TITLE PAGE

Protocol Number:	FOT12-CN-301
Title:	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
Sponsor:	Mundipharma (China) Pharmaceutical Co. LTD 18F, Tower D, Central International Trade Center, 6A Jianguomenwai Avenue, Chaoyang District. Beijing, China 100022
Test Drug:	Pralatrexate injection (Abbreviated as Pralatrexate)
Indication:	Relapsed or Refractory Peripheral T-cell Lymphoma
Phase:	Phase III
Release Date:	03-Apr-2015
GCP Statement:	This study is to be performed in full compliance with ICH and all applicable local Good Clinical Practices (GCP) and regulations. All required study documentation will be archived as required by competent authorities.
Confidentiality:	This document is confidential. It contains proprietary information of Mundipharma (China) Pharmaceutical Co. LTD. Any viewing or disclosure of such information that is not authorised in writing by the Sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

SIGNATURE PAGE FOR PROTOCOL FOT12-CN-301

Protocol Number: FOT12-CN-301

Title: 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.

Test Drug: Pralatrexate

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SIGNATURE PAGE FOR INVESTIGATORS

Protocol Number: FOT12-CN-301

Title: 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.

Test Drug: Pralatrexate

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with ICH and China Good Clinical Practice guidelines, including the Declaration of Helsinki and all its accepted amendments to date.

Investigator	Signature	Date

1 CLINICAL PROTOCOL SUMMARY

Name of Sponsor Mundipharma (China) Pharmaceutical Co. LTD		
Name of Finished Product: Folotyn®(pralatrexate injection)		**Name of Active Ingredient:** pralatrexate
Protocol No.: FOT12-CN-301	**EUDRACT No.:** not applicable	
Short Title of the Study: A single arm study evaluating the efficacy and safety of pralatrexate in subjects with relapsed or refractory peripheral T-cell lymphoma		
Full Title of the Study: 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.		
Investigator(s)/Centre(s): Multi-center in China		
Study Indication: Relapsed or Refractory Peripheral T-cell Lymphoma	**Phase of Development:** Phase 3	

Objectives and Endpoints:

Objectives

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

The secondary objective includes:

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

Endpoints

Primary endpoint

- Objective Response Rate by International Working Group Criteria

Secondary endpoints :

- Duration of Response (DOR)
- Time to Response (TTR)
- Progression-Free Survival (PFS)
- Overall Survival (OS)
- Safety measurements (physical examinations, clinical laboratory values, and treatment emergent AEs.)
- PK parameters

Study Design (Methodology):

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

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

Screening Phase:

The screening phase will be up to 28 days duration (depending on availability of lab results). All potential study patients will be screened and eligibility determined prior to enrollment. 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 (pralatrexate) is defined as the initiation of pralatrexate. Patients will attend the clinic weekly for 6 weeks of a 7-week cycle to receive pralatrexate, and will be examined by the treating physician. One cycle of pralatrexate therapy is 7 weeks in duration and consists of 6 weekly doses of pralatrexate administered via intravenous (IV) push over 3-5 minutes, followed by 1 week of rest.

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 (ie, 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.

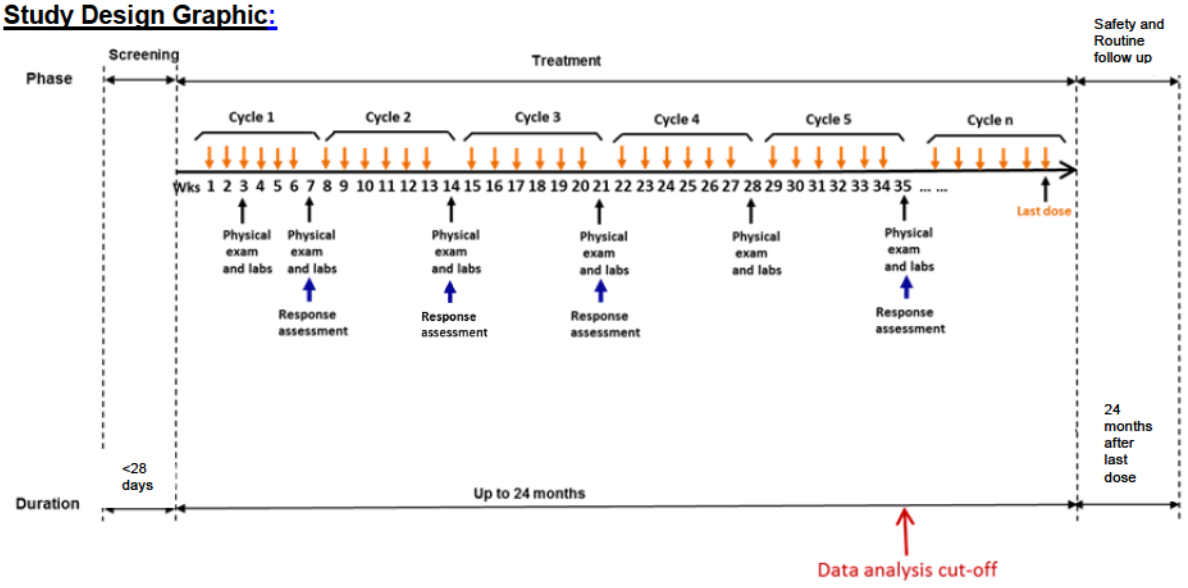
Treatment with pralatrexate will continue until 24 months of administration, or until documented disease progression; unacceptable adverse event(s) indicating intolerance of the lowest study dose allowed (20 mg/m^2/week); omission of 3 sequential doses of pralatrexate due to a treatment-related AE; 3-week 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.

Study Design Graphic:



Number of Subjects: 68 subjects will be treated

Criteria for Inclusion/Exclusion:

Inclusion Criteria:

1. Subject has histologically/cytologically confirmed PTCL, using the World Health Organization (WHO) disease classification:
    a. PTCL not otherwise specified (NOS)
    b. Angioimmunoblastic T-cell lymphoma
    c. Anaplastic large cell lymphoma, ALK+
    d. Anaplastic large cell lymphoma, ALK-
    e. Extranodal NK/T-cell lymphoma – nasal type
    f. Enteropathy-associated T cell lymphoma
    g. Hepatosplenic T-cell lymphoma
    h. Subcutaneous panniculitis-like T-cell lymphoma
    i. Adult T-cell lymphoma/leukemia (human T-cell leukemia virus [HTLV] 1+)
    j. Aggressive NK-cell leukemia
    k. Transformed mycosis fungoides
2. Subject has to have documented progressive disease (PD) after at least 1 prior systemic treatment.
3. Subject may not have received an experimental drug or biologic as their only prior therapy. Subject must have clear PD after the last treatment received. Subject should have at least 1 biopsy from initial diagnosis or in the relapsed setting to confirm the diagnosis of PTCL. Subject must have recovered from the toxic effects of prior therapy.
4. Subjects with an enlarged lymph node or extranodal mass lesion clearly measurable in two perpendicular directions and greater than 1.5 cm maximum diameter on computed tomography performed within 14 days prior to study enrollment.
5. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2.
6. At least 18 years of age.
7. Expected life expectancy ≥ 3 months.
8. Adequate hematological, hepatic, and renal function as defined by:
    - Absolute neutrophil count (ANC) ≥ 1000/uL (or 1×10^9/L), platelet count ≥ 100,000/uL (or 100×10^9/L) (at both screening and within 3 days prior to dosing on cycle 1, day 1)
    - Total bilirubin ≤ 1.5 mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 X upper limit of normal (ULN) (AST/ALT < 5 X ULN if documented hepatic involvement with lymphoma)
    - Creatinine ≤ 1.5 mg/dL (or 132.6 µmol/L) or a calculated creatinine clearance ≥ 50 mL/min
9. Women of childbearing potential must have agreed to practice a medically acceptable contraceptive regimen from study treatment initiation until at least 30 days after the last administration of pralatrexate and must have a negative serum pregnancy test within 14 days prior to the first day of study treatment. Subjects who are postmenopausal for at least 1 year (> 12 months since last

menses) or are surgically sterilized did not require this test.

10. Men who are not surgically sterile must agree to practice a medically acceptable contraceptive regimen from study treatment initiation until at least 90 days after the last administration of pralatrexate.

11. Subject gives written informed consent (IC).

Exclusion Criteria:

1. Subject has:
    a. Precursor T-cell lymphoma or leukemia
    b. T-cell prolymphocytic leukemia (T-PLL)
    c. T-cell large granular lymphocytic leukemia
    d. Mycosis fungoides, other than transformed mycosis fungoides
    e. Sézary syndrome
    f. Primary cutaneous CD30+ T-cell disorders: Lymphoid papulosis and primary cutaneous anaplastic large cell lymphoma
2. Active concurrent malignancy (except non-melanoma skin cancer or carcinoma in situ of the cervix). If there is a history of prior malignancy, the patient must be disease-free for ≥ 5 years.
3. Congestive heart failure Class III/IV according to the New York Heart Association's Heart Failure guidelines.
4. Human immunodeficiency virus (HIV)-positive diagnosis.
5. Has, or history of, brain metastases or central nervous system (CNS) disease.
6. Active uncontrolled infection, underlying medical condition including unstable cardiac disease, or other serious illness that would impair the ability of the subject to receive protocol treatment.
7. Has major surgery within 2 weeks of study entry.
8. Receipt of any conventional chemotherapy or radiation therapy (RT) within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to study treatment or planned use during the course of the study.
9. Receipt of corticosteroids within 7 days of study treatment, unless subject has been taking a continuous systemic dose of no more than 10 mg/day or equivalent dose of prednisone, or a local or inhaled or intranasal administration at fixed doses for at least 1 month prior to study treatment and tumor shrinkage was not observed.
10. Use of any investigational drugs, biologics, or devices within 4 weeks prior to study treatment or planned use during the course of the study.
11. Receipt of anti-tumor antibody therapy within 100 days prior to study treatment.
12. History of allogeneic hematopoietic stem cell transplantation. Or subjects with a history of autologous hematopoietic stem cell transplantation within 100 days prior to study treatment.
13. Previous exposure to pralatrexate.
14. Subject is pregnant or breast-feeding.

Treatment, Dose, and Mode of Administration:

Vitamin Administration

The eligible subjects will receive vitamin supplementation at screening phase, at least 10 days prior to pralatrexate administration on cycle 1, dose 1. Vitamin supplementation will consist of vitamin B12 1 mg intramuscular (IM) q 8-10 weeks and folic acid 1.2mg by mouth (PO) once a day (QD). Once the subject is on-study, the dosing of vitamin supplementation must adhere to the schedule defined by the protocol.

Once pralatrexate is permanently discontinued, vitamin supplementation should continue at least 1 month after the last pralatrexate dose, or longer at the discretion of the investigator.

Pralatrexate Administration

Pralatrexate will be administered via IV push over 3-5 minutes into a subject IV line containing normal saline (0.9% sodium chloride [NaCl]).

Pralatrexate will be administered at a dose of 30 mg/m^2/week for 6 weeks followed by 1 week of rest in a 7-week cycle. Pralatrexate administration occurs once a week during week 1 through week 6 of each cycle.

Dose omissions and/or reductions will be allowed according to the criteria outlined.

If an AE occurs that prevents the administration of pralatrexate on the scheduled dosing day (± 2 days), the dose will be omitted that week and the subject will be reassessed the following week to proceed to the next dose of the cycle. Omitted doses will not be made up at the end of the cycle.

The pralatrexate dose may be reduced to 20 mg/m^2/week if a subject experiences treatment related AEs as in Table 3. and Table 4 . No further dose reductions are allowed. If the subject develops an AE indicating intolerance of this lowest dose of 20 mg/m^2/week, the subject will be discontinued from study treatment. There will not be re-escalation of the pralatrexate dose once a dose reduction has occurred.

Prior and Concomitant Therapy

Permitted Therapies

In addition to protocol treatment, palliative and supportive care will be provided during this study, as clinically indicated, and in accordance with the standard practices of the institution.

All medications administered from signing the informed consent form through the Safety Follow-up Visit are to be recorded on the CRF. Additions, deletions, or changes of dosage of medications are also to be noted.

Prophylaxis and treatment of nausea and vomiting can be administered according to the standard of care within the institution, however administration is not recommended prior to the first dose of pralatrexate because of its low emetogenic potential.

Erythropoietin will be allowed if it is judged by the investigator to be in the best interest of the subject (eg, for patients with underlying anemia or unacceptable hematological toxicity).

Other hematopoietic growth factors (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]), with the exception of pegfilgrastim (Neulasta®), can be administered in accordance with the instructions for treatment modification for hematological toxicities as specified in the protocol.

The administration of appetite stimulating hormones (eg, megestrol acetate) will be allowed to control anorexia and cachexia. Use of prophylactic antibiotics will be allowed at the discretion of the investigator.

Transfusions will be allowed per the discretion of the investigator.

Therapies Not Permitted

The prior therapies that are not allowed are described in the Exclusion Criteria.

Any form of additional therapy for T-cell lymphoma will not be permitted during treatment with pralatrexate, including radiation therapy, other cytotoxic agents, biologic, immune response modifiers, and herbal products.

While on treatment with pralatrexate, steroids will not be allowed for prophylaxis or treatment except:

- As continuation of prior systemic steroid treatment at stable of no more than 10 mg/day or equivalent dose of prednisone;
- As continuation of local or Inhaled or intranasal steroids at fixed doses as used prior to study entry;
- For treatment of possible Addison's crisis in patients with prior history of steroid use.

