arsenic exposures were visually similar in Japanese, Korean, and Caucasian subjects at the doses studied. No statistically significant differences were found although only such a small number of subjects were evaluated in these studies. All the available data indicates there is no apparent ethnic difference in PK profiles in Japanese, Korean, and Caucasian subjects at the doses studied.

An appropriate control arm (placebo or active comparator) cannot be set for this study because PTCL is categorized as aggressive lymphoma, any salvage therapy has not been established as the standard treatment for the relapsed or refractory cases, and patients are usually treated with multidrug combination chemotherapy. In addition, Revised Response Criteria for Malignant Lymphoma by an International Working Group to Standardize Response Criteria for Non-Hodgkin's Lymphomas in 2007 is used for the assessment of tumor response in this study, and the assessment with this response criteria using objective indicators enables less biased evaluation. Moreover, the central assessment at the Efficacy and Safety Review Committee will determine the tumor response that is the primary endpoint of this clinical trial.

Therefore, the global, multi-center, single-arm, open-label, non-randomized design was considered appropriate for this clinical trial.

As for the dosage and dosing schedule of investigational drug in this clinical trial, “300 mg/m^2 once daily for 5 consecutive days followed by 16 days (3-week cycle) rest,” at which the tolerability and preliminary tumor response were confirmed in phase 1 studies in Japan and Korea (Study SP-02L01 SP-02L03) for relapsed or refractory PTCL, was selected.

1.4. Hypothesis

The study is expected to confirm the efficacy of SP-02L in subjects with PTCL, with the expected overall response rate (ORR) of 25% and the 10% threshold.

2. STUDY PLAN

2.1. Target Disease

Relapsed or refractory peripheral T-cell lymphoma (PTCL)

2.2. Study Phase

Phase 2

2.3. Objectives

2.3.1. Primary Objective

To evaluate the efficacy of SP-02L monotherapy in patients with relapsed or refractory PTCL.

2.3.2. Secondary Objectives

- To evaluate the safety of SP-02L monotherapy in patients with relapsed or refractory PTCL.
- To assess the pharmacokinetics (PK) profile of SP-02L at multiple doses in a subgroup of subjects [see Section 2.6].

2.4. Study design

This study is a phase 2 multinational, multicenter, single-arm, open-label, non-randomized study conducted in East Asia countries/regions. Subjects will receive SP-02L at 300 mg/m^2 once daily for 5 consecutive days followed by 16 days of rest per cycle of 21 days (3 weeks). SP-02L will be administered for 6 cycles to evaluate the efficacy and safety of SP-02L monotherapy by using various endpoints. If the subject wishes to continue investigational drug administration and the principal investigator judges that the continued administration of investigational drug is possible and necessary for the subject, the investigational drug administration can be continued beyond 6 cycles.

Pharmacokinetics will be assessed in subjects enrolled in part or all of the investigational sites in each of participating country or region at Cycle 1.

Study design is shown in Figure 1.

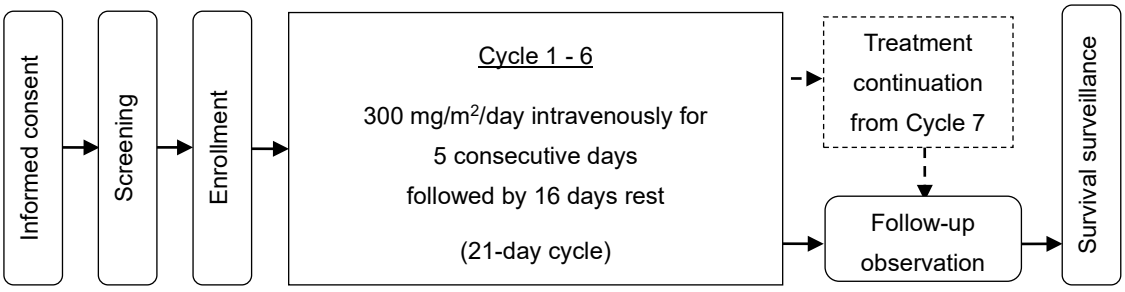

Figure 1: Study Design Schema

2.5. Endpoints

2.5.1. Primary Endpoint

The primary endpoint is tumor response (best overall response) according to the Revised Response Criteria for Malignant Lymphoma by an International Working Group to Standardize Response Criteria for Non-Hodgkin's Lymphomas in 2007.

The tumor response for 6 cycles that is confirmed by a central assessment at the Efficacy and Safety Review Committee is determined as the primary evaluation result, and that is confirmed by a local assessment at each investigational site is determined as the secondary evaluation result.

2.5.2. Secondary Endpoints

Secondary endpoints of this study are as follows. “Response” is defined as “complete response (CR)” or “partial response (PR)”.

- Progression-Free Survival (PFS）

  Defined as the time from the first day of investigational drug administration (Day 1 of Cycle 1) to the date of "progressive disease (PD)" or "relapsed disease (RD)", or the date of "death", which occurs earlier

- Time To Response (TTR)

  Defined as the time from the first day of investigational drug administration (Day 1 of Cycle 1) to the first day of tumor response observed for patients who achieved a CR or PR

- Duration of Response (DOR)

  Defined as the time from the first day of tumor response observed for patients who achieved a CR or PR to the date of PD or RD, or the date of "death", which occurs earlier

- Overall Survival (OS)

  Defined as the time from the first day of investigational drug administration (Day 1 of Cycle 1) to the date of "death" from any cause

- Occurrence of adverse events (AEs)
- Drug plasma concentration-time profile, PK parameters, and urinary excretion rates

2.6. Sample Size

The target number of subjects to be enrolled in this clinical trial is 65.

PK assessments will be performed only at the investigational sites only at the investigational sites where a principal investigator’s agreement to perform these procedures is made prior to the study start, and in approximately 10 subjects in each of participating country/region.

2.7. Estimated Study Duration

2.7.1. Study Duration for Individual Subject

The period from the first screening visit at which the subject signs the informed consent to the day before the first day of the investigational drug administration (Day 1 of Cycle 1) is defined as a “screening period”. The period from the first day of the investigational drug administration (Day 1 of Cycle 1) to the day before the first examination, observation and investigation scheduled during the follow-up period is defined as a “treatment period”. The day on which the last (latest) examination, observation and investigation scheduled during the follow-up period is performed is defined as “the end of follow-up period”. The period from the day of the first examination, observation and investigation scheduled during the follow-up period to the end of follow-up period is defined as a “follow-up period”.

The study period consists of “a maximum of 28 days of the screening period”, “21 days of the treatment period per cycle” and “21 days of the follow-up period, in general case”. The duration of this study is estimated to be a total of 175 days; 25 weeks; approximately 6 months, when the subject is treated for 6 cycles. Additionally, the survival surveillance will be continued for up to 2 years from the first day of the investigational drug administration (Day 1 of Cycle 1).

2.7.2. Entire Study Duration

As from December 2015, the study will be initiated at each investigational site as the country- or region-specific regulatory requirements are satisfied in each country/region and each investigational site completes all procedures required for study initiation at each site.

The end of survival surveillance in the last subject is planned to be completed in December 2021.

2.8. Study Organization and Structure

This is a global multi-center study planned to be conducted in Japan, Korea, Taiwan and Hong Kong. At least one medical institution in each of these countries/regions will participate in this study.

A list of names and addresses of the Development Sponsor, medical experts, committees, coordinating investigators and the institutions/CROs related to the entire study is provided in Appendix 3.

A list of names and addresses of the investigational sites in each country and region, names of departments, names of the principal investigators, names and addresses of the local sponsor (the Sponsor) and local CROs, and names and contacts of study monitors, is provided as a separate document for “Study Organization and Structure in Each Country and Region”.

3. SUBJECT ELIGIBILITY

3.1. Inclusion Criteria

To be eligible for the study participation, patients must fulfill all of the following criteria:

(1) Patients with ethnic background of each participating country/region;

(2) Patients aged ≥ 20 years of age at the date of obtaining the informed consent;

(3) Patients with histopathologically confirmed diagnosis of one of the following:

- PTCL- not otherwise specified (PTCL-NOS);
- Angioimmunoblastic T-cell Lymphoma (AITL);
- Anaplastic Large Cell Lymphoma (ALCL), anaplastic lymphoma kinase (ALK) positive/negative);

The pathology specimens supporting the local diagnosis should be submitted for the central pathology review by the Pathological Review Committee [See Section 6.3].

(4) Patients have a treatment history of at least one regimen with antitumor agents for the above diseases;

(5) Patients have an enlarged lymph node or extranodal mass lesion that is measurable on computed tomography (CT);

In this study, a measurable enlarged lymph node is defined as a lesion of > 1.5 cm in greatest transverse diameter regardless of short axis measurement or > 1.0 cm in short axis regardless of greatest transverse diameter, that is clearly measurable in 2 perpendicular dimensions. A measurable extranodal mass lesion is defined as a lesion of ≥ 1.0 cm in greatest transverse diameter (two times longer than the scan slice thickness). A nodular mass within the liver or spleen is defined as a space-occupying lesion of ≥ 1.0 cm in 2 perpendicular dimensions.

(6) Patients with Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0, 1, or 2 [See Appendix 1]; and

(7) Patients with a life expectancy of at least 3 months (e.g. no acute exacerbation of their primary disease) as determined by the principal investigator or sub-investigator.

3.2. Exclusion Criteria

To secure the safety of subjects and to eliminate potential factors that may have an effect on the evaluation of the investigational drug, subjects who meet any of the following criteria are not eligible for the study.

