Statistical Analysis Plan

A Multi-center, Single Arm, Safety and Efficacy Study of Pralatrexate with Vitamin B12 and Folic Acid Supplementation in Subjects with Relapsed or Refractory Peripheral T-cell Lymphoma

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LIST OF ABBREVIATIONS

AE	adverse event
ATC	Anatomical-Therapeutic-Chemical
AUC	area under the curve
BMI	body mass index
BOR	best overall response
BSA	body surface area
CI	confidence interval
CLss	steady state clearance
Cmax	maximum observed concentration
CNAP	chest, neck, abdomen, pelvis
CR	complete response
CRF	Case Report Form
CRu	complete response unconfirmed
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	coefficient of variation
DOR	Duration of Response
DP	decimal place
EBV	epstein-barr virus
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDR	early discrepancy rate
IDMC	Independent Data Monitoring Committee
IM	intramuscular
IMP	Investigational Medicinal Product
IV	intravenous
LDH	lactic dehydrogenase
LDR	late discrepancy rate
LLT	Lowest Level Term
MedDRA	Medical Dictionary for Regulatory Activities
ORR	objective response rate
OS	Overall Survival
PD	progressive disease
PFS	Progression-Free Survival
PK	pharmacokinetic(s)
PPP	Per Protocol Population
PR	partial response
PT	Preferred Term
PTCL	peripheral T-cell lymphoma
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	standard error
SD	standard deviation
SOC	System Organ Class

TEAE	treatment emergent adverse event
Tmax	time of Cmax observation
t1/2Z	terminal phase half-life
TTR	Time to Response
Vdss	steady state volume of distribution

1. INTRODUCTION

The analyses described in this document will be included in a Clinical Study Report (CSR) to support a regulatory submission. This Statistical Analysis Plan (SAP) describes all planned analyses that will be conducted and presented for FOT12-CN-301 study and is based upon Section 14 (Statistical Analysis) of the protocol version 1.0 dated April 3, 2015.

The primary analysis will be performed based on a data cut-off date defined after all subjects have been treated for 5 cycles. The final analysis will be performed based on all the subjects complete the study.

2. OBJECTIVES AND PARAMETERS

2.1. Objectives

2.1.1. Aim of the study

The aim of the study is to confirm the efficacy and safety of pralatrexate for the treatment of Relapsed or Refractory peripheral T-cell lymphoma (PTCL) in Chinese population.

2.1.2. Primary Objective

The primary objective of this study is to confirm the objective response rate (ORR) among Chinese subjects with relapsed or refractory PTCL treated with pralatrexate together with concurrent vitamin B12 and folic acid supplementation.

2.1.3. Secondary Objectives

- To evaluate further efficacy parameters (Duration of Response; Time to Response; Progression-Free Survival; Overall Survival) among Chinese subjects with relapsed or refractory PTCL treated with pralatrexate together with concurrent vitamin B12 and folic acid supplementation
- To evaluate the safety of pralatrexate with concurrent vitamin B12 and folic acid supplementation when administered to Chinese subjects with relapsed or refractory PTCL
- To determine the pharmacokinetic (PK) profile of pralatrexate among Chinese subjects with PTCL when administered with vitamin B12 and folic acid supplementation

2.2. Parameters

2.2.1. Primary Efficacy Variable

Objective response rate by International Working Criteria and per central review.

2.2.2. Secondary Efficacy Variables

- Duration of Response (DOR)
- Time to Response (TTR)
- Progression-Free Survival (PFS)
- Overall Survival (OS)

2.2.3. Safety Variables

- Treatment emergent AEs
- Physical examinations
- Clinical laboratory values

2.2.4. Pharmacokinetic Measurements

Pharmacokinetic evaluations will be performed. The PK profile of R-pralatrexate and S-pralatrexate will be determined in 15 subjects at pre-selected sites.

Standard PK parameters will be determined for both enantiomers in plasma (area under the curve [AUC], steady state volume of distribution [Vdss], steady state clearance [CLss], maximum observed concentration [Cmax], time of Cmax observation [tmax] and terminal phase half-life [t1/2Z]). Accumulation in exposure at steady state will also be reported, such as the ratio of AUC [ARAUC] and Cmax [ARCmax]. Collection of plasma to determine the full PK profile will be performed in 15 subjects at pre-selected sites.

3. STUDY DESIGN

3.1. Summary of Study Design

This is a single arm, open-label, multi-center study designed to evaluate the efficacy and safety of pralatrexate in Chinese subjects when administered concurrently with vitamin B12 and folic acid supplementation to subjects with relapsed or refractory PTCL.

This study includes 3 phases: Screening, Treatment (pralatrexate) and Follow-up phases.

Screening Phase:

The screening phase will be of up to 28 days duration (depending on availability of lab results). All potential study subjects will be screened and determined of the eligibility prior to enrolment. The eligible subjects will begin to receive vitamin supplementation at screening phase.

Unless otherwise specified, the protocol defined procedures and evaluations (*See Table 1. Schedule of Visits and Procedures*) will be performed within 28 days prior to the projected start of pralatrexate administration (cycle 1, dose 1).

Treatment (pralatrexate) Phase:

The start of study treatment is defined as the initiation of pralatrexate treatment. Vitamin supplementation will be initiated at least 10 days prior to pralatrexate administration on cycle 1, dose 1. Once the patient is on-study, the dosing of vitamin supplementation must adhere to the schedule defined by the protocol.