Duration of Treatment and Study Duration:

Pralatrexate administration will continue until a patient experiences any of the following:

- Development of PD
- Initiation of radiotherapy or systemic chemo/biologic therapy for T-cell lymphoma
- Development of an unacceptable AE indicating intolerance of the lowest study dose allowed (20 mg/m^2/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
- Administrative reasons

All subjects will be followed for at least 30 days after their last dose of pralatrexate for safety. Subjects who discontinue pralatrexate and have received at least 1 dose of pralatrexate are to attend the Safety Follow-up Visit and complete the Safety Follow-up Visit procedures. All patients will be followed for response, PFS, and survival for a duration of 24 months post last dose of pralatrexate.

Criteria for Evaluation:

Analysis Populations

The primary and secondary efficacy endpoints will be analyzed using the safety population. A subject will be considered evaluable for safety population if he/she receives at least 1 dose of pralatrexate.

The PK endpoints will be analysed using the PK population. The overall PK population is defined as all subjects who receive at least one dose of Investigational Medicinal Product (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.

Efficacy Evaluation

The primary analysis will be conducted once all subjects have completed cycle 5 treatment or discontinued before. Study treatment may continue per investigator judgment for a maximum of 24 months.

Response will be assessed on the basis of clinical, radiological, and pathological criteria. Response will be assessed by independent central review and by the treating investigator. Central review assessors will be blinded to the response assessments by the treating investigator. The primary analysis will be based on response assessed by central review.

Response rate by International Working Criteria :

Response rate is defined as number of responders divided by number of subjects, where a subject is considered a responder if she/he has obtained a CR, CRu or a PR.

The following procedures/tests will be included in the evaluation of response:

1. Radiographic imaging (use same imaging techniques as screening).
   - CT of chest, neck, abdomen, and pelvis
   - Other imaging documenting disease site other than chest, neck, abdomen, or pelvis, if applicable
2. Physical examination to assess liver, spleen, lymph nodes, and skin. Include medical photography and ruler measurements of any skin lesions. A sum of the longest diameter (LD) for all skin lesions will be calculated.
3. LDH level determination.
4. Bone marrow biopsy and aspirate should be performed and assessed by flow cytometry if the subject had bone marrow involvement with lymphoma prior to treatment and the subject has a confirmed CR by imaging and physical examination.
5. A tumor biopsy could be performed if needed to confirm a response evaluation.
6. Results of peripheral blood flow cytometry if applicable.

Response and progression of disease will be evaluated by using:

1. The IWC proposed by the NCI sponsored International Working Group
2. Bone marrow biopsies should be scored as follows:
   - Negative = no aggregates or only a few well circumscribed lymphoid aggregates and ≤ 3% blasts.
   - Positive = unequivocally cytologic or architectural evidence of malignancy (percentage of invasion and the lymphoma subtype should be indicated).
   - Indeterminate = increased number or size of aggregates without cytologic or architectural atypia.
3. Measurements of each cutaneous lesions utilizing medical photography and ruler:
   - A sum of the LD for all cutaneous lesions will be calculated and reported as the baseline sum LD and will be used as reference for tumor response
   - Response and progression of cutaneous disease will be evaluated using the following definitions:
     - CR = disappearance of all evidence of disease for at least 4 weeks.
     - PR = 50% or greater decrease in the sum of the LD of each lesion for at least 4 weeks.
     - PD = increase of ≥ 25% of the LD of any lesion or appearance of new lesions.
     - SD = less than a PR but does not meet criteria for PD.

If it is difficult to distinguish residual disease from normal tissue and confirmation of CR depends on this determination, it is recommended that the residual lesion be investigated (biopsy or fine needle aspirate) before confirming CR status.

If progression is determined at a time point or by a method not defined in the protocol, those data will be sent to central review.

Duration of Response:

Duration of response will be measured from first day of documented response to disease progression or death, whatever comes first. Subjects receiving subsequent therapy, including transplant before PD is documented, will be censored at that time, with a note indicating censoring occurrence, along with reason.

Time to Response: Time to response will be measured from first day of treatment to the first date of documented response.

Progression Free Survival:

PFS will be measured from treatment day 1 until event or censoring. An event is defined as the earliest of the following: death from any cause or disease progression. Subjects undergoing transplant or any other subsequent therapy prior to documentation of PD will be censored at that time.

Overall Survival:

OS will be measured from treatment day 1 until death or censoring.

Safety evaluation

Safety will be evaluated by assessment of physical examinations, clinical laboratory values, and treatment emergent AEs.

Pharmacokinetics evaluation

The PK profile of R-pralatrexate and S-pralatrexate will be determined in a subset of this subject population.

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 plasma concentration [Cmax], trough observed plasma concentration [Ctrough], time of Cmax observation [tmax] and terminal phase half-life [t1/2Z]). Collection of plasma to determine the full PK profile will be performed in 15 subjects at pre-selected sites.

Statistical Methods:

Efficacy Analyses

The primary endpoint is the objective response rate (ORR) 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 test for single proportion at two-sided significance level of 5%. The hypotheses under test will be H_0: ORR<15% vs. H_1: 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.

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]). Censoring rules will be detailed in the SAP.

Secondary endpoints based on tumor assessments (e.g. duration of response and PFS) will be analyzed twice, once using the independent review data and once using the investigator assessment data.

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

Safety Assessments:

The analysis of the safety parameter will be based on the safety population. The safety endpoints for this study are as follows:

- Incidence and severity of AEs
- Clinically significant changes in vital signs and physical examination findings
- Clinically significant changes in laboratory parameters.

Incidence and type of adverse events will be summarized. Laboratory values will be evaluated using mean values, the number of subjects who have clinically relevant values outside normal values, and shift tables.

All other safety variables will be analyzed descriptively. In general missing safety data will not be replaced. A more detailed description will be presented in the statistical analysis plan.

Pharmacokinetic Assessments:

Plasma concentration data will be listed by analyte (R-pralatrexate and S-pralatrexate) for subjects in the PK population. Plasma concentration data will be summarised by nominal time-point and treatment as continuous data (i.e. n, mean, standard deviation, standard error, median, minimum, and maximum) for subjects in the PK population. Additionally, the plasma concentration data will be presented graphically in the following way using both a linear and log linear scale:

- The mean plasma concentration data will be plotted over time
- For each subject, the individual plasma concentration data will be plotted over time

Pharmacokinetic parameters (AUCt, AUCINF, Cmax, Ctrough, tmax, LambdaZ, t1/2Z, CLss, Vdss) will be listed by analyte for subjects in the PK population. Data excluded from the PK analysis will be flagged with an asterisk.

Pharmacokinetic parameters (AUCt, AUCINF, Cmax, Ctrough, tmax, LambdaZ, t1/2Z, CLss, Vdss) for each analyte will be summarised descriptively for subjects in the PK population, adjusting for dose where necessary.

