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

Protocol Number: SP-02L02

Statistical Analysis Plan

Ver.1.3

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Approver		Signature	Date

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Abbreviations and Terms

List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
AITL	Angioimmunoblastic T-cell Lymphoma
ALCL	Anaplastic Large Cell Lymphoma
BSA	Body Surface Area
CI	Confidence Interval
CR	Complete Response
DCR	Disease Control Rate
DOR	Duration of Response
ECG	Electrocardiogram
eCRF	electronic Case Report Form
FAS	Full Analysis Set
IPI	International Prognostic Index
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall Response Rate
OS	Overall Survival
PFS	Progression-Free Survival
PIT	Prognostic Index for T-cell lymphoma
PD	Progressive Disease
PK	Pharmacokinetics
PKS	Pharmacokinetics Analysis Set
PPS	Per Protocol Set
PR	Partial Response
PTCL	Peripheral T-cell Lymphoma
PTCL-NOS	PTCL-not otherwise specified
RD	Relapsed Disease
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SD	Stable Disease
TTR	Time to Response

List of Terms

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
First screening visit	The day at 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 Cycle 1 (Day 1 of Cycle 1)
Treatment period	The period from the first day of Cycle 1 (Day 1 of Cycle 1) to the day before the first examination, observation and investigation scheduled during the follow-up period
Follow-up period	The period from the day of the first examination, observation and investigation scheduled during the follow-up period to the day of the last examination, observation and investigation scheduled during the follow-up period (including follow-up adverse event assessment)
Study period	Period consisting of screening period, treatment period and follow-up
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
Tumor response	“Complete Response (CR)” and “Partial Response (PR)”
Overall Response Rate	Proportion of subjects with “CR or PR” in the evaluable subject population
Disease Control Rate	Proportion of subjects with “CR, PR or Stable Disease (SD)” 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 documented "progressive disease" or "relapsed disease", or the date of "death", which occurs earlier
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 documented "progressive disease" or "relapsed disease", or the date of "death" which occurs earlier

1 OVERVIEW

This Statistical Analysis Plan (SAP) specifies details of the statistical analyses to be conducted for the clinical study titled “Asian Multinational Phase 2 Study of SP-02L (darinaparsin for injection) in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma (PTCL)” (hereafter referred as to “this study”).

The purpose of the SAP is to describe general or study-specific statistical methodology for this study. Statistical results to be reported as an interim report or a final clinical study report (CSR). The SAP would be revised when the protocol is revised. It would also be revised if the revision is judged to make the data more credible and useful in comparison with the original plan.

2 STUDY 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 (cf. Section 2.6 of protocol)

3 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 day (3 week). SP-02L will be administered for 6 cycles to evaluate the efficacy and safety of SP-02L monotherapy using various endpoints. If the subject wishes to continue investigational drug administration and the investigator judges that the continuous 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 participating country or region at Cycle 1.

4 END POINT

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 (the best overall response up to Cycle 6 based on a central assessment by Efficacy and Safety Review Committee)

Secondary Endpoints

- Progression-Free Survival (PFS)

- Time to Response (TTR)
- Duration of Response (DOR)
- Overall Survival (OS)
- Occurrence of adverse events (AEs)
- SP-02L plasma concentration-time profile, PK parameters, and fraction of dose excreted in urine

5 ANALYSIS SETS

5.1 Efficacy Analysis Set

The "full analysis set (FAS)" will consist of subjects who fulfill eligibility criteria (cf. Section 3 of protocol) and who take a tumor response assessment (cf. Section 6.14.2 of protocol) at least one time after the administration of investigational drug. A group of subjects who have no important protocol deviation including violation of eligibility criteria and/or dosage and administration 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.

5.2 Safety Analysis Set

A group of subjects who receive at least one dose of investigational drug is defined as the "safety analysis set (SAF)". SAF will be used for the analysis of all subject characteristics, investigational drug administration and safety endpoints.

5.3 PK Analysis Set

The "PK analysis set (PKS)" 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. PKS will be used for the analysis of PK endpoints.

6 HANDLING OF SUBJECTS AND DATA

Before the data is fixed to be analyzed, the project team will determine the handling of subjects.