Evaluation of response must be performed within 7 days prior to the projected first dose of cycle 2-4 and then within 7 days prior to the projected first dose of every even numbered subsequent cycle (i.e. prior to cycles 6, 8, etc). Although radiological response assessments have been scheduled every 14 weeks, unscheduled radiological response assessments will be performed earlier if clinical progression is suspected.

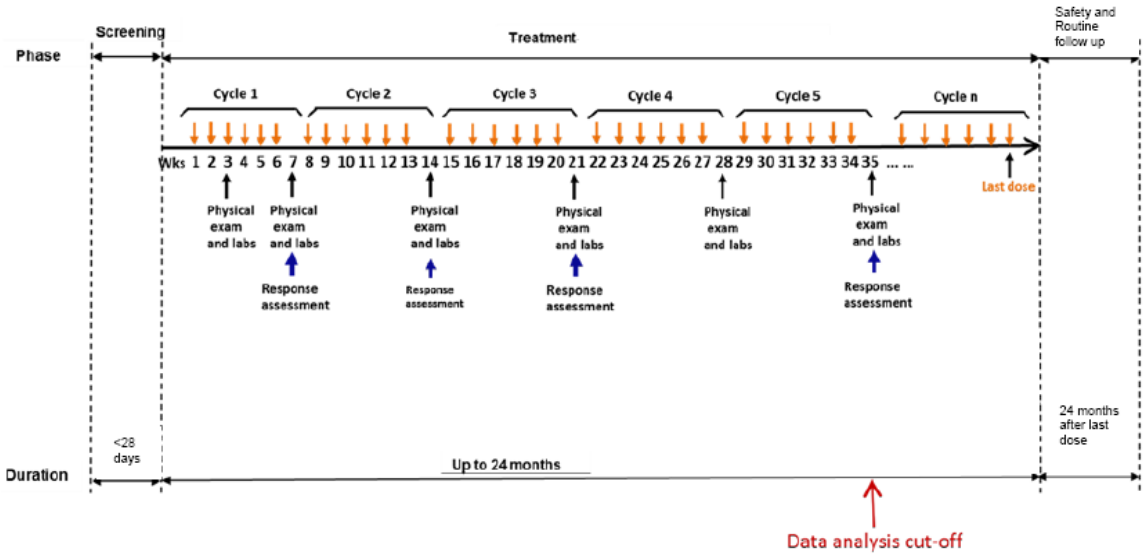
Treatment with pralatrexate will continue until 24 months of administration, or until documented disease progression; unacceptable adverse event(s) indicating intolerance of the lowest study dose allowed (20 mg/m2/week); omission of 3 sequential doses of pralatrexate due to a treatment-related AE; 3-week lapse between pralatrexate doses; development of an AE, intercurrent illness, condition, or procedural complication that may interfere with the subject's participation; investigator's decision to withdraw the subject; subject withdraws consent; pregnancy of the subject; noncompliance with trial treatment or procedure requirements; or administrative reasons.

Follow-up phase:

All patients who received at least 1 dose of pralatrexate are to attend the Safety Follow-up Visit [30 (± 5) days after the last dose of pralatrexate] and the protocol defined procedures and evaluations will be performed.

After the Safety Follow-up Visit, Routine Follow-up Visits will be based on standard clinical care. All patients who received at least 1 dose of pralatrexate are to attend Routine Follow-up Visits, which will occur every 3 months (± 2 weeks) for determination of progression of disease, subsequent treatment initiation for T-cell lymphoma and survival after the Safety Follow-up Visit for a total duration of 24 months after the last dose of pralatrexate. The protocol-defined procedures/evaluations should be performed at each Routine Follow-up Visit.

Figure 1 Study diagram



3.2. Sample Size Rationale

The primary objective is to demonstrate that the response rate in the Chinese population is greater than ≥15%. Assuming a true response rate of 29%, a sample size of 68 will provide 80% power to demonstrate a response rate of greater than 15% using a two-sided test at 5% significance level.

3.3. Assessment and Procedure

3.3.1. Schedule Overview

Table 1 presents the schedule of visits and procedures/CRF module

Table 1 Schedule of Visits and Procedures/CRF Modules

		CYCLE 1				SUBSEQUENT CYCLES			FOLLOW-UP		
Visit	**28 days Prior to Pralatrexate Dose 1**	**10 Days Prior to Pralatrexate Dose 1 through Cycle 1, Dose 1**	**Cycle 1, Dose 1**	**24, 48, 72 Hours post-end pralatrexate**	**Weeks 2-6**	**Within 7 Days Prior to Projected Dose 1**	**Dose 1**	**Weeks 2-6**	**Early Study Termination Visit**	**Safety FU Visit**	**Routine FU**
Eligibility Criteria/Informed Consent	X										
Medical/Surgical History	X										
Document Histopathology	X[1]										
Central pathology review[2]	X										
Unilateral bone marrow biopsy and aspirate	X[3]					X[5]			X[5,6]	X[7]	X[5]
CT of Chest, Neck, Abdomen, Pelvis (CNAP)	X					X[5]			X[5,6]	X[7]	X[5]
Other imaging of disease site other than CNAP[3]	X[4]					X[4,5]			X[4, 5, 6]	X[4,7]	X[4,5]
Medical photography with ruler measurement of cutaneous lesions[4]	X[4]					X[4,5]			X[4, 5, 6]	X[4,7]	X[4,5]
Record Prior Treatment and Response for PTCL	X										
Record Medications	X				X		X	X	X	X	
Record Baseline Symptoms		X									
Record AEs/Attribution		X		X	X		X	X	X	X[8]	X[8]
Record ECOG Performance Status	X				X[9]	X			X	X	
Physical Examination	X				X[9]	X			X	X	
Record Height in cm		X[10]									
Record Weight in kg		X[10]				X					
Calculate BSA		X[10]				X					
Vitamin B12 Administration		X[11]			X[11]		X[11]	X[11]			
Folic Acid Administration		X[12]									
Folic Acid Patient Diary Review		X	X		X		X	X	X	X	
Pralatrexate administration[13]			X		X		X	X			
12-Lead ECG	X										