Bioanalytical Methods:

Plasma will be frozen for subsequent PK analysis. The concentration of R-pralatrexate and S-pralatrexate at each time-point will be determined by liquid chromatography-tandem mass spectrometry (LC/MS/MS). 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.

Interim Analyses: None planned.

Primary Data Analysis and Cut-off date:

Based on the PROPEL study 29 out of 32 responses (91%) occurred within the first five cycles of treatment. Consequently the data cut-off date for the primary analysis will be defined once all subjects have been treated for 5 cycles.

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.

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β -hCG	beta-human chorionic gonadotropin
µL	Microliter
µmol	Micromole
AE	adverse event
AILD	angioimmunoblastic lymphoma
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BMB	bone marrow biopsy
BSA	body surface area
℃	degrees centigrade
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CI	confidence interval
CLnonren	nonrenal clearance
CLren	renal clearance
CLtot	total clearance
cm	centimetre
Cmax	maximum observed concentration
CNAP	Chest, neck, abdomen, pelvis
CNS	central nervous system
CRA	clinical research associate
CR	complete response
CRF	case report form
CRu	complete response unconfirmed
CT	computed tomography
CTA	Clinical Trial Agreement
CTCAE	Common Toxicity Criteria for Adverse Events
CTCL	cutaneous T-cell lymphoma
DHFR	dihydrofolate reductase
dL	decilitre
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EPOCH	etoposide, doxorubicin, vincristine, prednisone,
℉	degrees Fahrenheit
FDA	Food and Drug Administration
fe	fractional excretion
FPGS	folylpolyglutamate synthetase
g	gram
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GGH	gamma-glutamyl hydrolase
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
Hct	hematocrit
Hcy	homocysteine

Hgb	hemoglobin
HIV	human immunodeficiency virus
HTLV	human T-cell leukemia virus
IB	Investigator's Brochure
IC	informed consent
ICE	ifosfamide, carboplatin and etoposide
ICH	International Conference on Harmonization
IM	intramuscular
IMP	Investigational Medicinal Product
NIMP	Non-Investigational Medicinal Product
IND	investigational new drug
IRB	Institutional Review Board
IV	intravenous
IWC	International Workshop Criteria
kg	kilogram
K_i	inhibitory constant
K_m	binding constant
L	litre
LC/MS/MS	liquid chromatography/ mass spectrometry/ mass spectrometry
LD	longest diameter
LDH	lactic dehydrogenase
m^2	square meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mOsmol	milliosmole
MRI	magnetic resonance imaging
MTX	methotrexate
N	number
NaCl	sodium chloride
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphomas
NK	natural killer
No.	number
NOS	not otherwise specified
NSCLC	non-small cell lung cancer
OS	overall survival
PBS	phosphate buffered saline
PBSCT	peripheral blood stem cell transplant
PCR	polymerase chain reaction
PD	progressive disease
PDX	pralatrexate
PFS	progression-free survival
PK	pharmacokinetic(s)
pM	picomolar
pmol	picomole
PO	by mouth
PR	partial response
pralatrexate	(RS)-10-propargyl-10-deazaaminopterin
PT	prothrombin time
PTCL	peripheral T-cell lymphoma
PTT	partial thromboplastin time
q	every
QD	once a day
RD	relapsed disease

RFC	reduced folate carrier
RR	respiratory rate
RT	radiation therapy
SAE	serious adverse event
SAER	serious adverse event report
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SPD	sum of the products of the greatest diameters
$t_{½}$	half life
t1/2Z	terminal phase half-life
tmax	time of Cmax observation
T/NK	T/natural killer
T-PLL	T-cell prolymphocytic leukemia
TTP	time to progression
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
V_{dss}	steady state volume of distribution
V_{max}	maximum rate constant
WBC	white blood cells
WHO	World Health Organization

4 STUDY CONDUCT AND OVERSIGHT

4.1 Sponsor

This study will be conducted by qualified Investigators under the Sponsorship of Mundipharma (China) Pharmaceutical Co. LTD.

4.2 Declaration of Ethical Conduct

This study will be conducted in accordance with the standard operating practices of the Sponsor and Contract Research Organisation (CRO), which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as described in Section 15 of this protocol.

4.3 Investigators and Study Personnel

The study will be conducted at approximately 15 sites in China.

4.4 Randomisation

This is a non-randomised study.

4.5 Data Management

Data management and statistical analyses will be the responsibility of the Data Management and Statistics department at the CRO's site. Data from Case Report Forms (CRFs) including subject diaries, questionnaires and other external data, e.g. laboratory data, will be entered into a clinical database as specified in the CRO's data management plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. The Monitoring Plan and Data Management Plan will detail the data entry, cleaning, clarification, and validation procedures to be followed by all relevant study staff.

Data collection will be done by EDC. Data will be transferred to the CRO database and an electronic copy supplied to the site. Laboratory data collection will be specified in the Data Management Plan.

4.6 Monitoring

The study will be monitored by qualified personnel from the CRO. The Monitoring Plan for the study will detail this process. The Investigator will allow monitoring, audit and inspection of the clinical, laboratory, and pharmacy facilities as required, to assure compliance with Good Clinical Practice and Good Laboratory Practice. The EDC system and subject's corresponding original medical records (source documents) are to be fully available for review by the CRO representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations and Good Clinical Practice. All records at

the site are subject to inspection by the local competent authorities as well as by Sponsor's QA department.

4.7 Medical Monitoring

The name of the Study Physician along with the telephone and fax numbers of the other contact persons are listed in the study site file.

4.8 Central Review/Central Laboratory

4.8.1 Independent Data Monitoring Committee

The sponsor or designee will coordinate an Independent Data Monitoring Committee (IDMC), consisting of 3 members who are not directly involved with the conduct of this study. The IDMC will review the safety data periodically and provide recommendations whether to stop or continue the trial based on their safety findings. The pralatrexate dose reduction to 20 mg/m2/week for the remaining study period may also be recommended by IDMC if there are significant safety concerns on the treatment dose of 30 mg/m2/week.

The IDMC will meet at least 2 times to review clinical data: after the first 15 subjects complete cycle 1 and after 50% of the subjects to be recruited complete cycle 1. The working procedures of the Committee will be outlined in an IDMC Charter.

4.8.2 Central Pathology Review

The diagnosis of eligible PTCL histopathological subtype will be confirmed by Central Pathology Review.

The Central Pathology Review will be provided with tissue slides to confirm histopathology, and bone marrow aspirate and core biopsy slides to confirm presence or absence of bone marrow involvement, along with any supporting documentation.

For confirmation of treatment response, the following pathology tissue slides should be submitted to Central Pathology Review:

- If a subject is reported by the investigator to have a complete response (CR), and the subject's screening core bone marrow biopsy is positive or indeterminate for involvement of lymphoma, a repeat core bone marrow biopsy is required and the slides should be submitted
- If bone marrow aspirate or peripheral blood flow cytometry are performed, the result reports should be submitted
- If a tumor biopsy is performed to confirm a response evaluation, the slides should be submitted

The details for Central Pathology Review will be described in the Study Manual.