If it is considered that data including laboratory values, 12-lead electrocardiogram (ECG) readings or drug plasma/urine concentration measurements has been affected by abnormality of a sample (e.g. hemolysis or milky fluid), a technical error, the project team will decide whether or not to exclude that data from analysis prior to the data-lock.

In case that medical judgement is required, the advice from sponsor's medical experts including a cardiac safety advisor will be obtained.

7 ATTENSION ON ANALYSIS

7.1 Data for Statistical Analysis

Clinical data is collected from medical institution using electronic case report form (eCRF) or is electronically transferred from the central laboratory of drug plasma/urine concentration measurement and the central review organization of pathology and tumor response. The clinical data collected by eCRF or electronically transferred clinical data will be entered into database, cleaned, fixed and then used for statistical analysis. Data collection, input, cleaning and fixing are performed under responsibility of a study manager, clinical research associates and a data management person in charge. Fixed data is provided by a person in charge of data management to that of statistical analysis.

7.2 Descriptive Statistics

Following descriptive statistics will be summarized.

- Continuous variables

  Number of available data, Mean, Standard deviation (SD), Median, First and third quartile points, Minimum and Maximum

- Categorical variables

  Frequency and Percentage

7.3 Display Digit

- Mean, SD, median, first and third quartile points, and geometric average will be rounded to one more dps than the raw data.
- Minimum and Maximum data will be displayed as original decimal point of raw data.
- Percentages, Confidence Interval (CI) will be rounded to one decimal point.

7.4 Changes from the Protocol

We think that 65 would be more appropriate to consider the age standard of elderly in modern times, so we will change the age standard from 61 to 65.

8 STATISTICAL METHOD

8.1 Detail of Statistical Analysis

8.1.1 Significance Level and Confidence Interval

Tests with any significance level will not be performed. Confidence Interval will be calculated by Clopper-Pearson 'exact' method.

8.2 Consideration of Statistical Analysis

8.2.1 Adjustment by Covariates

Adjustment by covariates will not be performed.

8.2.2 Withdrawal and Missing

Analyses will be performed with no consideration for withdrawal of subjects. If date of birth is missing, values will be complemented as follows.

- If day is missing, 15 (middle of the month) will be completed.
- If day and month is missing, July 1 (middle of the year) will be completed.

The others will not be perform any imputation for missing value.

8.2.3 Interim Analysis and Data Monitoring

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

Interim evaluation for efficacy and safety including PK as needed (cf. Section 8.5.2 of Protocol) will be performed at the point when the number of efficacy evaluable subjects reaches 20 and necessary data is obtained from these subjects.

8.2.4 Multicenter Study

Analyses will be performed with no adjustment for Multicenter.

8.2.5 Adjustment for Multiplicity

Analyses will be performed with no adjustment for multiplicity.

8.2.6 Integrated Analysis

Not applicable.

9 SOFTWARE

All analyses will be performed using SAS® Ver9.2 (or later version).

10 SUBJECTS OF THE CLINICAL STUDY

10.1 Disposition of Patients

10.1.1 Subject Disposition

Numbers of subjects will be counted according to following terms.

- Informed consent obtained subjects
- Enrolled subjects
- Not-enrolled subjects
- Treated subjects
- Not-treated subjects
- Study Completion subjects
- Study Withdrawal subjects

10.1.2 Analysis Dataset

Numbers of subjects will be counted according to following terms.

- Efficacy analysis set of FAS
- Efficacy analysis set of PPS
- SAF
- PKS

10.1.3 Disposition of Withdrawn Subjects

Number of withdrawn subjects will be summarized with reasons for withdrawal.

10.1.4 Demographic and Other Baseline Characteristics

Descriptive statistics of following variables at screening period will be calculated by ethnic background (Japanese, Except Japanese, Korean, Taiwanese, Hong Konger/Chinese and others).