3.2.1. Laboratory Test Values

(1) Patient with inadequately maintained major organ functions as evidenced by the following laboratory test values taken at the screening visit. These laboratory test values should not be affected by blood transfusion or administration of hematopoietic growth factor agents, etc. Even though the patients who meet none of the following

criteria, subject's condition should not show an obvious tendency toward worsening as determined by the principal investigator or sub-investigator:

- Electrocardiogram (ECG): Fridericia-corrected QT interval (QTcF) ≥ 450 msec;
- Hemoglobin: < 8.0 g/dL;
- Neutrophil count: < 1,000/mm^3;
- Platelet count: < 50,000/mm^3;
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT): > 3 times ULN defined at the investigational site; or
- Creatinine: > 1.5 times ULN defined at the investigational site;

(2) Patients with a positive result for either hepatitis C virus antibody (HCV antibody) or hepatitis B virus (HBV) surface antigen (HBs antigen) test during the screening period. Alternatively, the patients with a negative result for HBs antigen; however, with a positive result for either HBV surface antibody (HBs antibody) or HBV core antibody (HBc antibody), and with an HBV deoxyribonucleic acid (DNA) level (HBV-DNA level) ≥ the detection sensitivity of the assay;

(3) Patients who are known to be positive for human immunodeficiency virus antibody (HIV antibody) or human T-cell leukemia virus type I antibody (HTLV-1 antibody);

3.2.2. Disease Related

(4) Patients who are known or suspected metastasis or invasion to the central nervous system, or lymphoma lesions in the central nervous system;

(5) Patients who have a concurrent active malignancy other than PTCL with the disease- or treatment-free period of < 5 years, excluding skin basal cell carcinoma, skin squamous cell carcinoma and carcinoma in situ of the cervix that are judged to have been cured;

(6) Patients who have concurrent or a past history of central nervous system disease (e.g. seizure, dementia, Parkinson's disease, Alzheimer's disease), cerebrovascular disorder (e.g. transient ischemic attack, cerebral infarction, cerebral hemorrhage), or psychiatric disorder (e.g. schizophrenia, depression, addiction);

(7) Patients who concurrently have any of the following conditions:

- Congenital long QT syndrome;
- Poorly controlled cardiac arrhythmia;
- Poorly controlled diabetes mellitus;
- Infections requiring systemic administration of antibiotic, antifungal or antiviral drugs;
- Acute hepatitis, chronic hepatitis, or liver cirrhosis; or
- Serious acute or chronic organ dysfunction (e.g. cardiac, hepatic, renal, or respiratory failure);

(8) Patients who have known or suspected hypersensitivity to arsenic;

3.2.3. Medications

(9) Patients who have used agents containing darinaparsin;

(10) Patients who have received anticancer chemotherapy (including continuous use of oral administration or injection of corticosteroids equivalent to > 10 mg/day of prednisolone, as anticancer therapy) or anticancer immunotherapy (excluding antibody therapy) within 3 weeks before the day of subject enrollment;

(11) Patients who have received antibody therapy (including investigational drugs) within 12 weeks before the day of subject enrollment;

(12) Patients who have received radiotherapy within 3 weeks before the day of subject enrollment;

(13) Patients who have received autologous hematopoietic stem cell transplant within 12 weeks before the day of subject enrollment, or patients who have received allogeneic hematopoietic stem cell transplant;

(14) Patients who underwent major surgery (e.g., surgery requiring systemic anesthesia, craniotomy, thoracotomy, or laparotomy) within 4 weeks before the day of subject enrollment;

(15) Patients who are participating in other clinical trials or received any investigational drug or device within 4 weeks before the day of subject enrollment;

3.2.4. General

(16) Patients who are unable to stay in the hospital for the period specified in the protocol [See Section 4.2.1];

(17) Female patients who are breast-feeding, pregnancy or planned pregnancy;

(18) Patients of reproductive potential who will not be able to use adequate contraceptive precautions during the treatment period and following 3 months after the last dosing of investigational drug; in the judgment of the principal investigator or sub-investigator; or

(19) Patients with considerable concern for compliance with the protocol, in the judgment of the principal investigator or sub-investigator.

4. MANAGEMENT OF SUBJECTS

4.1. Informed Consent

Before a subject's participation in the clinical study, the principal investigator or sub-investigator is responsible for obtaining written informed consent from the subject himself/herself after adequate explanation of the study methods etc. to the subject and before any protocol-specified screening procedures in the subjects. The acquisition of informed consent should be documented in the subject's medical records.

If a potential subject is illiterate or visually impaired, the investigators must provide an impartial witness to read the informed consent form to the subject and give the subject an opportunity to ask questions.

The informed consent form should be personally signed and dated by the subject, the principal investigator or sub-investigator, the witness (if applicable) and the person who conducted the informed consent discussion (if applicable). The original signed informed consent form should be retained in accordance with a rule of each investigational site, and a copy of the signed informed consent form should be provided to the subject.

4.2. Safety Considerations for Subjects

4.2.1. Hospitalization

Subjects will be managed under hospitalization for at least 5 days from the first day of investigational drug administration (Day 1 to Day 5 of Cycle 1). Subjects for pharmacokinetic assessment [See Section 6.16] will be managed under hospitalization until the completion of blood and urine collection at Day 6 of Cycle 1 to ensure the completion of all time points of blood sampling for determination of drug plasma concentration and that of urine collection for determination of drug urine concentration.

With no safety concern found in the results of protocol-specified examination, observation, the investigation performed during the hospitalization period, the principal investigators or sub-investigator will judge to discharges subjects.

The principal investigator or sub-investigator (or designated staff) will enter the dates of hospitalization and discharge during the study period, into the electronic case report forms (eCRF) of this study.

4.2.2. Methods of Contraception and Actions in Case of Pregnancy

The principal investigator or sub-investigator (or designated staff) will instruct subjects to use validated methods of birth control throughout the study period and until three months following the last dosing of the investigational drug. In this study, abstinence or combined use of two or more of adequate contraception methods including but not limited to condom, intra-uterine device (IUD), and oral contraception will be recommended.

The principal investigator or sub-investigator (or designated staff) must confirm negative pregnancy status of subjects at the screening visit and on Day 1 of each cycle (before the

start of investigational drug administration) [See Section 6.6].

If the subject becomes pregnant during the study period, the subject must immediately be withdrawn from the study.

If the pregnancy of subject or a subject's partner is confirmed during the study period or within three months after the last administration of the investigational drug, the appropriate monitoring of subject should continue until conclusion of the pregnancy; e.g., progress during pregnancy, findings of intrapartum period and findings of neonate.

The principal investigator or sub-investigator (or designated staff) must promptly notify the Sponsor, via study monitor, of the pregnancy of subject or a subject's partner. The contact information of a study monitor is provided as a separate document for "Study Organization and Structure in Each Country and Region".

4.2.3. Instructions for Medical Imaging Tests at External Medical Institution

In case that the investigational site will outsource the medical imaging tests including positron emission tomography (PET) to an external medical institution (hereinafter referred to as "collaborating medical institution"), the principal investigator will notify the Sponsor of the outsourcing of medical imaging tests to the collaborating medical institution. In addition, 2-party contract between the investigational site and the collaborating medical institution, or 3-party contract including the Sponsor should have been concluded for the outsourcing of medical imaging tests. Furthermore, the ordering procedures including how to share the information that the subject is participating in the clinical study, and the subject management procedures including how to get the information of AEs occurred at the collaborating medical institution, and also the image data submission procedures should be determined in advance.

In the informed consent form, the principal investigator should describe that the medical imaging tests will be performed at the collaborating medical institution. The principal investigator or sub-investigator (or designated staff) will provide subject with the explanation about the study including the fact that the medical imaging tests will be performed at the collaborating institution, and then will obtain the informed consent from the study [See Section 4.1].

4.3. Assignment of Subject Number

4.3.1. Notification of Informed Consent Acquisition and Assignment of Subject Number

The principal investigator or sub-investigator (or designated staff) shall enter the date of consent (date written in the informed consent form) into the electronic data capture (EDC) system.

Once the date of consent (date written in the informed consent form) is entered into the EDC system, a subject number will be assigned to an individual subject. In this study, subjects will be identified with subject numbers throughout the study period. The subject number will

consist of a total of 8-digits; the 3-digit protocol identifier (i.e., 2L2), followed by the 1-digit country/region number, the 2-digit site number, and the 2-digit subject number that will be assigned in sequential order at each investigational site. The subject number must remain unchanged throughout the study period; it must not be changed at the time of re-screening.

4.3.2. Enrollment

After the acquisition of the informed consent [See Section 4.1] and before the enrollment, the subjects will be screened for eligibility. Subjects who fail screening will be allowed to be re-screened.

The principal investigator or sub-investigator (or designated staff) will enter the results of subject eligibility assessment [See Section 3] into the EDC system.

Upon the subject's eligibility is confirmed by the EDC system: when the subject's eligibility data is accepted by EDC system, the procedures for subject registration will be completed. The date on which the EDC system has confirmed the subject's eligibility shall be regarded as the date of subject's enrollment (registration).

4.4. Completion or Withdrawal from Study in Individual Subject

The principal investigator or sub-investigator (or designated staff) will specify, if the enrolled subject has completed or been withdrawn from the study, date of the End of Study and the reason for withdrawal if applicable, and will enter them into the eCRF.

4.4.1. Definition of Completion of Study and Day of End of Study

The subjects who complete all of the examinations, observations and investigations scheduled during the follow-up period following the last treatment cycle, and also not meet any criteria for study withdrawal [See Section 4.4.2] will be determined as the subjects who completed study.

< Day of End of Study >

The day of "End of Study" will be at the end of follow-up period, except for the following cases:

- If a subject is withdrawn from the study before the first dosing of investigational drug, "the day on which the decision is made to withdraw the subject from the study" will be determined as the day of the End of Study.
- In a subject under the follow-up observation of ongoing AE [See Section 7.3], "the most recent (last) day on which an outcome of the AE is confirmed" will be determined as the day of the End of Study.
- If a subject is withdrawn from the study after the start of investigational drug administration and cannot continue any of the subsequent examination, observation and investigation; e.g., the subject is not willing to provide any own clinical data after the withdrawal of consent, or the pregnant subjects at a possible risk from protocol-specified examination, "the latest day on which the last examination, observation or investigation is performed" will be determined as the day of the End of Study.

- If a subject dies during the study period, “the day of death” will be determined as the day of the End of Study.

4.4.2. Study Withdrawal Criteria

A subject who meets any of the following criteria may be withdrawn from the study:

(1) Request to withdraw consent;

(2) Ineligibility found after enrollment;

(3) Pregnancy;

(4) Impossibility of continuation of protocol-specified examination, observation and investigation due to subject’s own reason; e.g., difficulties in visiting the investigational site due to subject’s change of residence;

(5) Subject’s serious non-compliance with the protocol; with the principal investigator’s or the Sponsor’s judgement for not continuing the study in the subject;

(6) Serious violation of GCP or significant deviation from the protocol; with the principal investigator’s or the study sponsor’s judgement for not continuing the study in the subject;

(7) Death of the subject; or

(8) At the discretion of the principal investigator or the Sponsor.

4.4.3. Procedures for Study Withdrawal

In a subject who is withdrawn from the study before the first dosing of investigational drug, the subsequent examination, observation and investigation are not required to be performed.