4.8.3 Independent Central Response Review

All treatment responses will be eventually evaluated by the Independent Central Review Committees as described in the Study Charters.

All radiographic images and digital photographs for subjects with cutaneous disease will be sent to the Independent Central Imaging Laboratory for the independent Central Radiology Review. The details will be described in the Site Imaging Manual and Independent Radiology Review Charter.

If applicable, all slides of tumor biopsies, core bone marrow biopsies or bone marrow aspirate, and results of peripheral blood flow cytometry will be collected for Central Pathology Review as confirmation as described in Site Pathology manual and Independent Pathology Review Charter.

Independent Central Oncology Review will be conducted by utilizing International Working Group Criteria (IWC, see appendix 18.4). The final response review will be performed by combining relevant clinical evidences (e.g., physical examination findings of liver and spleen etc.), Laboratory results (e.g., LDH), central radiology review results and central pathology review results. The details will be described in the Central Oncology Reviewer Charter.

Detailed description and measurement of tumor burden and eventual evaluation of the treatment response, will be reported through the Independent Response Central Review. However, the investigators will also assess response according to the IWC but will only report their overall response evaluation on the CRF.

4.8.4 Central Laboratory

A central laboratory will be used for pharmacokinetic (PK) analyses.

At each site, the local laboratory will be used for the hematology, chemistry, and pregnancy testing to assess study eligibility and safety. All laboratory data locally collected by study sites will be employed to analyze in corresponding study sites.

5 INTRODUCTION

5.1 Therapeutic Area/Background

T-cell lymphomas represent a very heterogenous array of aggressive non-Hodgkin's lymphomas (NHLs) and typically account for approximately 5-10% of all NHL cases in western countries and about 10-20% in Asian countries (Vose J et al., 2008). According to the most recent World Health Organization (WHO) classification schema published in 2008, mature T-cell lymphomas are divided into four different subcategories, including nodal, extranodal, cutaneous, and leukemic, each based on the predominant clinical behavior of that disease entity. There are considered to be at least 22 distinct sub-types of T-cell lymphoma distributed

among the four different subcategories. Most PTCL subtypes are, considered highly aggressive diseases that respond poorly to conventional chemotherapy.

The most common varieties are the nodal types, which include PTCL not otherwise specified, anaplastic large cell lymphomas, and angioimmunoblastic T-cell lymphomas.

For most subtypes of PTCL, the frontline treatment regimen is typically a combination chemotherapy, such as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or EPOCH (etoposide, vincristine, doxorubicin, cyclophosphamide, prednisone) or other multi-drug regimens. Because most PTCL patients will relapse, some oncologists recommend giving high-dose chemotherapy followed by an autologous stem cell transplant to some patients who had a good response to their initial chemotherapy program. While promising, there is no firm clinical data to support that undergoing a transplant in this setting is better than not undergoing a transplant.

Few studies that specifically investigated optimal treatment options for patients with relapsed or refractory PTCL have been conducted. High-dose therapy followed by an autologous stem cell transplant (SCT), or less commonly, an allogeneic SCT, is a common treatment goal for patients with relapsed and refractory T-cell lymphomas. However, peripheral blood SCT (PBSCT) has been successful only in patients with disease responsive to chemotherapy. The remainder of patients who have either refractory disease or are not candidates for PBSCT have historically been destined to succumb to their disease.

As PTCL is usually aggressive with low survival rate and the disappointing outcomes of the available therapies for PTCL, it is in need of additional new treatment options. This is especially true for subjects with relapsed or refractory disease who typically have a limited response to salvage therapy and an extremely poor overall survival (Campo et al., 1998).

PTCL has been thought to occur more frequently in Asia. It was reported that frequencies of PTCL in Vancouver to be 1.6% of all NHL compared to 18.3% in Hong Kong (Tang. et al., 2010). The frequencies of PTCL subtypes vary by geographic region. For example, NK-cell lymphomas (NKTCL) were reported more common in Asia and are associated with Epstein-Barr virus (Dearden et al., 2011). FDA has approved new emerging drugs for PTCL in most recent years, however, they are still need to be investigated systematically to prove the efficacy and safety in patients in Asia.

5.2 Investigational Drug

Pralatrexate is an antineoplastic folate analog designed to preferentially accumulate in cancer cells. Pralatrexate is an analog of the widely used antifolate, methotrexate. In comparison to methotrexate, pralatrexate has demonstrated superior in vitro and in vivo activity in leukemia, lymphoma, and breast and lung cancer models (DeGraw et al., 1993; Sirotnak et al., 1998; Toner et al., 2006; Wang et al., 2003). Furthermore, compared to methotrexate, pralatrexate is more effectively taken up by cancer cells through increased affinity for the reduced folate

carrier 1 (RFC-1) and more efficiently polyglutamylated by folylpolyglutamyl synthetase (FPGS) (Sirotnak et al., 1998).

Up to June 2013, twelve Phase 1 or 2 clinical studies with pralatrexate have been completed, and 7 Phase 1, 2 or 3 clinical studies with pralatrexate are ongoing. These studies with pralatrexate alone or in treatment combination were conducted in several tumour types including non-small cell lung cancer (NSCLC), malignant pleural mesothelioma (MPM), relapsed or refractory aggressive lymphomas, relapsed or refractory cutaneous T-cell lymphomas, advanced or metastatic relapsed transitional cell carcinoma of the urinary bladder, and relapsed or refractory PTCL.

A clinical trial (PDX-008) has been conducted with pralatrexate as a registration study for the treatment of patients with relapsed or refractory PTCL. This was a Phase 2, single arm, non-randomised, open-label, multi-center, international study designed to evaluate the safety and efficacy of pralatrexate when administered concurrently with vitamin B12 and folic acid supplementation to subjects with relapsed or refractory PTCL. Based on the study of PDX-008, the United States (US) Food and Drug Administration (FDA) granted accelerated approval in September 2009, for the use of pralatrexate in the treatment of patients with relapsed or refractory PTCL at a dose of 30 mg/m^2/week for 6 weeks in a 7-week cycle.

5.3 Study Rationale

The study is designed to confirm the safety and efficacy of pralatrexate in a Chinese patient population to support registration approval in China.

As T-cell malignancies are very uncommon and are made up of multiple varied sub-types, there are few studies that have specifically investigated optimal treatment options for subjects with relapsed or refractory disease. Since the primary endpoint of response rate can be directly attributed to the antitumor activity of the drug administered, a single-arm study with further secondary endpoints of duration of response, time to response, PFS and OS is considered appropriate to assess efficacy in heavily pre-treated PTCL subjects with relapsed or refractory tumors.