		CYCLE 1				SUBSEQUENT CYCLES			FOLLOW-UP		
Visit	28 days Prior to Pralatrexate Dose 1	10 Days Prior to Pralatrexate Dose 1 through Cycle 1, Dose 1	Cycle 1, Dose 1	24, 48, 72 Hours post-end pralatrexate	Weeks 2-6	Within 7 Days Prior to Projected Dose 1	Dose 1	Weeks 2-6	Early Study Termination Visit	Safety FU Visit	Routine FU
Hematology[14]	X	X[15]			X		X	X	X	X	
Chemistry[14]	X	X[15]			X	X[16]	X	X[17]	X	X	
Pregnancy Test (Urine or serum β-HCG)[18]	X	X				X					
Blood for pralatrexate PK[19]			X	X	X						
Record Subsequent Treatment for T-cell Lymphoma										X	X
Record Date of Death									X		X

Foot notes:

1) Include histopathology from original diagnosis of T-cell lymphoma and/or from tumor biopsy in relapse setting.
2) EBV will be tested by the central pathology review laboratory with the submitted slides.
3) Within 28 days of pralatrexate dose 1.
4) Perform if applicable to patient.
5) Evaluation of response must be performed within 7 days prior to the projected first dose of the cycle 2-4 and then within 7 days prior to the projected first dose of every even-numbered subsequent cycle (ie, prior to cycles 6, 8, etc).
6) The procedures outlined will be conducted, if a patient withdraws informed consent and refuses to attend the Safety Follow-up Visit and Routine Follow-up Visits. If possible, the procedures will be performed at the time the patient withdraws consent.
7) All subjects who received at least 1 dose of pralatrexate are to attend the safety follow-up visit 30 (± 5) days after the last dose of pralatrexate.
8) Only until subsequent therapy has started.
9) Cycle 1, week 3 only.
10) May be done up to 3 days prior to cycle 1, dose 1.
11) Vitamin B12, 1 mg IM q 8-10 weeks, initiated as described.
12) Folic acid, 1.2 mg, by mouth daily, initiated as described.
13) Administer pralatrexate IV push over 3-5 minutes.
14) Laboratory tests will be conducted in local laboratory, central laboratory, and laboratory for PK test respectively.
15) Chemistry labs (including LDH) must be completed within 3 days prior to cycle 1, dose 1. Hematology must be completed within 1 day prior to dosing on cycle 1, dose 1 and platelet count must have remained $\geqslant$100,000/μL (or 100×10^9/L) to proceed with pralatrexate dosing).
16) Collect LDH prior to first dose of cycle 2-4 and then prior to every even-numbered subsequent cycles (ie, prior to cycles 6, 8, etc.).
17) Collect blood for chemistry panel prior to the fourth dose of each cycle.
18) Serum β-human chorionic gonadotropin [β-hCG] pregnancy test for women who are not postmenopausal or surgically sterile will be performed within 14 days prior to cycle 1, dose 1. A urine pregnancy test should also be performed within 72 hours prior to first dose of each treatment cycles.
19) Collection of plasma to determine the full PK profile will be performed in 15 subjects at pre-selected sites. Cycle 1, week 1, 6: Pre-injection, end-injection, 30 and 60 minutes, and 3, 5, 8, 12, 18, 24, 48, and 72 hours post-end injection. Cycle 1, week 2-5: Pre-injection.

4. ANALYSIS POPULATIONS

Enrolled Population
The enrolled population is defined as all subjects who signed informed consent.

Safety Population
The safety population is defined as all subjects who receive at least one dose of IMP.

Per Protocol Population (PPP)
The Per Protocol Population is defined as all subjects in the safety population who fulfil the following criteria:

1) The absence of any major protocol deviations
2) The completion of a minimal 3 doses of exposure to the treatment regimen of one treatment cycle, except discontinuation due to toxicity and disease progression

All major protocol deviations will be agreed at the data review meeting prior to database lock.

Pharmacokinetic Population
The overall PK population is defined as all subjects who receive at least one dose of IMP and have at least one primary PK parameter. Subjects with non-zero baseline concentrations of >5% of Cmax for either analyte (R-pralatrexate or S-pralatrexate) will be removed from the PK population.

5. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

5.1. General Considerations for Data Analyses

In general, continuous data will be summarized using the following descriptive statistics: n, mean, standard deviation, median, minimum and maximum. The decimal places will be defined as table 2.

Table 2 decimal places for descriptive statistics

Label	No. of decimal places (dp)
N	Always present to 0 dp
Mean	1 dp more than raw data
Median	Same as raw data if the number of data points is odd. 1 dp more than raw data if the number of data points is even.
SD	2 dp more than raw data
Min	Same as raw data
Max	Same as raw data

Categorical data will be summarized as the number and percentage of subjects in each category.

All unscheduled records will be included in the corresponding listings but not included in the summary analyses.

All data processing, summarization and analyses will be performed using Version 9.1.3 (or later) of the SAS® statistical software package (Windows OS).