In a subject who is withdrawn from the study after the start of investigational drug administration and cannot continue any of the subsequent examination, observation and investigation; as cases such as the subject is not willing to provide any own clinical data after the withdrawal of consent or the subjects is pregnant at a possible risk from protocol-specified examination, the principal investigator or sub-investigator will take the best measures to stop the study in the subject, under the condition where the subject’s safety is ensured. In case of subjects have ongoing AEs, the best measures to follow the ongoing AEs should be carried out where possible.

In a subject who is withdrawn from the study after the start of investigational drug administration; on the condition that the subject still has a willing to provide own clinical data, the subsequent examination, observation and investigation scheduled during the current cycle and the follow-up period should be completed.

4.5. Replacement of Subject

No replacement of subject will be taken in this study. Until the day on which the Development Sponsor confirms that the number of subjects who have received the

investigational drug for at least 1 cycle reaches the planned sample size, the notification of informed consent acquisition from a new patient and assignment of subject number to the subject will be accepted [See Section 4.3.1].

4.6. Study Suspension or Termination

When the new information that seriously affects the continuation of the study is obtained, the Development Sponsor may decide to suspend or terminate the entire study, at all investigational sites. In case of study suspension or termination of the entire study, the Sponsor will notify it in writing with its reasons, to the principal investigators and investigational sites according to a country- or region-specific regulatory requirements.

If the study is suspended or terminated, the principal investigators will provide the appropriate subsequent treatment to subjects.

5. TREATMENT PROCEDURES

5.1. Packaging, Formulation and Storage of Investigational Product

The investigational drug will be manufactured by a contract manufacturing organization that is appropriately selected and approved by the Development Sponsor. The Local Sponsor will distribute the investigational drugs to each investigational site through CRO or the investigational drug delivery service company.

The investigational drug will be supplied as a sterile, white to off-white, lyophilized powder in glass vials containing 150 mg of darinaparsin per vial. Each vial and box will be labeled according to country- and region-specific regulations, and each box will have 10 vials of investigational drug. It should be stored under refrigeration at 2°C to 8°C (36°F to 46°F), except when being reconstituted and diluted for injection.

5.2. Preparation of Investigational Drug

Each vial contains 150 mg of darinaparsin. When completely reconstituted with 2.0 mL water for injection, the nominal concentration is 75 mg/mL. Within 1 hour of reconstitution, the required dose (mg) is drawn into at least one syringe and added to an infusion bag containing 250 mL of saline solution (Sodium Chloride Injection).

In case that a lot number of investigational drug is multiple at the investigational site, the investigational drugs of the same lot number will be used in a subject throughout a cycle whenever possible; a subject will not receive the investigational drug of multiple lot numbers within a cycle.

Details of investigational drug preparation are shown in Pharmacy Guide [See Appendix 2].

5.3. Drug Dosage

The principal investigator or sub-investigator (or designated staff) will enter the following information into the eCRF:

- Date of the investigational drug dosing,
- Start and stop time of dosing
- Dose (mg/m^2)
- Administration route
- Lot number of investigational drug
- Completeness of administration; completed, interrupted or postponed (skipped)
- Actual volume of administration, if the administration is interrupted
- Reasons, if the administration is interrupted or postponed (skipped)
- Continuation to the next cycle or discontinuation at the end of current cycle
- Reason for discontinuation

5.3.1. Dosage and Administration Schedule

Subjects will receive 300 mg/m^2 of darinaparsin once daily for 5 consecutive days (Day 1 to Day 5) per 21-day cycle (3-week cycle) which consists of 5-day therapy followed by 16-day rest. The treatment will be given for 6 cycles according to the criteria in case of postponement (skip) of administration, dose reduction or discontinuation of treatment [See Section 5.4]. At the end of Cycle 6, if the subject wishes to continue investigational drug administration and the principal investigator judges that the continued administration of investigational drug is possible and necessary for the subject, the investigational drug administration can be continued beyond 6 cycles. Prior to the start of administration in Cycle 7, the principal investigator should notify the Sponsor via a study monitor of the continuation of treatment beyond 6 cycles. The contact of study monitor is provided as a separate document for “Study Organization and Structure in Each Country and Region”.

The dose (mg) of the investigational drug given to each subject will be calculated by multiplying the subject’s body surface area (BSA, m^2) by 300 (mg). The maximum dose will be 600 mg; a dose exceeding 600 mg per body must not be administered.

The BSA will be calculated using DuBois’s formula shown below, based on the subject’s height (cm) and body weight (kg) measured during the screening period.

$$S = W^{0.425} \times H^{0.725} \times 0.007184$$

S: Body surface area (m^2)
W: Weight (kg)
H: Height (cm)

If there are ±10% changes in the body weights measured on Day 1 of each cycle (before the start of investigational drug administration) from the weight measured in the screening period, BSA will be re-calculated to adjust the dose.

The interval period between cycles from Cycle 1 to Cycle 6 (interval period between Day 21 of a current cycle and Day 1 of the next cycle) will be allowed from -1 day up to +7 days for any reason. The interval period between cycles from Cycle 7 (including the interval period between Day 21 of Cycle 6 and Day 1 of Cycle 7) will be allowed from -1 day up to +14 days for any reason.

5.3.2. Administration

The investigational drug will be reconstituted and diluted according to the preparation procedures described in Section 5.2, and will be given intravenously over 1 hour (± 10 minutes) on each day of administration. After the infusion, a flushing with a sufficient amount of saline will be done to ensure all the drug remaining in the infusion route is infused fully to the subject.

Since the injection site abnormalities have been frequently reported in subjects who received the investigational drug via a peripheral line in the previous clinical studies, the

administration of the investigational drug is recommended to be given through the central vein (e.g., via an implantable subcutaneous infusion port, a central venous catheter, a peripherally inserted central venous catheter). If any abnormal finding at the injection site is observed during the infusion via a peripheral line, the administration will be held at the discretion of the principal investigator or sub-investigator. Saline may be infused via a three-way stopcock. The IV infusion may be given from another peripheral vein or via a central venous line or port.

The following matters should be noted when the investigational drug is administered:

- During the injection via a peripheral line, full care should be taken to avoid extravasation. If any extravasation is observed, the dose will be held immediately, medical procedures will be provided for it, and a change in the peripheral vein for IV infusion will be considered.
- No other drug for injection should be given concurrently via the same IV line.
- The investigational drug administration will be started at the same time as much as possible in subjects for pharmacokinetic assessment in Cycle 1 [See Section 6.16].

5.4. Skip of Administration, Dose Reduction and Study Discontinuation

The medically important investigational-drug-related AEs that were reported in the previous clinical studies are including nervous system disorders (e.g. coordination abnormal) and psychiatric disorders (e.g. confusional state). Therefore, any finding of abnormalities or signs in nervous or psychiatric system will require to consider carefully for the skip (postponement) of administration, dose reduction or discontinuation of the investigational drug administration, regardless of the following criteria.

5.4.1. Drug Administration Skip Criteria

In case there is no alternative way on medical judgement of the principal investigator or sub-investigator, the investigational drug administration on the day may be skipped (postponed). In subject receiving the IV infusion, the infusion may be interrupted and stopped. If a Grade ≥ 3 AE related to the investigational drug is reported during the period from Day 1 to the completion of the investigational drug administration on Day 5, the IV infusion should be interrupted and stopped, and also the investigational drug administration subsequently planned in the current cycle should be skipped.

However, in case of nausea, vomiting and diarrhea, only when the symptoms of these events are improved by symptomatic treatment; e.g., antiemetic drug for nausea and vomiting, and antidiarrheal drug for diarrhea, the investigational drug administration may be continued without a skip of administration.

5.4.2. Dose Reduction Criteria

If a Grade ≥ 3 AE related to the investigational drug is reported during the preceding cycle, the dose level of the investigational drug may be reduced to 200 mg/m^2. However, the administration at 300 mg/m^2 can be continued, at the discretion of the principal investigator, based on the consideration for the subject’s response to symptomatic treatment; e.g.,

antiemetic drug for nausea and vomiting, and antidiarrheal drug for diarrhea, or supportive care; e.g., hematopoietic growth factor agents for hematological toxicity due to the investigational drug.

Dose reduction will be allowed only one time for each subject, and the dose will not be returned to 300 mg/m^2.

5.4.3. Study Discontinuation Criteria

If a subject meets any of the following criteria before the start of dosing in each cycle from Cycle 2, the subject will discontinue (not continue) the study without starting the investigational drug administration in the next cycle:

(1) PD or RD at the tumor response assessment [See Section 6.14.2]

(2) Clinical judgment of “symptomatic progression” by the principal investigator or sub-investigator; based on clinical symptoms or laboratory findings, etc., in case of no results of radiological assessment with PET/CT image data

(3) Start of treatment with proscribed concomitant drugs or therapies [See Section 5.5.2]

(4) A Grade 4 AE that is related to the investigational drug

In case of the transient changes in laboratory test values without any clinically significant symptoms; e.g., the severity of changes in laboratory test values has recovered to “≤ Grade 2” within 7 days, the investigational drug administration will be continued at the discretion of the principal investigator

(5) No improvement in the severity of an AE that is related to the investigational drug to “≤ Grade 1” or “Grade at pretreatment”

The start of next cycle can be postponed for up to 3 weeks to allow the investigational-drug-related AE to be resolved. If the AE is not resolved to “≤ Grade 1” or “Grade at pretreatment” even though the start of next cycle is postponed for 3 weeks, the subject will complete the study after the completion of the examinations, observations and investigations scheduled during the follow-up period.

(6) No resolution or relapse of a similar investigational-drug-related AE at ≥ Grade 3 despite a dose reduction of the investigational drug [See Section 5.4.2]

However, the subject may continue receiving the investigational drug at a reduced dose at the discretion of the principal investigator, in case that the subject shows the response to the investigational drug; i.e., the tumor response in the subject is not assessed as PD or RD.

(7) The principal investigator or sub-investigator decision not to continue investigational drug administration due to the occurrence of an investigational-drug-related AE, other than the events defined in (4), (5), and (6) above or other reasons.

5.5. Concomitant Therapy

5.5.1. Permitted Concomitant Therapy and Limited Concomitant Therapy

Throughout the study period, concomitant therapies including concomitant use of drugs required for medical reasons are permitted to use, except for the proscribed therapies described in Section 5.5.2. The use of antiemetic agents for nausea and/or vomiting, antidiarrheal agents for diarrhea, antimicrobial agents, antiviral agents, antifungal agents and gargles for opportunistic infection, and prophylactic antihyperuricemic agents for tumor lysis syndrome are also allowed.