5.4 Risk / Benefit Assessment

Approximately 944 patients have been enrolled in the pralatrexate clinical development program and approximately 797 subjects have received pralatrexate. In addition, 638 patients have received pralatrexate in Investigator Sponsored Studies (ISS) and 38 patients have received pralatrexate in Named Patient Programmes (NPP). (Pralatrexate DSUR August 2014)

As per the current IB for praletraxate (October 2013), the most frequently occurring treatment-related AEs in the 767 patients were stomatitis (n = 473, 62%), fatigue (n = 305, 40%), nausea (n = 275, 36%), and epistaxis (n = 166, 22%). The most frequently occurring treatment-related Grade 3 or higher AEs in patients who received pralatrexate across all studies were stomatitis

(n = 154, 20%), thrombocytopenia (n = 95, 12%), neutropenia (n = 93, 12%), anemia (n = 64, 8%), lymphopenia (n = 36, 5%), and fatigue (n = 36, 5%).

In the PDX-008 study of pralatrexate in patients with relapsed or refractory PTCL, 109 patients were considered evaluable for efficacy. Twenty-nine percent (n = 32) of evaluable patients experienced either a CR, a CRu, or a PR, as assessed by central independent review. Thirty-nine percent of patients (n = 43) experienced either a CR/CRu or PR, as assessed by the study investigators.

Sixty-nine patients (63%) in the efficacy analysis set did not have evidence of response to their most recent prior therapy. Of these 69 patients, 17 patients (25%) responded to pralatrexate as assessed by central review per IWC. For the overall efficacy analysis set, 26 patients (24%) did not have evidence of response to any prior therapy. Of these 26 patients, 5 patients (19%) responded to pralatrexate per IWC.

The Kaplan-Meier estimate for the median duration of response assessed by central review using IWC for the 32 responding patients, was 306 days (95% confidence interval [CI], 103-not estimable) or 10.1 months, with a range of 1-673 days. The median duration of response based on response assessed by local investigator, based on 43 responding patients, was 246 days (95% CI, 154-379) or 8.1 months, with a range of 1-677 days.

The demonstrated efficacy of pralatrexate in relapsed/refractory PTCL from the PDX-008 study led to accelerated approval on 24 Sep 2009 allowing marketing of the drug in the US as FOLOTYN (pralatrexate injection) for use in this patient population. Pralatrexate has been available for commercial distribution in the US since October 2009.

Responses have also been observed and reported in patients who received pralatrexate with T-cell and B-cell lymphoma (studies PDX-02-078 and PDX-009), CTCL (PDX-010), HL (PDX-009), NSCLC (PDX-97-006 and PDX-007), and advanced solid tumors (PDX-99-083). In addition, efficacy data from a study in NSCLC (PDX-012) showed an estimated difference in OS favoring pralatrexate over erlotinib in the full analysis set, the primary efficacy set, and certain subsets.

Patients with lymphoproliferative malignancies, including HL and NHL, particularly T-cell and B-cell lymphomas, are in need of additional treatment options. This is especially true for patients with recurrent or refractory disease who typically have a limited response to salvage therapy and an extremely poor overall survival. Nearly all of the patients were heavily pretreated and had failure with or became refractory to prior therapies. Results of PDX-008, PDX-02-078, PDX-009, and PDX-010 provide evidence that patients with lymphoproliferative malignancies have shown significant response to pralatrexate therapy.

Given the poor prognosis for patients with advanced, relapsed, or refractory solid tumors in general, there is a significant need for new effective agents in this patient population as well. In those patient populations (both lymphoproliferative malignancies and solid tumors) for which

responses to pralatrexate have been observed, the efficacy of pralatrexate may be studied further.

6 STUDY OBJECTIVES

6.1 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 PTCL in Chinese population.

6.2 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.

6.3 Secondary Objectives

The secondary objectives include:

- 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

7 STUDY SUMMARY AND GRAPHIC

7.1 Overall Study Design and Plan

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 determine 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/m^2/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.

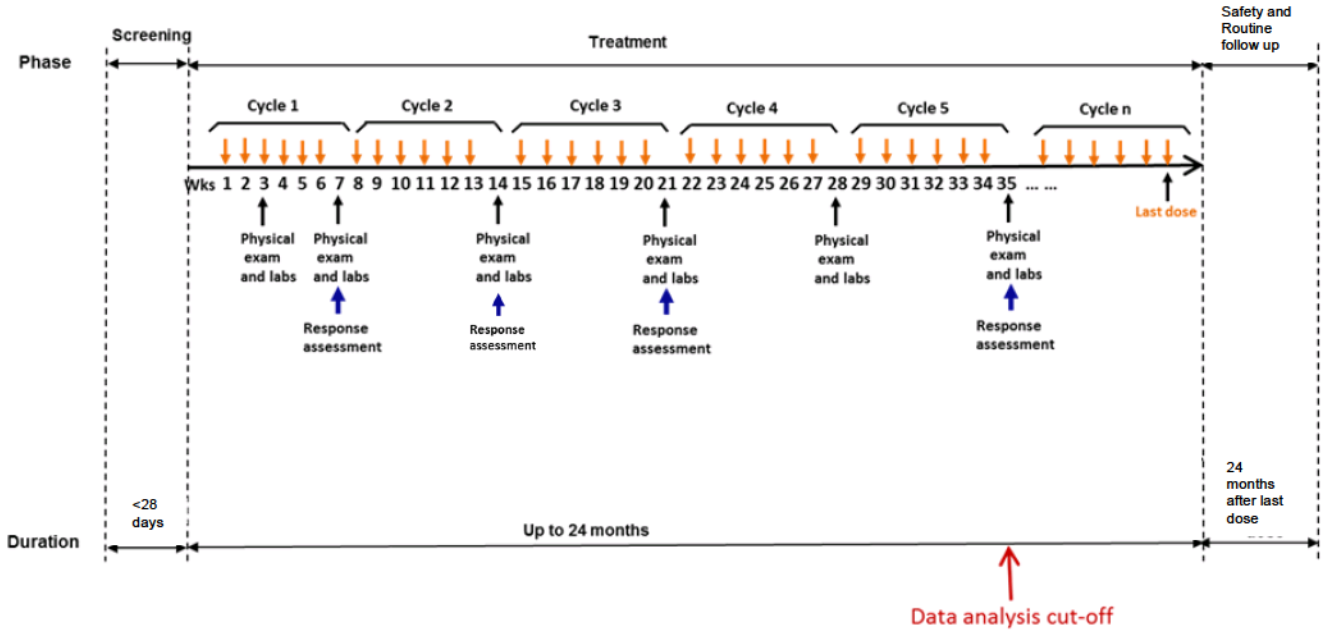
Follow-up phase:

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.