- Numerical Variables
  - Age (years)
  - Sum of the product of the greatest diameter (SPD) of target lesion (major axis and minor axis) (cm^2)
  - Height (cm)
  - Weight (kg)
  - Body surface area (BSA) (m^2)
    (BSA (m^2) ＝Weight (kg) $^{0.425}$×Height (cm) $^{0.725}$×0.007184)
  - Number of prior medication (chemotherapy or immune therapy)

- Categorical Variables
  - Sex
  - Ethnic group/Race

- Eastern Cooperative Oncology Group (ECOG) Performance Status Scale
- Histopathological classification of lymphoma
- Clinical Symptom Caused by Primary Disease (Concomitant Symptom)
- Clinical stage by Ann Arbor Classification
- International Prognostic Index (IPI) risk group
- Prognosis Index for T-cell lymphoma (PIT) risk group
- Presence of prior medication (chemotherapy or immune therapy)
- Response to most recent therapy
- Presence of prior radiation therapy
- Presence of prior transplant of hematopoietic stem cell transplant
- Other therapy
- Presence of liver enlargement
- Presence of spleen enlargement
- Presence of bone-marrow infiltration
- Presence of Medical History
- Presence of Allergy and/or drug sensitivity
- Neurological and mental status assessments
  - Presence of finding of cranial nerve abnormalities
  - Presence of finding of sensory abnormalities
  - Presence of finding of motor abnormalities
  - Presence of finding of coordination (gait) abnormalities
  - Presence of finding of reflex abnormalities
  - Presence of finding of mental status abnormalities
- Presence of pregnancy

10.1.5 Compliance of Study Drug Administration

Compliance of SP-02L administration (number of administration completed and skipped) and total volume of administration will be summarized by cycle and all cycles in total and by ethnic background (Japanese, Except Japanese, Korean, Taiwanese, Hong Konger/Chinese and others).

11 EFFICACY EVALUATION

11.1 The Best Overall Response Based on Central Assessment

Based on a central assessment of tumor response by Efficacy and Safety Review Committee, the response up to Cycle 6 will be summarized to calculate the overall response rate (ORR), the disease control rate (DCR), the best overall response and their 90% Confidence Interval (90% CI) respectively, and count the number of subjects per cycle. A binomial test will be performed for the null hypothesis “true objective response rate is less than or equal to the threshold objective response rate of 0.1 that is assessed to be ineffective”.

The same analysis will be performed by histopathological classification (PTCL-not otherwise specified [PTCL-NOS], Angioimmunoblastic T-cell Lymphoma [AITL], Anaplastic Large Cell Lymphoma [ALCL] ALK-positive and ALCL ALK-negative, other lymphoma), clinical stage according to Ann Arbor classification (Stage I, Stage II, Stage III, Stage IV), prognosis risk group according to IPI, prognosis risk group based on PIT, response to most recent therapy (Yes (CR/CRu/PR), No (SD/PD), Unknown/Unable to assess), ethnic background (Japanese, Except Japanese, Korean, Taiwanese, Hong Konger/Chinese and others), sex and age (< 65 years old or ≥ 65 years old).

11.2 The Best Overall Response Based on Local Assessment

Based on a local assessment of tumor response at each investigational site, the same analysis described in 11.1 will be performed for the response up to Cycle 6.

11.3 Comparison of Best Overall Response between Central Assessment and Local Assessment

Based on the central assessment and local assessment of tumor response, cross tabulation will be performed for the best overall response up to Cycle 6 in total and by ethnic background (Japanese, Except Japanese, Korean, Taiwanese, Hong Konger/Chinese and others).

11.4 Other Tabulations for The Best Overall Response

Based on a local assessment of tumor response at each investigational site, the same analysis described in 11.1 will be performed for the response in the entire period.

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 based on the central assessment and local assessment of tumor response in total and by ethnic background (Japanese, Except Japanese).

11.5 Percent Change from Baseline of Tumor Size

Based on the central assessment and local assessment of tumor size, the percent change from baseline will be plotted using Spider plot.

11.6 Analyses for Survival Time

PFS, TTR, DOR and OS will be summarized to calculate lower quartile, median, upper quartile and their 90%

CI by using Kaplan-Meier method in total and by ethnic background (Japanese, Except Japanese, Korean, Taiwanese, Hong Konger/Chinese and others). As for PFS and OS, Kaplan-Meier curve will be displayed. The same analysis will be performed by histopathological subtypes (PTCL-NOS, AITL, ALCL ALK-positive, ALCL ALK-negative, other lymphoma).