The use of drugs, which have been given to the subject before the start of investigational drug administration, for the treatment of chronic complication or as a symptomatic therapy for the primary disease will be continued during the study period at a consistent dosage and dosing schedule through the study period as far as possible, except when intolerable AEs due to these concomitant drugs occur.

5.5.2. Proscribed Therapy

Throughout the study, from the day of obtaining the informed consent to the end of follow-up period, none of the medications or treatments listed below should be proscribed for any reason. In any case a subject starts any of the medications or treatments for justifiable reasons, the subject will discontinue the study with the completion of examination, observation and investigation specified in the current cycle and the follow-up period:

- Anticancer chemotherapy other than the investigational drug, and anticancer immunotherapy

  Continuous oral administration or injection of corticosteroid: equivalent to more than 10 mg/day of prednisolone, is also prohibited. However, single use or use as needed is allowed for the purpose including the treatment for fever or pretreatment for blood transfusion.

- Radiotherapy
- Hematopoietic stem cell transplants
- Cellular immunotherapy (e.g., cancer vaccine therapy)
- Gene therapy
- Major surgery; e.g., surgery with general anesthesia, craniotomy/thoracotomy /laparotomy)
- Any other investigational drugs, therapeutic drugs that are not approved by each country or region; excluding drugs which are already approved for off-label use, and investigational devices

6. STUDY PROCEDURES

The principal investigator or sub-investigator (or designated staff) will enter the results of examination, observation and investigation specified in this Section 6, and also the dates and times for blood and urine collection, as needed, into the eCRF.

The frequent performance of such invasive examinations and medical imaging tests; such as bone marrow biopsy and CT/PET imaging test, are considered medically and ethically unfavorable. Therefore, the bone marrow biopsy, CT and PET data that are obtained from routine medical practice before obtaining the informed consent from the subject may be allowed to be used as screening data of this study; only when these invasive examinations and medical imaging tests are performed within 28 days before subject enrollment. For the use of such data, a prior consent from the subject is required. However, PET data should be taken according to the study-specific procedures that is standardized by the Central Imaging Review institution of this study.

The principal investigator or sub-investigator will be allowed to add the time points of examinations, observations and investigations as needed for the follow-up observation of AEs.

6.1. Subject Background

The following information regarding the subject background will be collected upon obtaining consent from the subject.

- Date of birth
- Sex
- Ethnic background: ethnic group, race

6.2. Medical History of Primary Disease

The following information regarding the medical history of primary disease will be collected on any day between Day -28 to Day -1 of the screening period.

- Histopathological diagnosis (histopathological subtype) of primary disease; made at the investigational site
- Date of diagnosis
- Clinical stage by the Ann Arbor Classification at a screening visit
- Prognostic risk group by International Prognostic Index (IPI) at a screening visit
- Prognostic risk group by Prognostic Index for T-cell lymphoma (PIT) at a screening visit
- Clinical symptoms caused by the primary disease (clinical symptoms associated with primary disease)
- Prior medication: name of regimen or drugs, periods of medication and responses to medication as needed

6.3. Lymphoid Tissue Specimen Submission

Upon the subject's enrollment, 15 unstained tissue specimens taken from the lymphoid tissue (lymph nodes, in principle); on which a local pathological diagnosis of primary disease is confirmed, will be submitted to the central laboratory of each country or region. Unstained tissue specimens will be prepared on coated glass slides; formalin-fixed paraffin-embedded ≤5 μm-thick sections will be mounted on the coated glass slides. If prior biopsies were performed multiple times before subject enrollment, the principal investigator or a pathologist at each investigational site should submit the tissue specimens that are considered most valid basis for a local pathological diagnosis; either of the biopsy samples taken at an initial onset or at a relapse of disease are acceptable. According to the requests from the Pathological Review Committee, supplemental submission of unstained or stained tissue specimens may be requested.

If less than 15 unstained tissue specimens can be submitted, as many unstained tissue specimens as possible and the previously-stained tissue specimens; that should include the specimen stained by hematoxylin and eosin staining, supporting the local pathological diagnosis should be submitted. The stained tissue specimens will be borrowed from the investigational site in accordance with each investigational site's procedures.

Details of the procedure for tissue specimen submission to the central laboratory of each country or region are specified in a separate document. At the central laboratory, the unstained tissue specimens will be stained at the direction of the Pathological Review Committee, and then all of tissue specimens will be submitted to the Pathological Review Committee.

6.4. Performance Status

Performance status will be determined according to ECOG performance status scale [See Appendix 1] on any day during the screening period (Day -28 to Day -1).

6.5. Medical History

The following information regarding the past and/or concurrent diseases including drug sensitivity and allergy will be collected on any day during the screening period (Day -28 to Day -1):

- Diagnosis or symptom, and date of diagnosis
- Drug sensitivity or allergy: if applicable, name of drug or allergen, severity

Before the start of the first dosing of investigational drug on Day 1 of Cycle 1, whether or not the concurrent disease is ongoing at the start of investigational drug administration will be assessed.

6.6. Pregnancy Status

For subjects other than male and postmenopausal or surgically sterilized female subjects, a urine human chorionic gonadotropin (hCG) pregnancy test will be conducted on any day

during the screening period (between Day -28 to Day -1) and also before the start of investigational drug administration on Day 1 of each cycle. “Menopause” is defined as being at a state of absence of menstrual periods for at least 12 months, excluding the cases of absent menstruation due to a medical reason such as medication.

Throughout the study period, the principal investigator or sub-investigator (or designated staff) should confirm that the subject or subject’s partner is not pregnant.

6.7. Height and Weight Measurement

Body height (cm) and weight (kg) will be measured on any day during the screening period (between Day -28 to Day -1). To determine the dose (mg) of the investigational drug, a body surface area (BSA: m^2) will be calculated using the DuBois’s formula, based on the subject’s height and weight. [See Section 5.3.1]

The subject’s body weight will be also measured before the start of investigational drug administration on Day 1 of each cycle. If the weight changes by ±10% compared to the weight measured at the screening visit, BSA will be recalculated using the DuBois’s formula to adjust the dose. [See Section 5.3.1]

6.8. Physical Examination

At each time point shown in Table 2, the principal investigator or sub-investigator will perform a physical examination. At the physical examination, careful assessment for neurological and mental status should be performed, especially for the following findings.

- Findings suggestive of cranial nerve abnormalities
- Findings suggestive of sensory abnormalities
- Findings suggestive of motor abnormalities
- Findings suggestive of coordination stance / gait abnormalities
- Findings suggestive of reflexes abnormalities
- Findings suggestive of mental status abnormalities

Table 2: Time Points of Physical Examination in Cycle

	Time Point	Time Window
Screening Period	Any day between Day -28 and -1	
Treatment Period	Day 1; before the investigational drug administration	Before the start of infusion
	Day 5; after the investigational drug administration: Cycle 1 only	After the end of infusion
	Day 8	± 2 days (Day 6 - 10)
	Day 15	+ 6 days (Day 15 - 21)
Follow-up Period	Day 22	+ 7 days (Day 22 - 29)

6.9. Vital Sign and Arterial Oxygen Saturation Measurement

Systolic and diastolic blood pressure (mmHg), pulse rate (beats per minute), body temperature (°C), and percutaneous arterial oxygen saturation (SaO_2) (%) by using a pulse oximeter will be measured, at the time points shown in Table 3.

Table 3: Time Points of Vital Sign and Arterial Oxygen Saturation Measurement in Cycle

	Time Point	Time Window
Screening Period	Any day between Day -28 and -1	
Treatment Period	Day 1; before investigational drug administration	Before the start of infusion
	Day 5; after investigational drug administration: Cycle 1 only	Within 60 minutes after the end of infusion
	Day 8	± 2 days (Day 6 - 10)
	Day 15	+ 6 days (Day 15 - 21)
Follow-up Period	Day 22	+ 7 days (Day 22 - 29)

6.10. Electrocardiogram (ECG)

A standard 12-lead ECG test will be performed to measure heart rate (min) and RR interval (msec), QRS interval (msec), PR interval (msec), QT interval (msec) and QT corrected (QTc) interval according to Fridericia's formula (msec), as well as to check for overall ECG findings, at the time points shown in Table 4.

Table 4: Time Points of 12-lead ECG in Cycle

	Time Point	Time Window
Screening Period	Any day between Day -28 and -1	
Treatment Period	Day 1: ・ 0 hour after the start of investigational drug administration	Before the start of infusion
	・ 1 hour (at the end of infusion)	Within 60 minutes after the end of infusion
	Day 5: Cycle 1 only	
	・ 0 hour after the start of investigational drug administration	Before the start of infusion
	・ 1 hour (at the end of infusion)	Within 60 minutes after the end of infusion
	Day 8	± 2 days (Day 6 - 10)
Follow-up Period	Day 22	+ 7 days (Day 22 - 29)

6.11. Laboratory Tests

6.11.1. Hepatitis Virus Screening

The following hepatitis virus tests will be performed on any day during the screening period (from Day -28 to Day -1). HBV-DNA quantitative assay is not mandatory in subjects with negative results for both HBs antibody and HBc antibody.

- HCV antibody
- HBs antigen
- HBs antibody
- HBc antibody
- HBV-DNA quantification

6.11.2. Hematology, Blood Chemistry, and Blood Coagulation Tests

Hematology, blood chemistry and blood coagulation tests shown in Table 6 will be obtained at the time points shown in Table 5. Blood samples for laboratory tests should be preferably collected in the fasting state where possible, because laboratory tests include glucose measurement.