5.2. Missing Data

In general, all available data will be included in the analyses and will be summarized as far as possible. Unless otherwise specified there will be no substitution of missing data, i.e. missing data will not be replaced but will be handled as 'missing' in the statistical evaluation.

For plasma concentration data, all values below the quantifiable limit will be set to 0 for descriptive summary statistics.

For partial dates, no imputation rule will be derived for listings. For tables, when calculating duration of PTCL, if initial diagnosis date of PTCL does not have complete information of day, month, and year, it will be imputed with the criteria as

Imputation for incomplete start dates:

If year, month and day are missing then use the minimum of the subject's first visit date or the consent date.
If month and day are missing then use January 1.
If only day is missing, then use 1 for the first day of the month.

Imputation for incomplete end dates:

If year, month, and day are missing then use the subject's last visit date.
If month and day are missing then use December 31.
If only day is missing, then use the last day of the month.
Do not expand the record past the subject's last visit.

When defining TEAE, if any AEs have partial start date, it will be imputed with the criteria as

If year, month and day are missing then use the minimum of the subject's first visit date or the consent date.
If month and day are missing, first compare with year of first dose. If they are same then use first dose date else use January 1.
If only day is missing, first compare with year and month of first dose. If they are same then use first dose date else use 1 for the first day of the month.

No partial dates will be imputed for efficacy endpoint calculation.

5.3. Baseline Definition

Baseline is defined as the last non missing value before first intake of IMP in cycle 1.

5.4. Response Assessment Date

For the efficacy analysis, investigator response assessment date is calculated as

- If the response is PD, then choose the earliest dates among target, non-target and new lesion measurement per cycle.

- If the response is non PD, then choose the latest dates among target and non-target lesion measurement per cycle.

5.5. Best Response to Prior Treatment of PTCL

- If the subject has any responses of CR, CRu, PR, SD, PD or NA, the best response should be CR > CRu > PR > SD > NA > PD.

5.6. Reference Code

- Exact binomial test: Proportion and CI

```
ods output BinomialProp = xx1  BinomialCLs = xx2;
proc freq data=xxx;
   tables response / binomial(exact);
   weight Count;
run;
```

- Kaplan-Meier method: Quartile and corresponding CI, Product-Limit Survival Estimates

```
proc lifetest data = xxx;
  time aval*CNSR(1);
    ods output censoredSummary = xx1
                quartiles = xx2
                ProductLimitEstimates = xx3;
    survival out = xx4 confband=ALL bandmin=100 bandmax=500
maxtime=600;
run;
```

- CI for Geometric Mean

First log-transformed for each value, i.e. logaval = log(aval).

```
proc means data = xxx n mean std median max min noprint clm
alpha=0.05;
  var logaval;
  output out = xx1 LCLM=lclm uclm=uclm;
run;
```

Then the transformed back lower limit is exp(lclm) and upper limit is exp(uclm).

- CI for ratios of AUC and Cmax between visits

First log-transformed for each value, i.e. logaval = log(aval).

```
ods output conflimits=<out>;
proc ttest data=<data> alpha=0.10;
     paired <lnAval_week6> * <lnAval_day1>;
run;
```

6. STATISTICAL METHODS

6.1. Disposition of Subjects

The number and percentage of subjects screened, failed screening along with the primary reason for screen failure will be summarized for subjects in the enrolled population. The enrollment status will also be listed.

The number and percentage of subjects in each population and the reasons for exclusion from the PPP will be summarized for subjects in the enrolled population. The exclusion reason will also be listed.

The number and percentage of subjects enrolled from each site will be summarized and listed for subjects in the enrolled, safety and per protocol population.

The number and percentage of subjects under study treatment, discontinued from study treatment and the primary reason for discontinuation from study treatment will be summarized in the safety population. The corresponding listing will be provided.

For the follow up phase (safety and/or routine follow up phases), the number and percentage of patients entered the follow-up phase will be summarized.

6.2. Demographic and Baseline Disease Characteristics

Demographic and baseline variables will be summarized and listed for all subjects in the safety population and PK population.

The duration of PTCL is from the initial diagnosis date or first prior treatment date of PTCL, whichever occurs earlier, to the date of inform consent signed off. If initial diagnosis date does not have complete information of day, month, and year, it will be imputed as the rule defined in section 5.2.

Continuous variables include age, height, weight, BMI (weight (kg)/height (m)^2), BSA, duration of PTCL and number of regimen of prior systemic therapy (including Chemotherapy, Autologous stem cell transplant).

Categorical variables include age group, gender, race, ethnicity, subtype of PTCL both from investigator and central review, ECOG performance status, documented progressive disease on prior treatment of PTCL, prior treatment of PTCL, best response to any of prior treatment of PTCL and last response to all the prior treatments of PTCL.

6.3. Protocol Deviations

The following protocol deviations may exclude a subject from the PPP:

- Failure to comply with the major inclusion/exclusion criteria, e.g., not meeting the Inclusion Criterion #1 the histopathological subtype confirmed by central pathology review
- Being non-compliant with study treatments
  - Without completing of a minimal 3 doses of exposure to the treatment regimen of one treatment cycle, except discontinuation due to toxicity and disease progression
- Taking any prohibited concomitant therapies

Major protocol deviations will be agreed at the data review meeting prior to database lock. Major protocol deviations will be summarized and all the protocol deviations will be listed.

6.4. Medical/Surgical History (Other than PTCL)

Medical/surgical history (other than PTCL) will be summarized and listed by System Organ Class (SOC) and Preferred Term (PT) in the safety population.