"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 local assessment of tumor response by investigator at each site (cf. Section 6.14.2 of protocol) is defined as “the date of progression”.
- PD or RD includes not only the results of tumor response assessment based on diagnostic imaging data but also investigator’s clinical judgment of “Symptomatic Progression” based on clinical symptoms and findings, and clinical laboratory test result, etc.). In this case, the date of the 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 of local assessment of tumor response will be defined as “the date of censoring”:

- Subsequent therapy for primary disease is initiated
- Investigational drug is withdrawn due to adverse drug reaction
- Subject is lost to follow up

If a subject is surviving on the date of data cut-off, the most recent date 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”. If treatment-duration exceeds 2 years, the date after 2 years is defined as “the date of censoring”.

12 SAFETY EVALUATION

Following analyses will be performed on SAF except 12.2.5 and 12.2.5 will be performed on PKS.

12.1 Adverse Event

12.1.1 Summary of Adverse Events

Number of subjects with AE will be counted according to following terms in total and by ethnic background (Japanese, Except Japanese, Korean, Taiwanese, Hong Konger/Chinese and others).

- AE
- Serious AE
- Adverse drug reaction
- Serious Adverse drug reaction
- AE leading to withdrawn from the study
- Adverse drug reaction leading to withdrawn from the study
- AE of NCI-CTCAE Grade 3 or higher
- Adverse drug reaction of NCI-CTCAE Grade 3 or higher

12.1.2 Number of Subjects with Any Adverse Event

The occurrence of AEs will be summarized by system organ class and by preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, and by ethnic background (Japanese, Except Japanese, Korean, Taiwanese, Hong Konger/Chinese and others) and by severity.

The bar graph will be produced to show the occurrence of AEs by severity.

When one subject experiences same PT of AE more than once, the severest event will be counted (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE] Grade 1 < Grade 2 < Grade 3 < Grade 4 < Grade 5). Adverse event of NCI-CTCAE Grade 3 or higher will be also summarized in the same way.

12.1.3 Number of Subjects with Adverse Drug Reaction

An adverse drug reaction is defined as an AE with possible relationship with the investigational drug.

The same analyses described in 12.1.2 will be performed for adverse drug reaction.

12.1.4 Number of Subjects with Any Serious Adverse Event

The same analyses described in 12.1.2 except graph will be performed for serious AE.

12.1.5 Number of Subjects with Serious Adverse Drug Reaction

The same analyses described in 12.1.2 except graph will be performed for serious adverse drug reaction.

12.1.6 Number of Subjects with Adverse Event of Special Interest

The same analyses described in 12.1.2 except graph will be performed for AESI. AESI is defined AEs that will be coded as “Psychiatric disorders”, “Nervous system disorders” or “Hepatobiliary disorders” of system organ class according to the MedDRA dictionary.

12.1.7 Number of Subjects with Any Grouping Adverse Event

The occurrence of AEs will be summarized by any grouping Adverse Event, preferred term according to the MedDRA dictionary, and by ethnic background and by severity. Grouping Adverse Event is following.

Grouped Term	Preferred Terms
Fatigue/malaise	Fatigue, Malaise
Hepatic function test abnormal	Aspartate aminotransferase increased, Alanine aminotransferase increased, Gamma-glutamyltransferase increased
Anaemia	Anaemia, Haemoglobin decreased
Thrombocytopenia	Thrombocytopenia, Platelet count decreased
Neutropenia	Neutropenia, Neutrophil count decreased
Lymphopenia	Lymphopenia, Lymphocyte count decreased
Leukopenia	Leukopenia, White blood cell count decreased
Injection site reaction	Infusion site pain, Injection site pain, Injection site reaction, Injection site rash, Infusion site pruritus, Infusion site rash
Hyperglycaemia	Hyperglycaemia, Blood glucose increased
Taste disorder	Taste disorder, Dysgeusia
Hyperbilirubinaemia	Hyperbilirubinaemia, Blood bilirubin increased
Hypoalbuminaemia	Hypoalbuminaemia, Blood albumin decreased
Hypomagnesaemia	Hypomagnesaemia, Blood magnesium decreased
Hyponatraemia	Hyponatraemia, Blood sodium decreased
Hypokalaemia	Hypokalaemia, Blood potassium decreased
Catheter site related reaction	Catheter site pain, Catheter site related reaction, Catheter site haemorrhage, Catheter site erythema, Catheter site bruise, Catheter site pruritus, Catheter site rash, Catheter site oedema, Catheter site discharge, Catheter site swelling
Abdominal pain	Abdominal pain, Abdominal tenderness, Abdominal pain lower, Abdominal pain upper
Sepsis/Bacteraemia	Sepsis, Bacteraemia, Enterococcal bacteraemia, Escherichia sepsis, Pseudomonal sepsis, Device related sepsis, Neutropenic sepsis, Staphylococcal bacteraemia

Grouped Term	Preferred Terms
Neuropathy peripheral	Neuropathy peripheral, Peripheral sensory neuropathy

12.1.8 Number of Subjects with Any Grouping Adverse Drug Reaction

The same analyses described in 12.1.7 will be performed for Adverse Drug Reaction.