Table 5: Time Points of Blood Collection for Hematology, Blood Chemistry, and Blood Coagulation Tests in Cycle

	Time Point	Time window
Screening Period	Any day between Day -28 and -1	
Treatment Period	Day 1; before investigational drug administration	Before the start of infusion
	Day 5; after investigational drug administration: Cycle 1 only	Within 60 minutes after the end of infusion
	Day 8	± 2 days (Day 6 - 10)
	Day 15	+ 6 days (Day 15 - 21)
Follow-up Period	Day 22	+ 7 days (Day 22 - 29)

Table 6: Test Items of Hematology, Blood Chemistry, and Blood Coagulation Tests

Hematology	Hemoglobin, Hematocrit, RBC count, WBC count, WBC differential, Platelet count
Blood Chemistry	Sodium (Na), Potassium (K), Chloride (Cl), Calcium (Ca), Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), Lactic dehydrogenase (LDH), Total bilirubin, Total protein, Albumin, C-reactive protein (CRP), Creatinine, Blood urea nitrogen, Uric acid, Glucose
Blood Coagulation	Prothrombin time-INR (PT-INR), Prothrombin time (PT), Activated partial thromboplastin time (APTT)

6.12. Concomitant Medication/Procedures

Throughout the study period; from the day of obtaining the informed consent to the end of the follow-up period, the information listed below about concomitant medication or therapeutic procedures such as blood transfusion, wound care and oxygen inhalation will be collected.

However, the use of dilute solutions such as water for injection or saline; which are not intended for treatment; except for fluid therapy to prevent or correct problems with their fluid and/or electrolyte status, will not be determined as concomitant medication. The use of antiseptic solution, cleaning agent or heparin used for preventing blood coagulation (heparin lock) within a cannula/catheter placed in a peripheral vein; which do not have direct effect on the subject's body, will not be determined as concomitant medication. Blood transfusions should be determined as concomitant procedures.

- Medication / procedures
- Date started
- Date stopped
- Only for medication: total daily dose, unit and route
- Indication

6.13. Adverse Events

See Section 7.

6.14. Lymphoma Lesions Assessment

In this study, tumor responses will be assessed according to Revised Response Criteria for Malignant Lymphoma by an International Working Group to Standardize Response Criteria for Non-Hodgkin's Lymphomas in 2007.

Prior to the initiation of study, the PET/CT imaging devices to be used for this study will be specified, and will be used throughout the study. The same device should be used for a series of imaging tests in an individual subject. The Central Imaging Review institution will radiographically assess the PET/CT imaging devices/systems prior to the study initiation and at any change in imaging devices at each investigational site, confirm the results of phantom testing, if needed, and determine the procedures of imaging tests.

6.14.1. Baseline Assessment

The following imaging tests and examinations will be performed during the screening period (from Day -28 to Day -1) for the assessment of lymphoma lesions present at baseline:

- Radiological assessment of tumors with contrast enhanced computed tomography (contrast-enhanced CT) image data at baseline

  Slice thicknesses of ≤ 5 mm will be obtained from the area covering disease lesions in the neck (infraorbital margin) to pelvis (femoral) region. Simple CT may be acceptable in a subject with known contraindication to CT contrast agents. In case that any

inadequate CT images are obtained for any reason, CT image data by Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) may be alternatively used. The detailed procedures/conditions of contrast-enhanced CT scan are specified in a separate document.

- Radiological assessment of tumors with FDG-PET data at baseline

  The area covering disease lesions in the neck (infraorbital margin) to pelvis (femoral) region will be scanned. The detailed procedures/conditions of FDG-PET scan are specified in a separate document.

- Enlargement of liver or spleen (splenomegaly and hepatomegaly) will be assessed by CT scan and palpation
- Infiltration in bone marrow will be assessed by bone-marrow biopsy (biopsy should be preferred whenever possible) or aspiration (clot sections)
- For subjects with gastrointestinal lesion: lymphoid cell infiltration will be assessed by endoscopy and biopsy
- For subjects with skin lesion: photographs of skin lesion will be taken

Based on the radiological assessment at baseline, target lesions and non-target lesions will be chosen, nodal lesions or extranodal lesions will be classified, the size in 2 perpendicular dimensions of target lesions will be measured, the sum of the products of the greatest diameters (SPD) of target lesions will be calculated, and the results of FDG-PET results will be assessed.

Target and non-target lesions will be selected in consideration of reproducibility at the subsequent assessment of radiographic tumor response in the study. When nodular lesions in the liver or spleen are selected as target lesions or non-target lesions, nodular mass in the spleen will be classified as nodal lesions; and nodular mass in the liver will be classified as extranodal lesions. The enlargement of liver and spleen will be separately assessed including assessment by palpation.

<Target lesion>

- Up to 6 measurable lesions will be selected, for both enlarged lymph nodes and extranodal mass lesions. Larger lesions in order of the long diameter are preferred. See Inclusion Criteria [See Section 3.1 (5)] for the definition of measurable lesions.
- If one or more measurable lesions are found in a single lymph node region or a single organ, except for the lesion with the greatest long diameter, lesions should be selected from disparate regions of the body if possible.
- Any measurable lesions in the mediastinal or the retroperitoneal sites should be selected.

<Non-target lesion>

- All other sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including any measurable lesions that are not chosen as target lesions.

6.14.2. Tumor Response Assessment

At the following time points, the clinical assessments and radiological assessments will be performed by the same examinations and imaging tests under the same procedures and conditions at baseline assessment, and the tumor responses will be assessed throughout the study. Any site of new lesion will be identified. Bone marrow assessment (biopsy or aspiration) will be required only if bone marrow is positive at baseline and the radiographic responses is judged to be CR.

- Any day between Day 15 and Day 21 in Cycle 3
- Any day between Day 15 and Day 21 in Cycle 6
- If administration of investigational drug is continued beyond 6 cycles, any day between Day 15 and Day 21 every 3 (± 1) cycles from Cycle 7
- If administration of investigational drug is discontinued at a cycle other than the above, any day between Day 15 and Day 42 in the last cycle; however, before the initiation of the subsequent treatment of primary disease

According to the response criteria defined in Table 7, the local assessment of tumor response will be performed by the principal investigator or sub-investigator.

Table 7: Revised Response Criteria for Malignant Lymphoma by an International Working Group to Standardize Response Criteria for Non-Hodgkin's Lymphomas in 2007

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
RD or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

6.14.3. Radiological Assessment at the Central Imaging Review Institution

The principal investigator or sub-investigator (or designated staff) will submit imaging data by CT and FDG-PET at the following time points to the Central Imaging Review Institution. Details of the procedures of imaging data submission to the Central Imaging Review Institution are specified in a separate document.

- Screening period (between Day -28 and Day -1)

- Any day between Day 15 and Day 21 in Cycle 3
- Any day between Day 15 and Day 21 in Cycle 6
- If the administration of investigational drug is discontinued at Cycles 1, 2, 4 and 5, any day between Day 15 and Day 42 in the last cycle; however, before the initiation of the subsequent treatment of primary disease

The Central Imaging Review Institution will measure the tumor size of lymphoma lesions and evaluate FDG accumulation; according to the predefined procedure, and submit the radiological assessment results to the Efficacy and Safety Review Committee.

6.15. Survival Surveillance

6.15.1. Surveillance of Progression of Disease and Relapsed Disease

If PD, RD or “death” is not confirmed by the end of follow-up period, tumor response assessment [See Section 6.14.2] will be continued at intervals of three months or less until PD, RD or “death” is confirmed.

PD or RD includes not only the results of the radiological assessment with imaging data but also “symptomatic progression” at the principal investigator’s or sub-investigator’s judgement based on clinical symptoms or laboratory findings, etc. The development of secondary cancer is not defined as progression event, and surveillance of PD, RD or “death” will be continued.

6.15.2. Surveillance of Subsequent Treatment for Primary Disease

Throughout the survival surveillance period [See Section 6.15.3], the information of subsequent treatment for primary disease; e.g., antitumor chemotherapy, antitumor immunotherapy, radiotherapy, and hematopoietic stem cell transplant; including the name of medications, the date of treatment initiation and the tumor responses will be surveyed.

6.15.3. Survival Surveillance

A survival surveillance will be continued, at intervals of six months or less whenever possible, for up to 2 years from the date of initiation of investigational drug administration (Day 1 of Cycle 1) to confirm “survival” or “death” of subjects. When the subject’s death is confirmed, the “date of death” or “the most recent date (date of the last day) of survival confirmation” should be specified. The surveillance via telephone is allowed.

6.16. Pharmacokinetics

Pharmacokinetics (PK) assessment will be performed only in Cycle 1 only at the investigational sites where the principal investigator has agree to perform PK assessment in advance. The remaining portion of samples after the completion of determination of drug concentration will be appropriately discarded at a central laboratory.

6.16.1. Blood Collection for Determination of Drug Plasma Concentration

At the time points shown in Table 8, blood samples (approximately 10 mL containing ≥4 mL

of plasma) for determination of plasma drug concentration will be collected from a vein of forearm of the opposite arm of the infusion site. The collected blood samples will be processed at the investigational sites and then submitted to the central laboratory according to a specific procedure. The detailed procedures of blood collection, sample processing and submission are specified in a separate document, and will be provided to the investigational sites together with a set of sample collection kits including tubes for blood collections and containers for shipment.

At the central laboratory, plasma concentration of arsenic, darinaparsin and its metabolites will be analyzed. The results of analysis will be reported to the investigational sites by the Sponsor or CRO.

Table 8: Time Points of Blood Collection for Drug Plasma Concentration in Cycle 1

Time Point		Time window
Day 1:	0 hr after the start of investigational drug infusion,	Within 60 min prior to the start of infusion
	1 hr (immediately after the end of infusion),	Within 15 min after the end of infusion
	2 hrs (1 hr after the end of infusion),	± 15 min
	4 hrs (3 hrs after the end of infusion),	± 15 min
	6 hrs (5 hrs after the end of infusion),	± 30 min
	8 hrs (7 hrs after the end of infusion).	± 30 min
Day 2:	0 hr	Within 60 min prior to the start of infusion
Day 3:	0 hr	
Day 4:	0 hr	
Day 5:	0 hr after the start of investigational drug infusion,	Within 60 min prior to the start of infusion
	1 hr (immediately after the end of infusion),	Within 15 min after the end of infusion
	2 hrs (1 hr after the end of infusion),	± 15 min
	4 hrs (3 hrs after the end of infusion),	± 15 min
	6 hrs (5 hrs after the end of infusion),	± 30 min
	8 hrs (7 hrs after the end of infusion).	± 30 min
Day 6:	Same time of the infusion start on Day 5	± 60 min
Day 8:	Same time of the infusion start on Day 5	± 60 min
Day 15:		+ 6 days (Day 15 - 21)

6.16.2. Urine Collection for Determination of Drug Urine Concentration

At the time periods shown in Table 9, the entire urine will be accumulated in Cycle 1. The urine accumulation will be started after the subject completely urinates, and completed after the subject completely urinates during each time period of urine collection.