6.5. Concomitant Medication

Concomitant medication will be summarized and listed by coded term using WHO Drug Dictionary in the safety population.

The number and percentage of subjects taking concomitant medications will be summarized by ATC anatomical class (ATC level 1), pharmacological class (ATC level 2), pharmacological sub-class (ATC level 3) and coded term for subjects in the safety population.

6.6. Exposure

6.6.1. IMP Analyses

The following variables will be defined to assess exposure to study treatment:

- Number of infusions
- Duration of treatment (weeks): First calculate [(Date of last dose - date of first dose) + 7] ÷ 7 per subject per cycle. Then sum all the cycle durations for each subject.
- Cumulative dose (mg/m^2) = Sum of all total doses administered (mg/m^2)
- Dose intensity (mg/m^2/week) = Cumulative dose (mg/m^2) ÷ Duration of treatment (week)
- Relative dose intensity (%) = Dose intensity ÷ Planned weekly dose intensity x 100, whereas planned weekly dose intensity (mg/m^2/week) = 30 mg/m^2/week

All these variables will be summarized as continuous data. Additionally, the relative dose intensity will be categorically summarized (ie, number and percentage of subjects with relative dose intensity of <60%, 60-<80%, 80-<90%, 90-<110%, 110-<120%, >=120%).

Moreover, the number and percentage of subjects with any dose reduction, temporarily interrupted, permanently discontinued, not administered and corresponding reason will be presented.

The number and percentage of total cycles subjects received as well as the maximum cycle number will be presented.

Listing of exposure will also be provided.

6.6.2. Vitamin Supplementation Analyses

Vitamin B12 administration will be listed by subject.

Compliance of folic acid will be summarized by cycle. The compliance will be calculated as (duration per cycle – number of days with dose skipped per cycle)/ duration per cycle. Also the listing will be provided.

6.7. Safety Analyses

Safety data that will be evaluated includes adverse events (AEs), serious adverse events (SAEs), laboratory assessment, vital signs, ECG and other tests. Safety data will be summarized for subjects in the safety population.

6.7.1. Adverse Events (AEs) and Serious Adverse Events (SAEs)

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system to give a System Organ Class (SOC) and Preferred Term (PT) for each event. Events will also be graded for severity according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Only TEAEs (treatment emergent adverse event) will be summarized. A treatment emergent AE is defined as any AE with an onset date on or after the first dose of IMP if the AE is absent before the first dose of IMP, or worsened after the first dose of IMP. This will also include AEs with an onset date up to and including 30 days after the last dose of IMP. In addition, this will include AEs with an onset date after 30 days considered as related to IMP by the investigator.

An overview summary table of TEAEs including treatment related TEAEs, CTCAE grade>=3 TEAEs, treatment related CTCAE grade>=3 TEAEs, treatment emergent SAEs, treatment related and emergent SAEs, significant TEAEs (leading to death, requiring treatment given, leading to IMP dose decreased, withheld transiently, discontinuation) will be provided.

In general, the number and percentage of subjects reporting any TEAEs will be summarized by the preferred term nested within the SOCs. Although a MedDRA term may be reported more than once for a subject, that subject will be counted only once in the incidence count for that MedDRA term.

A summary of TEAEs by SOC, PT and maximum CTCAE grade will also be provided. In addition, the number of reported TEAEs will be summarized.

Also, a listing of AEs will be prepared, including AE start/end date, CTCAE grade, relationship to IMP, serious or not, action taken to IMP and AE outcome.

TEAE leading to withdrawal and Treatment emergent SAEs would be tabulated.

Moreover, in order to ensure that the true occurrence rate of AEs is not obscured in cases where certain AEs are reported with similar preferred terms, certain AE terms will be grouped used the MedDRA version 18.0. For this presentation, certain similar preferred terms will be identified, grouped, and coded to a single preferred term, which are deemed to represent the same conditions from a medical perspective, in order to present the event in a uniform manner. The grouping of AE terms will be as follows:

- Liver Function Test Abnormal (including Alanine Aminotransferase Increased, Alanine Aminotransferase, Aspartate Aminotransferase, Aspartate Aminotransferase Increased, and Transaminases Increased)
- Mucosal Inflammation (including Stomatitis, Stomatitis Haemorrhagic, Anal Inflammation, Vaginal Inflammation, Proctitis, Oesophagitis, Mouth Ulceration, Oral Mucosal Erythema, Pharyngeal Inflammation, Pharyngitis, Gingivitis, and Balanoposthitis,)
- Thrombocytopenia (including Platelet Count Decreased)
- Oedema (including Oedema Peripheral)
- Dry Mouth (including Lip Dry and Dry Throat)
- Dyspepsia (including Gastritis and Gastrooesophageal Reflux Disease)
- Odynophagia (including Oesophageal Pain)
- Pruritus (including Pruritus Generalized)
- Anemia (including Hemoglobin Decreased)
- Hypokalemia (including Blood Potassium Decreased)
- Neutropenia (including Neutrophil Count Decreased)
- Leukopenia (including White Blood Cell Count Decreased)
- Lymphopenia (including Lymphocyte count decreased)

Summary of the incidence of all TEAEs, treatment-related, CTCAE grade>=3 AEs and SAEs grouped by the similar preferred terms as above will also be presented.

6.7.2. Laboratory Assessment

Clinical laboratory data to be summarized includes haematology, blood chemistry, and urinalysis.

Clinical laboratory results recorded at each visit and change from baseline to each visit will be summarized as continuous data for each parameter.