7.2 Study Diagram

Figure 1 Study diagram



7.3 Efficacy Parameters

7.3.1 Primary Efficacy Variable

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

7.3.2 Secondary Efficacy Variables

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

7.4 Safety Variables

- Treatment emergent AEs
- Physical examinations
- Clinical laboratory values

7.5 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], trough observed plasma concentration [Ctrough], time of Cmax observation [tmax] and terminal phase half-life [t1/2Z]). Collection of plasma to determine the full PK profile will be performed in 15 subjects at pre-selected sites.

8 SELECTION OF SUBJECTS

8.1 Number of Subjects

Eligible patients will be enrolled to the study to achieve 68 evaluable subjects.

8.2 Inclusion Criteria

Subjects to be included in the study are those who meet all of the following criteria:

1. Has histologically/cytologically confirmed PTCL, using the World Health Organization (WHO) disease classification:
    a. PTCL not otherwise specified (NOS)
    b. Angioimmunoblastic T-cell lymphoma
    c. Anaplastic large cell lymphoma, ALK+
    d. Anaplastic large cell lymphoma, ALK-
    e. Extranodal NK/T-cell lymphoma – nasal type
    f. Enteropathy-associated T cell lymphoma
    g. Hepatosplenic T-cell lymphoma
    h. Subcutaneous panniculitis-like T-cell lymphoma
    i. Adult T-cell lymphoma/leukemia (human T-cell leukemia virus [HTLV] 1+)
    j. Aggressive NK-cell leukemia
    k. Transformed mycosis fungoides
2. Has documented progressive disease (PD) after at least 1 prior systemic treatment.
3. May not have received an experimental drug or biologic as their only prior therapy. Patient must have clear PD after the last treatment received. Patient should have at least 1 biopsy from initial diagnosis or in the relapsed setting to confirm the diagnosis of PTCL. Patient must have recovered from the toxic effects of prior therapy.
4. Subjects with an enlarged lymph node or extranodal mass lesion clearly measurable in two perpendicular directions and greater than 1.5 cm maximum diameter on computed tomography performed within 14 days prior to study enrollment.
5. Eastern Cooperative Oncology Group (ECOG) Performance Status $\leqslant$ 2.
6. At least 18 years of age.
7. Expected life expectancy $\geqslant$ 3 months.
8. Adequate hematological, hepatic, and renal function as defined by:

a. Absolute neutrophil count (ANC) ⩾ 1000/uL (or 1 × 109/L), platelet count ⩾ 100,000/uL (or 100 × 109/L) (at both screening and within 3 days prior to dosing on cycle 1, day 1);
b. Total bilirubin ⩽ 1.5 mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ⩽ 2.5 X upper limit of normal (ULN) (AST/ALT < 5 X ULN if documented hepatic involvement with lymphoma);
c. Creatinine ⩽ 1.5 mg/dL(or 132.6 μmol/L) or a calculated creatinine clearance ⩾ 50 mL/min.

9. Women of childbearing potential must have agreed to practice a medically acceptable contraceptive regimen from study treatment initiation until at least 30 days after the last administration of pralatrexate and must have a negative serum pregnancy test within 14 days prior to the first day of study treatment. Subjects who are postmenopausal for at least 1 year (> 12 months since last menses) or are surgically sterilized did not require this test.
10. Men who are not surgically sterile must agree to practice a medically acceptable contraceptive regimen from study treatment initiation until at least 90 days after the last administration of pralatrexate.
11. Patient gave written informed consent (IC).

8.3 Exclusion Criteria

Subjects to be excluded from the study are those who meet any of the following criteria:

1. Subject has:
    a. Precursor T-cell lymphoma or leukemia
    b. T-cell prolymphocytic leukemia (T-PLL)
    c. T-cell large granular lymphocytic leukemia
    d. Mycosis fungoides, other than transformed mycosis fungoides
    e. Sézary syndrome
    f. Primary cutaneous CD30+ T-cell disorders: Lymphoid papulosis and primary cutaneous anaplastic large cell lymphoma
2. Active concurrent malignancy (except non-melanoma skin cancer or carcinoma in situ of the cervix). If there is a history of prior malignancy, the patient must be disease-free for ⩾ 5 years.
3. Congestive heart failure Class III/IV according to the New York Heart Association's Heart Failure guidelines.
4. Human immunodeficiency virus (HIV)-positive diagnosis.
5. Has, or history of, brain metastases or central nervous system (CNS) disease.
6. Active uncontrolled infection, underlying medical condition including unstable / uncontrolled chronic diseases or other serious illness that would impair the ability of the patient to receive protocol treatment.
7. Has major surgery within 2 weeks of study entry.

8. Receipt of any conventional chemotherapy or radiation therapy (RT) within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to study treatment or planned use during the course of the study.
9. Receipt of corticosteroids within 7 days of study treatment, unless patient has been taking a continuous systemic dose of no more than 10 mg/day or equivalent dose of prednisone, or a local or inhale or intranasal administration at fixed doses for at least 1 month prior to study treatment and tumor shrinkage is not observed.
10. Use of any investigational drugs, biologics, or devices within 4 weeks prior to study treatment or planned use during the course of the study.
11. Receipt of anti-tumor antibody therapy within 100 days prior to study treatment.
12. History of allogeneic hematopoietic stem cell transplantation. Or subjects with a history of autologous hematopoietic stem cell transplantation within 100 days prior to study treatment.
13. Previous exposure to pralatrexate.
14. Patient is pregnant or breast-feeding.

8.4 Removal of Patients from Therapy

Study treatment discontinuation is defined as stopping administration of pralatrexate. Once pralatrexate is permanently discontinued, vitamin supplementation should continue at least 1 month after the last pralatrexate dose, or longer at the discretion of the investigator. Study treatment will be discontinued for the following reason(s):

- Development of PD
- Initiation of radiotherapy or systemic chemo/biologic therapy for T-cell lymphoma
- Development of an unacceptable AE indicating intolerance of the lowest study dose allowed (20 mg/m^2/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
- Administrative reasons

9 ASSESSMENTS AND PROCEDURES

9.1 Schedule Overview

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 B_{12} 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	X
Record Date of Death											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.

9.2 STUDY PROCEDURES

9.2.1 Screening

The procedures and evaluations required for enrolment into the study are summarized below. All potential study subjects will be screened and eligibility determined prior to enrolment.