After the measurement of a total volume (mL) of urine collected at each time period, ≥ 20 mL of urine will be taken in the container and submitted to the central laboratory according to a specific procedure. The detailed procedures of urine collection, sample processing and submission are specified in a separate document, and will be provided to the investigational sites together with a set of sample collection kits including containers for shipment.

At the central laboratory, urine concentration of arsenic, darinaparsin and its metabolites will be analyzed. The results of analysis will be reported to the investigational sites by the Sponsor or CRO.

Table 9: Time Periods of Urine Collection for Drug Urine Concentration in Cycle 1

Time Periods			Time window
Day 1:	Start of urine accumulation	0 hr from the start of infusion	Within 60 min prior to the start of infusion
	~ End of urine accumulation	For 4 hrs (3 hrs after the end of infusion)	± 15 min
	Start of urine accumulation	4 hr from the start of infusion	
Day 2:	~ End of urine accumulation	Until 24 hrs after the start of infusion on Day 1	Within 60 min prior to the start of infusion on Day 2
Day 5:	Start of urine accumulation	0 hr from the start of infusion	Within 60 min prior to the start of infusion
	~ End of urine accumulation	For 4 hrs (3 hrs after the end of infusion)	± 15 min
	Start of urine accumulation	4 hr from the start of infusion	
Day 6:	~ End of urine accumulation	Until 24 hrs after the start of infusion on Day 5	± 60 min of same time of the infusion start on Day 5

6.17. Reference: Volume of Blood Sample Collection

As shown in Table 10, Table 11 and Table 12, the standard blood sample collection volume from the screening period to the end of Cycle 1 is 42-47 mL per subject who are not subject to drug plasma PK assessment and 222-227 mL per subject who are subject to the assessment. The standard volume in each cycle from Cycle 2 is 24 mL and 8 mL in the follow-up period. When a subject completes the study at the end of 6 cycles, the standard volume is approximately 170-175 mL in a subject who is not subject to drug plasma PK assessment and 350-355 mL in a subject who is subject to the assessment.

Table 10: Blood Sample Collection Volumes from Screening Period to Cycle 1

Test Items	Volume of Blood Sample Collection per Time Point (approximately)	Frequency	Subtotal Volume
Hepatitis virus	2-7 mL	x 1	2-7 mL
Hematology	2 mL	x 5	10 mL
Clinical chemistry	4 mL	x 5	20 mL
Blood coagulation	2 mL	x 5	10 mL
Determination of Drug Plasma Concentration	10 mL	x 18	180 mL
Total Volume	Blood Collection for Determination of Drug Plasma Concentration	No	42 - 47 mL
		Yes	222 - 227 mL

Table 11: Blood Sample Collection Volumes in Each Cycle from Cycle 2

Test Items	Volume of Blood Sample Collection per Time Point (approximately)	Frequency	Subtotal Volume
Hematology	2 mL	x 3	6 mL
Clinical chemistry	4 mL	x 3	12 mL
Blood coagulation	2 mL	x 3	6 mL
Total Volume			24 mL

Table 12: Blood Sample Collection Volumes in Follow-up Period

Test Items	Volume of Blood Sample Collection per Time Point (approximately)	Frequency	Subtotal Volume
Hematology	2 mL	x 1	2 mL
Clinical chemistry	4 mL	x 1	4 mL
Blood coagulation	2 mL	x 1	2 mL
Total Volume			8 mL

7. SAFETY DATA COLLECTION AND REPORTING

7.1. Definitions

7.1.1. Adverse Events

An adverse event (AE) is defined as “any untoward medical occurrence in a subject administered an investigational drug and which does not necessarily have a causal relationship with this treatment”.

This definition of AEs includes any such medical occurrences or exacerbation of pre-existing medical conditions or events (primary disease, underlying disease or concurrent diseases etc.). Obvious exacerbation of the pre-existing medical conditions; worsening in severity, increase in frequency, or extending of duration of the events, in the judgment of the principal investigator or sub-investigator, will qualify as an AE.

The principal investigator or sub-investigator will identify a “term” of diagnosis or syndrome of the AE as much as possible. Diseases or clinical signs with accompanying symptoms, the diseases or clinical signs will be identified and qualified as AEs.

The principal investigator or sub-investigator is responsible to confirm the changes in laboratory test results (vital signs, ECGs, laboratory test values, etc.) from baseline values in an individual subject. The clinically significant abnormal changes; including any change for which a new treatment or alternative treatment, in the judgment of the principal investigator or sub-investigator, will qualify as AEs. Diseases or clinical sings accompanying abnormal laboratory findings, the diseases or clinical signs will qualify as AEs.

7.1.2. Serious Adverse Events

A serious adverse event (SAE) is defined as an adverse event that

- is fatal
- is life threatening (an event that places the subject at immediate risk of death)
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is any other medically important condition

A hospitalization meets the regulatory definition for “serious” is any inpatient hospital admission that includes a minimum of an overnight stay in a health care facility. A hospitalization only for the previously scheduled treatment or examination (operations or medical tests planned in advance) will not qualify as an AE.

Any AE that does not clearly meet one of the definitions above may be considered by the principal investigator or sub-investigator whether the event meets the criteria of “any other medically important condition” in the definitions of a SAE.

7.2. Procedures for Adverse Events Reporting

The principal investigator or sub-investigator (or designated staff) will collect and identify the following information on AEs during the period from the start of investigational drug administration to the end of follow-up period, and enter a description of the event into the eCRF.

- Term of adverse event
- Date of onset
- Seriousness; serious or not serious
- Severity
- Relationship to the investigational drug; if “No,” the reason for “No”
- Any action taken; if “Yes,” the details of the action
- Outcome and date of outcome confirmation (date of resolution, date of confirmation or examination of resolving/not resolved events, date of death, etc.)

Relationship (Causality)

Relationship of an AE to the investigational drug should be assessed from the point of view that “there is a reasonable possibility that the investigational drug caused the AE”. The principal investigator or sub-investigator should determine either of “Yes” or “No”.

Severity Assessment

Severity of an AE will be assessed by the principal investigator or sub-investigator, using the 5-grade scale according to NCI-CTCAE Version 4.0. For those events not found in NCI-CTCAE Version 4.0, the principal investigator or sub-investigator will clinically determine the severity based on the definition in Table 13.

7.3. Follow-up Observation of Adverse Events

Investigational-drug-related AEs that are ongoing at the end of follow-up period will be followed, in case that the principal investigator or sub-investigator judges the follow-up observation of AEs is clinically required.

The follow-up observation of AEs will be continued for 4 weeks after the end of follow-up period, and “date of resolution/resolving of AE” or ”date of subject’s death” will be specified as the date of outcome confirmation.

If an AE has not resolved (have not been resolving or become stable) within 4 weeks after the end of follow-up period, the day of the first observation of AEs during the period ≥ 4 weeks after the end of following-up period will be specified as the date of outcome confirmation.

Table 13: Adverse Event Grading (Severity) Scale

Grade	Description
Grade 1 (Mild)	・ Mild ・ Asymptomatic or mild symptoms ・ Clinical or diagnostic observations only ・ No intervention indicated
Grade 2 (Moderate)	・ Moderate ・ Minimal, local or noninvasive intervention indicated ・ Limiting age-appropriate instrumental Activities of Daily Living (ADL)*1
Grade 3 (Severe)	・ Severe or medically significant but not immediately life-threatening ・ Hospitalization or prolongation of hospitalization indicated ・ Disabling ・ Limiting self care ADL*2
Grade 4 (Life-threatening)	・ Life-threatening consequences ・ Urgent intervention indicated
Grade 5 (Death)	・ Death related to AE

*1: Instrumental ADL; refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

*2: Self care ADL; refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden

7.4. Reporting of Serious Adverse Events

The principal investigator or sub-investigator (or designated staff) must submit an initial SAE report of any SAE to the Sponsor or CRO with any means of contact within 24 hours since knowing of the event.

The principal investigator must submit the follow-up SAEs report about the information on SAEs. A form provided in advance by the Sponsor or CRO or a form designated by the investigational site must be used, and submitted to the Sponsor or CRO, and the investigational site or site IRB. Follow-up SAE report will include any additional information or change in the information recorded in previous reports.

For contact information of the Sponsor and CRO, see “Organization and Structure of Clinical Study in Each Country and Region.”

8. DATA COLLECTION AND MANAGEMENT

8.1. Data Entry to Electronic Case Report Form (eCRF)

The principal investigator or sub-investigator (or designated staff) enters protocol-specified data into the eCRF by using the EDC system in this study; in an accurate, complete and easy-to-read manner at appropriate times, in English in principle. The study collaborators, other than the sub-investigator, who are designated by the principal investigator will be allowed only to transcribe data from the source documents into eCRF.

The principal investigator will review the data in eCRF, confirm the completeness and accuracy of data, and then provide an electronic signature in the predefined form in eCRF. In accordance with the investigational institution's own policy, the eCRF data that are exported in PDF will be retained at the site.

8.2. Correction or Change to Data in eCRF

If the principal investigator or sub-investigator (or designated staff) makes changes or corrections to data in the eCRF, the information on the former data before changes or corrections, persons who make changes or corrections, and date on which changes or corrections are made will be recorded in the audit trail in the EDC system. In any change or correction in the important data such as the date of obtaining the informed consent or the relationship between investigational drug and AEs, the reason for data changes or corrections should be specified and entered in eCRF.

The principal investigator will review the changes or corrections to data in the eCRF, confirm the data to be complete and accurate, and then provide an electronic signature in the predefined form in eCRF. In accordance with the investigational institution's own policy, the audit trail that is exported in PDF will be retained at the site.

The Development Sponsor or the data management CRO should review the data in eCRF in terms of data consistency, omission or apparent contradiction, or violation of GCP or the protocol. For a question resulting from the review, a query for a given data on eCRF will be created and sent to an investigational site. The principal investigator or sub-investigator (or designated staff) will respond to the queries by re-investigation and making changes or correction to data in eCRF if needed.

In this study, the changes or corrections to data in eCRF will not be made by a person designated by the Development Sponsor.

8.3. Data in eCRF as Source Data

The data entered in eCRF should match exactly the corresponding written record in source documents. The principal investigator will create a record that explains the reason for any inconsistency.