Normal and abnormalities (with/without clinical significance) in each laboratory parameter will be summarized by cycle and listed.

Shift tables of normal and abnormalities from baseline to the post baseline will be generated.

Scatter plots will be produced for each laboratory parameter comparing baseline and end of study values. In addition, clinically laboratory parameters will be plotted over time using a box and whisker plot.

Each parameter will be assigned an LNH classification according to whether the value is lower than (L), within (N) or higher than (H) the reference range for that parameter. Results will be summarized using shift tables to evaluate categorical changes from baseline to end of study with respect to reference range values (lower than, within, higher than).

Clinical laboratory values after first dose of IMP will be evaluated for markedly abnormal values. Laboratory ranges used to identify markedly abnormal laboratory values will be defined in table 3. The number and percentage of subjects reporting markedly abnormal values will be summarized for each parameter. Each subject can be counted once in the parameter high and the parameter low categories, as applicable.

Table 3 Laboratory Ranges Used to Identify Markedly Abnormal Laboratory Values

	Units	
Laboratory Parameter	**Lower Limit**	**Upper Limit**
Haematology		
Haemoglobin	<10 g/dL (100 g/L) or <6.2 mmol/L	——
Platelets	<75.0 × 10^9/L or <75000/mm^3	——
Leukocytes	<3.0 × 10^9/L or <3000/mm^3	——
Lymphocytes	<1.0 × 10^9/L or <1000/mm^3	——
Neutrophils	<1.5 × 10^9/L or <1500/mm^3	——
Clinical Chemistry		
Electrolytes		
Sodium	< LLN	>150 mmol/L
Potassium	< LLN	>5.5 mmol/L
Bicarbonate (HCO3-)	≤15 mEq/dL or ≤15 mmol/L	——
Liver Function Tests		
Alkaline phosphatase	——	>3 × ULN
AST	——	>3 × ULN
ALT	——	>3 × ULN
GGT (GGTP)	——	>3 × ULN
Total bilirubin	——	>1.5 × ULN
Renal Function Tests		
Creatinine	——	>1.5 × ULN
Other Chemistry		

Calcium	<8 mg/dL or <2.0 mmol/L	>11.5 mg/dL or >2.9 mmol/L
Phosphorous (inorganic phosphate)	<2.5 mg/dL or <0.8 mmol/L	—
Glucose	<55 mg/dL or <3.0 mmol/L	>160 mg/dL or >8.9 mmol/L
Uric acid	——	> ULN
Cholesterol	——	>300 mg/dL or >7.75 mmol/L
Triglycerides	——	>2.5 × ULN
Albumin	<3 g/dL	——

6.7.3. Vital Signs

Vital sign parameters to be summarized include systolic blood pressure, diastolic blood pressure, pulse rate, respiration rate, and axillary temperature.

Vital sign results recorded at each visit and change from baseline to each visit will be summarized as continuous data for each parameter.

Scatter plots will be produced for each vital sign parameter comparing baseline and end of study values. In addition, vital signs will be plotted over time using a box and whisker plot.

Vital sign results for each parameter will be assigned an LNH classification according to whether the value is lower than (L), within (N) or higher than (H) the reference range for that parameter. Vital sign results will be summarized using shift tables to evaluate categorical changes from baseline to end of study with respect to reference range values (lower than, within, higher than). The range will be defined in table 4.

Table 4 Reference Range for Vital Sign Parameter

Vital Sign Parameter	**Reference Range**
Systolic blood pressure	90-140 mmHg
Diastolic blood pressure	60-90 mmHg
Pulse rate	60-100 bpm
	12-20 breaths per minute
Axillary Temperature	≤ 37 °C

Vital sign values after first dose of IMP will be evaluated for clinically notable abnormalities. Criteria used to identify clinically notable vital sign abnormalities will be defined in table 5. The number and percentage of subjects reporting clinically notable abnormalities will be summarized for each parameter. Each subject can be counted once in the parameter high and the parameter low categories, as applicable.

Table 5 Criteria Used to Identify Clinically Notable Vital Sign Abnormalities

Vital Sign Parameter	**Value**	**Change From Baseline [a]**
Systolic blood pressure	≥ 180 mmHg	Increase of ≥ 20 mmHg
	≤ 90 mmHg	Decrease of ≥ 20 mmHg
Diastolic blood pressure	≥ 105 mmHg	Increase of ≥ 15 mmHg
	≤ 50 mmHg	Decrease of ≥ 15 mmHg
Pulse rate	≥ 120 bpm	Increase of ≥ 15 bpm

	≤ 50 bpm	Decrease of ≥ 15 bpm
Respiration rate	< 8 breaths/minute	-
	> 24 breaths/minute	-
[a] Both value and change from baseline criteria must be met to qualify as a clinically notable vital sign abnormality.		

6.7.4. ECG

Clinically significant ECG findings as determined by the Investigator will be summarized and listed.

6.7.5. Other Tests

Physical examination will be summarized by normal/abnormal and listed by visit.

PTCL related symptoms and results of bone marrow examination will be listed.

6.8. Efficacy Analyses

6.8.1. Primary Efficacy Variable

The primary endpoint is the objective response rate (ORR) by International Working Criteria defined as the proportion of subjects with CR, CRu or PR as Best Overall Response (BOR). The objective response rate will be tested using the exact binomial test for single proportion at two-sided significance level of 5%. The hypotheses under test will be H0: ORR=15% vs. H1: ORR≠15%.