12.2 Laboratory/ECG/Vital sign Parameters Evaluation

12.2.1 Summary of Laboratory Parameters

Descriptive statistics of hematologic/biochemical/blood coagulation test parameters specified in the following table will be calculated by time point for both of measured values and changes from baseline.

If laboratory test value is less than or equal to detection limit value, the value is treated as detection limit value.

Hematological test parameters	Hemoglobin, Hematocrit, Red blood cell (RBC) count, White blood cell (WBC) count, Differential leukocyte count (Band Neutrophils, Segmented Neutrophils, Neutrophils, Lymphocyte, Monocyte, Eosinophil, Basophil), Platelet count
Biochemical test parameters	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 test parameters	Prothrombin time-INR (PT-INR), Prothrombin time (PT), Activated partial thromboplastin time (APTT)

12.2.2 Neurological and Mental Status Assessments

Neurological and mental status will be summarized in shift tables by time point according to following items.

- Presence of finding of cranial nerve abnormalities
- Presence of finding of sensory abnormalities
- Presence of finding of motor abnormalities
- Presence of finding of coordination (gait) abnormalities
- Presence of finding of reflex abnormalities
- Presence of finding of mental status abnormalities

12.2.3 Summary of Vital Sign Parameters

Descriptive statistics of following vital sign parameters will be calculated by time point for both of measured

values and changes from baseline.

- Systolic/Diastolic blood pressure (mmHg)
- Pulse rate (beats/minute)
- Temperature (˚C)
- Percutaneous arterial oxygen saturation (SaO_2) by a pulse oximeter (%)

12.2.4 Summary of ECG Parameters

Descriptive statistics of following ECG test parameters will be calculated by time point for measured values.

- Heart rate (/minute)
- RR interval (msec)
- QRS interval (msec)
- PR interval (msec)
- QT interval (msec)
- Fridericia corrected QT interval (QTcF) (msec)

12.2.5 Summary of PK Parameters

Details of calculation of PK parameter and summarization/analyses for concentration and PK parameter are described in “Pharmacokinetic analysis plan”.

13 LISTING

- Study Completion Status
- Withdrawn patients
- Study Visit Dates
- Demographic and Baseline Information
- Primary Disease Diagnosis by Investigators' and Central Pathology Review
- Prior Medication (Chemotherapy or Immune Therapy)
- Prior Radiation
- Prior Transplants
- Other Prior therapy
- Medical History
- Allergy / Drug Sensitivity
- Hepatitis Virus Screening
- Study Drug Administration
- Tumor Measurements for Target Lesions
- Tumor Assessment of Non-Target Lesions
- Assessment of Clinical Finding of Lymphoma
- Assessment of Tumor Response
- Time to Event
- Subsequent Therapy
- Adverse Events, Sorted by Subject
- Adverse Events, Sorted by System Organ Class, Preferred Term and Subject
- Serious Adverse Events, Sorted by Subject
- Serious Adverse Events, Sorted by System Organ Class, Preferred Term and Subject
- Glossary of Adverse Events by System Organ Class
- Glossary of Adverse Events by Verbatim Term
- Adverse Events, Sorted by Severity, Dose Group, System Organ Class, Preferred Term and Subject
- Hematology Laboratory Evaluations
- Other Blood Differentiation
- Clinical Chemistry Laboratory Evaluations
- Coagulation Laboratory Evaluations
- Physical Examination
- Vital Signs
- Concomitant Medications
- Concomitant Procedures
- Hospitalization
- ECG Assessments

- Pharmacokinetic Sample Time and Concentration
- PK parameters and fraction of dose excreted
- Ratio of peak area and peak area of metabolites
- Comments