The data entered in eCRF may be qualified as the source documents, if a given data on eCRF itself is only source data; i.e., no written or electronic source document is existing. In this study, the data in eCRF may be qualified as source data if no source document exists for the items listed below and all of relevant comments:

- Subject background: ethnic background/race
- Primary disease:
  - Clinical symptoms caused by the primary disease (clinical symptoms associated with primary disease)
  - Clinical stage by the Ann Arbor classification
  - Prognostic risk group by International Prognostic Index (IPI)
  - Prognostic risk group by Prognostic Index for T-cell lymphoma (PIT)
- Medical history:
  - Concurrent diseases at the start of investigational drug dosing
  - Severity of drug sensitivity or allergy
- Pregnancy test: reason for the absence of pregnancy test
- 12-lead ECG: overall ECG findings (presence of abnormalities)
- Concomitant procedures: reason for starting therapeutic procedures
- Adverse Events (AEs):
  - Severity
  - Seriousness
  - Relationship to the investigational drug
  - Reason/rationale for denying the relationship

8.4. Deviations from the Protocol

The principal investigator or sub-investigator (or designated staff) should keep a record of all actions deviating from the protocol for any reason.

The principal investigator or the investigational site may deviate from or modify the protocol for medically justifiable reasons, without prior written agreement with the Sponsor and prior written IRB approval, such as when necessary to eliminate imminent hazards to the subject. However, the principal investigator should subsequently take procedures according to the regulatory requirements of each country or region in an expedited manner.

8.5. Committees and Coordinating Investigators

8.5.1. Pathological Review Committee

The Pathological Review Committee will consist of multiple pathologists who are not responsible for a medical expert, principal investigator or sub-investigator, coordinating investigator, or a member of another committee of this study. The Committee will be charged with the following tasks.

- Guidance and advice for the protocol and procedure for a central pathological diagnosis
- Guidance and advice for the procedures at central laboratory activities where pathology specimens are collected, stored and unstained tissue specimens are stained.
- Staining of unstained samples as needed

- Diagnosis by each member of the Pathological Review Committee (individual diagnosis)
- Central pathological diagnosis by the Pathological Review Committee (consensus diagnosis)

The histopathological classification based on World Health Organization (WHO) Classification Version 4 (2008) is used for the central pathological diagnosis at the Pathological Review Committee. If the central pathological diagnosis at the Pathological Review Committee differs from that at each investigational site, the central pathological diagnosis at the Pathological Review Committee will be given priority.

8.5.2. Efficacy and Safety Review Committee

The Efficacy and Safety Review Committee will consist of the hematologists and radiologists who are not responsible for a medical expert, principal investigator or sub-investigator, coordinating investigator, or a member of another committee of this study. The Committee will be charged with the following tasks.

- Guidance and advice for the protocol and procedure for a central assessment of tumor response
- Guidance and advice for the procedures at the Central Imaging Review Institution
- Central review based on the results of radiological assessment of tumor response at the Central Imaging Review Institution and the results of a local assessment of tumor response based on “non-imaging data” at each investigational site.
- Overall evaluation of efficacy and safety
- Advice for the termination/suspension of the study (appropriateness of continuation of the study)

The Efficacy and Safety Review Committee will be held to perform an interim review of efficacy and safety (and pharmacokinetics as needed) at the point when the number of subjects evaluable for efficacy reaches 20 and have all necessary data available.

8.5.3. Coordinating Investigators

At each country or region, in principle, at least one coordinating investigator will be assigned. The coordinating investigators will be charged with the following tasks, at request of the Development Sponsor. No committee will be organized.

- Guidance and advice for protocol development and revision
- Coordination among different countries/region participating in this study as for the content of protocol
- Coordination among different countries/region in this study as for interpretational questions about the protocol

9. STATISTICAL CONSIDERATIONS

9.1. Subsets

9.1.1. Handling of Subjects and Data

Prior to the analysis, the Development Sponsor will determine the handling (inclusion) of subjects based on the consultation with medical experts. If it is considered that data including laboratory values, 12-lead ECG or drug plasma or urine concentration measurements has been affected by abnormality of a sample (e.g. hemolysis or milky fluid) or a technical error, the Development Sponsor will decide, prior to the data analysis, whether or not to exclude that data from analysis based on the consultation with medical specialists.

9.1.2. Efficacy Analysis Set

A subject group consisting of subjects who fulfill eligibility criteria [See Section 3.1] and who take a tumor response assessment [See Section 6.14.2] at least one time after the administration of the investigational drug is defined as a “Full Analysis Set (FAS)”. A subject group consisting of subjects who have no important protocol deviation including violation of eligibility criteria and/or dose and dosage that may affect the efficacy evaluation is defined as “Per Protocol Set (PPS)”. FAS will be used for the primary analysis of efficacy endpoints, and PPS will be used for the secondary analysis of efficacy endpoints.

9.1.3. Safety Analysis Set

A group of subjects who receive at least one dose of investigational drug is defined as the “safety analysis set”. The safety analysis set will be used for the analysis of safety endpoints.

9.1.4. PK Analysis Set

The “PK analysis set” will consist of all subjects who receive at least one dose of investigational drug and have at least one point of drug plasma or urine concentration data. PK analysis set will be used for the analysis of PK endpoints.

9.2. Sample Size Considerations

The required sample size of 55 is calculated in SAS® POWER Procedure using Fisher's exact test, when the one-sided significance level is 5% with a statistical power of 90%, with the expected overall response rate (ORR) of 25% and the 10% threshold. Considering for the subjects who are excluded from analysis resulting from the central pathological diagnosis, the planned sample size is 65 subjects.

9.3. Interim Analysis

No interim analysis and no early termination for efficacy are planned in this study.

An interim review for efficacy and safety including PK as needed [See Section 8.5.2] will be performed at the point when the number of efficacy evaluable subjects evaluable for efficacy reaches 20 and have all necessary data available.

9.4. Planned Methods of Analysis

Upon submission of the New Drug Application for SP-02L, an appropriate data cut-off date should be determined as the primary endpoint is evaluable. Detailed analytical method in this study will be specified in the statistical analysis plan.

In this study, no analysis will be performed considering withdrawal. No imputation for missing values will be performed. No adjustment for covariates, the investigational sites or multiplicity will be performed.

9.4.1. Data summarization

Of the demographic variables and baseline (subject background factors) and data, continuous variables will be summarized by n, mean, standard deviation (or standard error for efficacy), median, Q1, Q3, minimum, and maximum values. Categorical variables will be summarized by frequency and percentage.

9.4.2. Analysis of Efficacy Endpoints (Tumor Response)

Based on a central assessment of tumor response at Efficacy and Safety Review Committee, the best overall responses for 6 cycles will be summarized to calculate the ORR and 90% confidence interval (90% CI). Based on a local assessment at each investigational site, the best overall responses for 6 cycles and in the entire period will be summarized to calculate ORR and 90% CI.

The best overall response will be summarized and the ORR will be calculated by histopathological classification, clinical stage according to Ann Arbor classification , prognosis risk group according to international prognostic index (IPI), prognosis risk group based on Prognosis Index for T-cell lymphoma (PIT), ethnic background, sex and age (< 61 years old or ≥ 61 years old).

To assess the tumor response in each subject, the waterfall plot will be produced to show the rate of tumor shrinkage at best overall response.

9.4.3. Analysis of Efficacy Endpoints (Survival Time and Others)

Progression-free survival (PFS), time to response (TTR), duration of response (DOR) and overall survival (OS) will be summarized overall and by histopathological subtype. PFS and OS will be analyzed by using Kaplan-Meier method overall and by histopathological subtype.

Progressive disease (PD), relapsed disease (RD) or death which occurs earlier is defined as “progression event”, and “the date of progression” will be identified for analyses of PFS and DOR in accordance with the following rules:

- The date of judgment of PD or RD based on the radiological assessment of tumor response [See Section 6.14.2] is defined as “the date of progression”.
- PD or RD includes not only the results of radiological assessment with imaging data but “symptomatic progression” at the principal investigator’s or sub-investigator’s judgement based on clinical symptoms or laboratory findings, etc. In this case, the date of the investigator’s judgement is defined as “the date of progression”.

- If “death” occurs earlier than the judgement of “PD” or “RD”, the date of death is defined as “the date of progression”.

If no progression event is confirmed prior to the following events, the most recent date (date of the last day) of radiological assessment of tumor response [See Section 6.14.2 will be defined as “the date of censoring”:

- Subsequent anticancer treatment for primary disease initiated
- Investigational drug is discontinued for toxicity (investigational-drug-related AEs)
- Subject is lost to follow up

If a subject is surviving on the date of “data cut-off”, the most recent date (date of the last day) of confirmation of subject’s existence is defined as “the date of censoring” for the analysis of OS. For a subject lost to follow-up, the last date when the subject’s existence is confirmed prior to the subject’s lost to follow-up is defined as “the date of censoring”.

9.4.4. Analysis of Safety Endpoints

The incidence of AEs will be summarized by system organ class and by preferred term according to the ICH-MedDRA, and by ethnic background and severity. Incidence of investigational-drug-related AEs, serious AEs (SAEs) and investigational-drug-related SAEs will be also summarized, respectively, in the same way.

SAEs, SAEs of ≥ Grade 3, and significant AEs in the judgement of the Development Sponsor; e.g. neurological disorder and psychiatric disorder, will be summarized or described.

Vital signs, laboratory values and ECG parameters will be summarized by item and time point.

9.4.5. PK Analysis

Plasma drug concentrations will be summarized overall and by ethnic background, and the graphs of mean plasma drug concentration-time profiles will be provided. The following PK parameters for each subject will be estimated using non-compartmental methods and summarized overall and by ethnic background.

- Maximum drug concentration time: t_{max}
- Maximum drug concentration: C_{max}
- Area under the blood concentration time curve: $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$
- Half-life period: $t_{1/2}$
- Systemic clearance: CL
- Distribution volume: Vd_{ss} and Vd_z
- Mean retention time: MRT_{last}

Urine excretion rates will be calculated and summarized overall and by ethnic background.

9.4.6. Additional Analyses

At the discretion of the Development Sponsor, additional analyses of the data will be conducted as deemed appropriate. Details of additional analyses are specified in the statistical analysis plan.

10. STUDY ADMINISTRATION AND ETHICAL CONSIDERATIONS

10.1. General Ethical Requirements

This study will be conducted in accordance with the ethical principles of the Declaration of Helsinki, ICH-GCP, country- and region-specific GCP, the currently approved protocol/amendment(s) of this study, the clinical trial contract that is concluded between each investigational site and the Sponsor (and CRO), and other agreements that are concluded between the medical institution and the Sponsor (and CRO).