The primary analysis will be based on the independent review data using the safety population. An additional analysis based on the investigator assessment data will be performed. All analyses will be repeated using the per-protocol population.

Also present number of subjects achieved response by site.

6.8.2. Secondary Efficacy Variables

- Duration of Response (DOR)

Duration of response will be derived based on responders. Duration of response will be measured from first response date, i.e. first achieved CR/CRu/PR, to the date of disease progression or death, whatever comes first. The subject will be considered as event if the response is PD or the subject died after achieving CR/CRu/PR, and the event end date will be the PD date or death date, whatever comes first. The duration is calculated as (minimum (first PD or death date) – first response date + 1)/30.4375.

If the subject receives subsequent therapy, including transplant, before PD or death, the subject will be censored at that time. The subject who withdraw consent to participate in the study prior to progression will be censored at the date of their last evaluable assessment of response. The subject who withdraw from treatment prior to progression

without withdrawing consent will be followed for disease status whenever possible. Otherwise the subject will be censored at the date of last tumor assessment date.

Duration of complete response will also be calculated. The algorithm is the same of DOR but change endpoint from CR/CRu/PR to CR/CRu.

- Time to Response (TTR)

Time to first response will be derived based on responders. Time to first response will be measured from first treatment date to the first date of documented response. If the response is CR, CRu or PR, then the subject will be considered as event and event end date will be the earliest date of archived any of CR, CRu or PR. The duration is calculated as (minimum (CR date, CRu date, PR date) – first treatment date + 1)/30.4375.

Time to best response will also be calculated. Time to best response will be measured from first treatment date to the date of documented best response (CR is better than CRu, CRu is better than PR). The event rule and censor rule is the same as time to first response.

- Progression Free Survival (PFS)

PFS will be measured from first treatment date until PD or death, whatever comes first. The subject will be considered as event if the response is PD or the subject died, and the event end date will be the PD date or death date, whatever comes first. The duration is calculated as (minimum (first PD or death date) – first treatment date + 1)/30.4375.

If the subject receives subsequent therapy, including transplant, before PD or death, the subject will be censored at that time. The subject who withdraw consent to participate in the study prior to progression will be censored at the date of their last evaluable assessment of response. The subject who withdraw from treatment prior to progression without withdrawing consent will be followed for disease status whenever possible. Otherwise the subject will be censored at the date of last tumor assessment date. If the subject has no assessment, then the subject will be censored at first treatment date.

- Overall Survival (OS)

OS will be measured from first treatment date until death. The subject will be considered as event if the subject died, and the event end date will be the death date. The duration is calculated as (death date) – first treatment date + 1)/30.4375.

The subject who withdraw consent to participate in the study, including consent to be followed, will be censored on the date of withdrawal. The subject who withdraw from treatment without withdrawing consent will be followed for survival status whenever possible. Otherwise the subject will be censored at the date of last contact date.

Time to response endpoints will be summarized as continuous variable using descriptive statistics. Also will be categorized by response occurred cycle.

Other secondary time-to-event endpoints (e.g. duration of response, PFS, and OS) will be presented using Kaplan-Meier curves (product limit estimates) together with a summary of associated statistics (e.g. median survival time, first and third quartiles, survival rates including the corresponding two-sided confidence intervals [CIs]).

Response will be assessed by independent central review and by the treating investigator. Then for the secondary endpoints based on tumor assessments (e.g. duration of response, time to response and PFS)), they will be analysed twice, once using the independent review data and once using the investigator assessment data.

Shift table will be presented to compare response between investigator assessment and central review assessment.

The secondary analyses will be performed using the safety population and repeated using the per-protocol population.

Listing of tumor assessment will be presented with independent review data investigator assessment data.

6.8.3. Discordance between Independent Central Review and Investigator Assessment

The early discrepancy rate and late discrepancy rate as defined below will be summarized. The agreement between independent central review and investigator is represented in a tabular form (table 6) below.

Table 6 Independent Central Review versus Investigator Disease Progression Assessment

	Independent Central Review	
	PD	No PD
Investigator PD	a = a1 + a2 + a3	b
No PD	c	d
a1: number of agreements on timing and occurrence of PD. a2: number of times investigator declares PD later than independent central review. a3: number of times investigator declares PD earlier than independent central review.		

The early discrepancy rate (EDR) is defined as

$$EDR = (b + a3)/(a + b)$$

The EDR represents the positive predictive value of investigator assessment and quantifies the frequency with which the investigator declares progression early relative to independent central review as a proportion of the total number of investigator assessed PD's.

The late discrepancy rate (LDR) is defined as

$$LDR = (c + a2)/(b + c + a2 + a3)$$

The LDR quantifies the frequency that investigator declares progression later than independent central review as a proportion of the total number of discrepancies.

6.9. Subgroup Analyses

For the objective response rate, subgroup analyses will be performed. If any category is less than 5 subjects, then only generate number of responder and response rate, i.e. no need to create CI and p-value.

The following subgroups will be examined.