10.2. Protocol Management

The Sponsor provides the protocol and an example of informed consent form, and sample of eCRF as needed to the principal investigator. Any amendment of these documents will be promptly notified to the principal investigator with the reason for amendment, except when necessary to eliminate immediate hazards to the subjects [See Section 8.4] or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of the name or address of investigational site, name and title of principal investigator, name and address of the Sponsor or CRO, and name, title and contact information of monitors)

The Sponsor should obtain the principal investigator's agreement for the protocol or amendments if the protocol is amended and to conduct the study in compliance with the protocol. To confirm this agreement, the Sponsor and investigator will sign and date on the page of "Investigator's Agreement" in the protocol or any alternative document. The Sponsor will designate a Study Manager in each of participating country or region as a person who is authorized to represent the Sponsor and sign the above document.

10.3. Quality Control and Quality Assurance

The Sponsor and CRO are responsible for implementing and maintaining quality assurance and quality control systems with written SOPs.

10.3.1. Monitoring and Audit

Monitors will visit the investigational sites and carry out the monitoring. The purposes of study monitoring are to verify that the rights, safety and well-being of human subjects are protected, the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s), and the data entered in eCRF and in other study reports are accurate, complete and verifiable from source documents.

The auditors should evaluate study conduct and compliance with GCP and the protocol, as quality control functions, according to the audit plan. The observations and findings of the auditor(s) should be documented and submitted to the Sponsor. A global auditor who is appointed by the Development Sponsor may visit the CROs and the investigational sites in each country or region to evaluate study conduct in each country or region to confirm the compliance of the study with the ICH-GCP from a unified perspective (Global Audit).

10.3.2. Direct Access to Source Documents

The principal investigator and medical institutions are required to permit direct access to all study-related documents, data, and records, including source documents related to the subject's original medical records and data, on the occasion of monitoring and auditing by the Sponsor or CRO as well as the inspection by the IRB or domestic and foreign regulatory authorities. The principal investigator or sub-investigator is obligated to inform and obtain the written consent of each subject to permit the direct access to the subject's source documents related to the subject's original medical records and data, on the occasion of monitoring and audit as well as the site inspection by the IRB or regulatory authorities.

10.4. Retention of Study Records

The principal investigator and the investigational site, including IRB and person in charge of the management of the investigational drug, should not destroy, without prior agreement with the Sponsor or CRO, any study-related documents or records, in conformance with ICH-GCP and country- or region-specific GCP.

The Sponsor or CRO should notify the principal investigator or the investigational site in writing when these documents no longer need to be retained (at the end of retention period).

10.5. Subject Confidentiality

The principal investigator and the investigational site must ensure that subject's confidentiality is maintained as follows:

- On data, documents and records submitted to the Sponsor or CRO, such as data entered into eCRFs and the Serious Adverse Events Reports, a subject should be identified by a subject number only.
- Data and documents that are not for submission to the Sponsor or CRO, including signed informed consent forms, should be kept in strict confidence at the investigational site.

Employees of the Sponsor and the CRO, whether incumbent or not, should not disclose, without legitimate reasons, any confidential information obtained through direct access to the source documents.

10.6. Health Damage Compensation

Subjects will receive compensation for any study-related health damage caused to them in compliance with "Compensation for Health Damage on Subjects" that is a separate document prepared by the Sponsor in each country or region. The Sponsor will purchase health insurance as an action for performance of liability for compensation and liability indemnity, as necessary.

10.7. Publication

If the entire results obtained from this study are to be disclosed (submission of paper/article, publication of book or presentation at professional meetings, etc.), the Development Sponsor will decide the authorship or presenter, based on the discussion with medical experts, in accordance with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors). A copy of any publication or written presentation of the data or script of any oral presentation of the data must be provided to the Development Sponsor for review and approval prior to submission for publication or presentation, including abstracts for professional meetings.

If any specific data on individual subject at each investigational site is to be published, the author or presenter will have discussion, in advance, with the Sponsor about the contents.

11. REFERENCES

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- Swerdlow SH, Campo E, Harris NL, et al.: WHO classification of tumours of haematopoietic and lymphoid tissues, fourth edition. Lyon, France: IARC; 2008
- Cheson BD, Pfistner B, Juweid ME, et al.: Revised Response Criteria for Malignant Lymphoma. J Clin Oncol 2007, 25; 579-586
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- Drafting Committee for Hepatitis Management Guidelines and the Japan Society of Hepatology: JSH Guidelines for the Management of Hepatitis B Virus Infection. Hepatology Research 2014, 44; 1-58
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- U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research: Guidance for Industry - Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. May 2015

Appendix 1: ECOG Performance Status Scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair

Appendix 2: Pharmacy Guide

1. Packaging and Formulation

The investigational drug will be supplied as a sterile, white to off-white, lyophilized powder in glass vials containing 150 mg of darinaparsin per vial. Each vial and box will be labeled according to country- and region-specific regulations, and each box will have 10 vials of investigational drug. The label will comply with local regulations.

2. Labeling

A box and each vial of investigational drug will be properly labeled identifying the limited use to clinical study, name of the investigational drug, lot number, name and address of the sponsor, appropriate storage conditions, and appropriate country- and region-specific caution statement.

3. Storage and Expiry Date

The investigational drug should be stored under refrigeration at 2°C to 8°C (36°F to 46°F), except when being prepared for injection.

The expiry date of the investigational drug will be notified in writing by the Sponsor or CRO based on the results of stability studies that is being conducted concurrently with this study.

4. Calculation of Administration Dose

The dose (mg) of the investigational drug given to each subject will be calculated by multiplying the subject's body surface area (BSA, m^2) by 300 (mg). The maximum dose will be 600 mg; a dose exceeding 600 mg per body must not be administered.

The BSA will be calculated using DuBois's formula shown below, based on the subject's height (cm) and body weight (kg) measured during the screening period.

$$S = W^{0.425} \times H^{0.725} \times 0.007184$$

S: Body surface area (m^2)
W: Weight (kg)
H: Height (cm)

If there are ±10% changes in the body weights measured on Day 1 of each cycle (before the start of investigational drug administration) from the weight measured in the screening period, BSA will be re-calculated to adjust the dose.

5. Preparation

The preparation of investigational drugs will be performed at each investigational site by using aseptic techniques at room temperature.

Since SP-02L is a cytotoxic antitumor drug, handling of the drug should strictly comply with precautions as required for the handling of toxic chemicals. Protectors (goggles, gloves, masks, etc.) are required at the preparation. If the drug or drug solution attached to the skin,

the attached area should be washed well with soap and water immediately and if to the mucosa, rinsed well immediately. If the drug solution spills out, it should be wiped out with an absorbable material and the area should be cleaned with water and alcohol more than three times.

Each vial contains 150 mg of darinaparsin. When completely reconstituted with 2.0 mL water for injection, the nominal concentration is 75 mg/mL. Within 1 hour of reconstitution, the required dose (mg) is drawn into at least one syringe and added to an infusion bag containing 250 mL of saline solution (Sodium Chloride Injection).

In case that a lot number of investigational drug is multiple at the investigational site, the investigational drugs of the same lot number will be used in a subject throughout a cycle whenever possible; a subject will not receive the investigational drug of multiple lot numbers within a cycle.

6. Administration

The investigational drug will be reconstituted and diluted according to the preparation procedures described in above 5, and will be given intravenously over 1 hour (± 10 minutes) on each day of administration. After the infusion, a flushing with a sufficient amount of saline will be done to ensure all the drug remaining in the infusion route is infused fully to the subject.

Since the injection site abnormalities have been frequently reported in subjects who received the investigational drug via a peripheral line in the previous clinical studies, the administration of the investigational drug is recommended to be given through the central vein (e.g., via an implantable subcutaneous infusion port, a central venous catheter, a peripherally inserted central venous catheter). If any abnormal finding at the injection site is observed during the infusion via a peripheral line, the administration will be held at the discretion of the principal investigator or sub-investigator. Saline may be infused via a three-way stopcock. The IV infusion may be given from another peripheral vein or via a central venous line or port.

The following matters should be noted when the investigational drug is administered:

- During the injection via a peripheral line, full care should be taken to avoid extravasation. If any extravasation is observed, the dose will be held immediately, medical procedures will be provided for it, and a change in the peripheral vein for IV infusion will be considered.
- No other drug for injection should be given concurrently via the same IV line.
- The investigational drug administration will be started at the same time as much as possible in subjects for pharmacokinetic assessment in Cycle 1.

Destruction of Used Investigational Drugs

Used investigational drugs and boxes (empty boxes) will be destroyed locally in accordance with the investigational site's policy. The local destruction of used investigational drugs will be documented, as needed, according to the investigational site's policy. In case that the investigational site is incapable of local destruction of used investigational drugs and empty

boxes, the detailed procedures of destruction will be specified in the procedure manual of investigational drug management.

7. Supply and Return of Drug

After the conclusion of the clinical trial contract, the Sponsor will ship investigational drugs, via CRO or an investigational drug delivery service company, to the person in charge of the investigational drug management (e.g. pharmacist) at the investigational site. On receipt of the investigational drugs, the person in charge of the investigational drug management will conduct an inventory of the supplies and check condition of drugs. Also a “Proof of Receipt of Investigational Drug” should be completed and submitted to the Sponsor and a “Proof of Delivery of Investigational Drug” should be retained at the investigational site.

At the end of study, or as otherwise directed, the Sponsor will collect unused investigational drugs, via CRO or an investigational drug delivery service company. On return of unused investigational drugs, the person in charge of the investigational drug management will complete the check of amount and condition of unused drugs. A “Proof of Return of Investigational Drug” must be completed and submitted to the Sponsor, and a “Proof of Collection of Investigational Drug” should be retained at the investigational sites.

8. Investigational drug Accountability

The person in charge of the investigational drug management will prepare an “Investigational Product Accountability Record” including the following items and maintain it with updated information at all times.

- investigational drug substance code or product code
- receipt date and quantities, and expiry date of investigational drug
- lot number
- subject identification (subject number)
- dispensing log: date and quantity of dispensing and remaining quantity after subject dispensing
- information to identify the pharmacist who dispenses the investigational drugs
- date and quantity of investigational drug returned to the drug management unit, if appropriate
- record of destruction or loss of unused investigational drug
- record of destruction of used investigational drug (empty vial) as needed