- Age group (<55, 55-<65 or >=65)
- Gender (male or female)
- PTCL subtype from Investigator

  PTCL not otherwise specified (NOS)
  Angioimmunoblastic T-cell lymphoma
  Anaplastic large cell lymphoma, ALK+
  Anaplastic large cell lymphoma, ALK-
  Extranodal NK/T-cell lymphoma - nasal type
  Enteropathy-associated T cell lymphoma
  Hepatosplenic T-cell lymphoma
  Subcutaneous panniculitis-like T-cell lymphoma
  Adult T-cell lymphoma/leukemia (human T-cell leukemia virus[HTLV] 1+)
  Aggressive NK-cell leukemia
  Transformed mycosis fungoides
  Other

- Best response to any of prior treatment of PTCL (responder (CR + CRu + PR) or non-responder)
- Last response to all the prior treatments of PTCL (responder (CR + CRu + PR) or non-responder)
- Number of regimen of Prior Systemic Therapy (1, 2, 3 or >=4)
- Time from most recent therapy (<3 months or >=3 months)
- LDH level at baseline (above normal or normal/low)

6.10. Pharmacokinetic Analyses

The PK profile of R-pralatrexate and S-pralatrexate will be determined in 15 subjects at pre-selected sites.

The collection times for full pralatrexate PK are as follows:

- Cycle 1, dose 1: Pre-injection, end-injection, 30 and 60 minutes, and 3, 5, 8, 12, 18, 24, 48, and 72 hours post-end injection.
- Cycle 1, doses 2 – 5: Pre-injection
- Cycle 1, dose 6: Pre-injection, end-injection, 30 and 60 minutes, and 3, 5, 8, 12, 18, 24, 48, and 72 hours post-end injection.

6.10.1. Plasma Concentration

Plasma concentration data will be listed by analyte (R-pralatrexate and S-pralatrexate) for subjects in the pharmacokinetic population.

Plasma concentrations for each analyte will be summarized descriptively by nominal time-point for subjects in the pharmacokinetic population as continuous data. All values below the quantifiable limit will be set to 0 for descriptive summary statistics. Individual and mean (SD) plasma concentration profiles for each analyte for subjects in the pharmacokinetic population will be presented graphically in a linear and log linear scale.

6.10.2. Pharmacokinetic Parameters

Noncompartmental method (Phoenix WinNonlin, Version 6.3 or higher version, Certara, Princeton, USA) will be used to derive pharmacokinetic parameters. The following pharmacokinetic parameters will be reported, AUCINF, AUCt, Cmax, CLss, LamdaZ, tmax, t1/2Z, Vdss, %AUCextra, ARAUC and ARCmax. PK parameters and relate CDISC standard terminology is listed in Table 7. Main formulas for calculation of PK parameters is listed in Table 8.

Table 7 Relate CDISC standard terminology of PK parameters

PK parameters	CDISC standard terminology
ARAUC	ARAUC
ARCmax	ARCMAX
AUCINF	AUCIFO
AUCt	AUCLST
%AUCextra	AUCPEO
AUCtau	AUCTAU
CL(CLss)	CLO
Cmax	CMAX
R2ADJ	R Squared Adjusted
LamdaZ	LAMZ
t1/2Z	LAMZHL
tmax	TMAX
Vd(Vdss)	VZO

Table 8 Main formulas for calculation of PK parameters

PK parameters	Unit	Formulas
ARAUC	Ratio	$ARAUC=AUCt_{week6}/AUCt_{day1}$
ARCmax	Ratio	$ARCmax=Cmax_{week6}/Cmax_{day1}$
AUCINF	h*ng/mL	Log linear trapezoid(Linear up log down) AUCINF=AUCt+Clast/ LamdaZ

AUCt	h*ng/mL	Log linear trapezoid(Linear up log down)
%AUCextra	%	%AUCextra=(AUCINF-AUCt)/AUCINF*100
AUCtau	h*ng/mL	AUC between the dose interval
CL	L/h	CL=DOSE/AUCINF
Cmax	ng/mL	Directly obtained from the observed concentration vs. time curve
LamdaZ	h^{-1}	Estimated terminal slope of the linear regression of log-transformed
t1/2Z	h	t1/2Z=LN2/ LamdaZ
tmax	h	Directly obtained from the observed concentration vs. time curve
Vd	L	Vd=DOSE/(AUCINF* LamdaZ)

Pharmacokinetic parameters will be listed by analyte for subjects in the PK population. Data excluded from the PK analysis will be flagged with an asterisk. If the %AUCextra is greater than 20% of AUCINF, this will be flagged in the listings. LambdaZ, t1/2 and AUCINF will not be included in statistical summaries or analysis if the adjusted R^2 in LambdaZ estimation is less than 0.8.

Pharmacokinetic parameters for each analyte will be summarised descriptively for subjects in the PK population, adjusting for dose where necessary. Descriptive statistics including mean, SD, coefficient of variation (CV), SE, number of subjects with available data (n), minimum, maximum, and median will be calculated for all pharmacokinetic parameters (except tmax) by analyte, study day, and the actual administered dose. Additionally, geometric means and geometric CV will be calculated for AUCt, AUCINF and Cmax. The algorithm is

$$\text{Geometric means} = \exp[(\log(y_1) + \ldots + \log(y_n))/n]$$

$$\text{Geometric SD} = \exp(SD(\log(y1),\ldots,\log(yn)))$$

$$\text{Geometric CV (\%)} = (\exp((\log(\text{Geometric SD}))^2) - 1)^{1/2} \times 100$$

Tmax will be summarized by n, mean, minimum, maximum and median.

Log-transformed AUCt and Cmax at Day 1 and Week 6 will be used to calculate two-sided 90% confidence intervals for paired observations. Mean values and their associated confidence intervals will then be back transformed to provide point estimates and 90% confidence intervals for the ratios. Incomplete pairs will be excluded from the calculation. Only subjects who provided non-missing values for both periods, so that a non-missing day 1 to week 6 difference can be calculated, will be included.

7. ATTACHMENTS

1. Tables, listings and figures shell will be attached.

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