Unless otherwise specified, the following procedures and evaluations will be performed within 28 days prior to the projected start of pralatrexate administration (cycle 1, dose 1):

1. Obtain written IC.
2. Review eligibility criteria.
3. Review medical chart for past medical/surgical history.
4. Record medications and prior treatment for PTCL.
5. Record response to prior treatment(s) for PTCL.
6. Document histopathology from:
   - Original diagnosis of PTCL, and/or
   - Tumor biopsy in the relapsed setting

   Send the pathology specimen(s) to central pathology review (see Study Manuals provided by the sponsor for detailed guidance regarding sample requirements and the preparation and shipment of slides).
7. Documentation of known measurable disease parameters by the following radiographic imaging procedures (the imaging exam do not need to be repeated if it is performed within 14 days prior to pralatrexate dose 1):
   - Contrast-enhanced CT of chest, neck, abdomen, and pelvis. Please refer to the site imaging manual issued by central imaging lab for detailed technical requirements
   - Other imaging techniques documenting disease site other than chest, neck, abdomen, and pelvis, if applicable
8. Documentation of any cutaneous lesions using medical photography and ruler measurements of each lesion, if applicable (refer to Study Manuals).
9. Unilateral bone marrow aspirate and biopsy assessment within 28 days of pralatrexate dose 1. If bone marrow aspirate flow cytometry has been performed, send result reports to the central pathology reviewer.
10. Obtain a 12-lead electrocardiogram (ECG). Repeat ECG during study only if clinically indicated.
11. Perform a comprehensive physical examination.
12. Assess and record ECOG Performance Status.
13. Local laboratory: Collect blood for hematology, chemistry (including serum β-human chorionic gonadotropin [β-hCG] pregnancy test for women who are not postmenopausal or surgically sterile [within 14 days prior to cycle 1, dose 1]).

14. Collect blood for serum creatinine, calculate creatinine clearance using the glomerular filtration rate (GFR) according to the Cockroft and Gault Equation:

$$GFR^* = \frac{(140 - \text{age [years]}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine}}$$

*For female subjects, multiply by 0.85

15. If peripheral blood flow cytometry has been performed, send result reports to the central pathology reviewer. .

9.2.2 Patient Assignment

Patient enrollment will be competitive among participating sites. Each patient who is evaluated for participation in this study will be assigned a unique screening number.

Once it has been determined that a patient meets inclusion and exclusion criteria, the site must fax an enrollment form to the sponsor or designee to confirm the eligibility. The patient will be assigned a unique patient enrollment number and will be entered into the study. Confirmation of enrollment status and patient number will be faxed back to the site.

9.2.3 Vitamin Administration

Vitamin supplementation will be initiated at least 10 days prior to pralatrexate administration on cycle 1, dose 1. Vitamin supplementation will consist of vitamin B12 1 mg intramuscular (IM) q 8-10 weeks and folic acid 1.2 mg by mouth (PO) once a day (QD). Once the patient is on-study, the dosing of vitamin supplementation must adhere to the schedule defined by the protocol.

1. Administer or ensure vitamin B12 supplementation at 1 mg IM q 8-10 weeks:
   - If patient has not received vitamin B12 1 mg IM within the previous 8-10 weeks, administer at this time. This schedule should be maintained throughout the course of the study.
   - If patient has received vitamin B12 1 mg IM within the previous 8-10 weeks, review date of previous vitamin B12 dosing and continue administration q 8-10 weeks.

2. Administer or ensure folic acid supplementation at 1.2 mg, PO QD:
   - If patient has not initiated folic acid 1.2mg PO QD, begin at this time.
   - If patient has initiated folic acid, ensure that the dosing regimen conforms to the protocol schedule.
   - Provide the patient with a prescription for folic acid, instructions for administration, and a patient diary for documentation of self-administration.

Once pralatrexate is permanently discontinued, vitamin supplementation will continue for at least 1 month after the last pralatrexate dose, or longer at the discretion of the investigator.

9.2.4 Pralatrexate Administration Cycle 1

9.2.4.1. Pralatrexate Cycle 1, Dose 1

The following baseline evaluations and procedures must take place upon treatment initiation (pralatrexate cycle 1, dose 1), unless otherwise noted below:

1. Record current medications.
2. Review the patient's diary of folic acid administration to ensure protocol compliance.
3. Assess and record baseline symptoms.
4. Record study procedure-related AEs and attribution.
5. Record weight in kilograms (kg), height in centimeters (cm) and calculate body surface area (BSA). The patient's weight and BSA (refer to Section 18.5), to calculate the pralatrexate dose, may be assessed up to 3 days prior to cycle 1, dose 1.
7. Local laboratory: Collect pre-injection blood for hematology within 1 day and chemistries (including LDH) within 3 days prior to cycle 1, dose 1. Platelet count must remain $\geqslant$ 100,000/ μ L and ANC $\geqslant$1000/ μ L to proceed with pralatrexate dosing.
8. Local laboratory: Collect urine for β-hCG pregnancy test for women who are not postmenopausal or surgically sterile (within 72 hours prior to cycle 1, dose 1). The result must be negative.
9. Central laboratory: Collect pre-injection blood sample for pralatrexate PK analysis (only in pre-selected sites, see Section 11).
10. Administer pralatrexate IV push over 3-5 minutes.
11. Central laboratory: Collect blood samples for post-pralatrexate PK analysis at the scheduled time points (see Section 11).

9.2.4.2. Cycle 1: 24, 48, and 72 Hours Post-end Dose 1 Pralatrexate Injection (For applicable time-points for each patient, see Section 11)

1. Central laboratory: Collect blood samples for pralatrexate PK analysis at 24, 48, and 72 hours post-end cycle 1, dose 1 pralatrexate injection (only in pre-selected sites, see Section 11).

2. Record study procedure-related AEs and attribution.

9.2.4.3. Cycle 1, Weeks 2-6

1. Record AEs and attribution.
2. Record concomitant medications.
3. Review the patient's diary of folic acid administration to ensure protocol compliance. Review dosing procedures with patient and re-supply if needed.

4. Review date of previous vitamin B12 injection. Administer vitamin B12 1 mg IM q 8-10 weeks.
5. Local laboratory: Collect blood for hematology and chemistries within 1 day prior to each pralatrexate dose.
6. Central laboratory: Collect pre-injection blood sample for pralatrexate PK analysis (only in pre-selected sites, see Section 11).
7. If the patient is not experiencing any AEs that warrant treatment discontinuation, administer pralatrexate IV push over 3-5 minutes.

9.2.4.4. Cycle 1, Week 3

In addition to the above weekly evaluations and procedures, the following should be performed or obtained during cycle 1, week 3:

1. Perform a physical examination.
2. Assess and record ECOG Performance Status.

9.2.4.5. Cycle 1, Week 6

1. Central laboratory: Collect post-injection blood samples for pralatrexate PK analysis (only in pre-selected sites, see Section 11).

9.2.5 Procedures for Subsequent Cycles

Subjects may continue to receive pralatrexate unless the patient experiences any of the criteria noted in protocol Section 8.4.

9.2.5.1. Response Evaluation, Prior to Cycle 2-4 and the Following Even Cycles

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).

The following procedures/tests are to be performed for evaluation of response:

1. Radiographic imaging (use same imaging technique as screening):
   - Contrast-enhanced CT of chest, neck, abdomen, and pelvis. For detailed technical requirements, please refer to the Study Manual issued by central imaging lab.
   - Other imaging techniques documenting disease site other than chest, neck, abdomen, or pelvis, if applicable.
   - Unscheduled imaging exams which may impact the response evaluation.
2. Physical examination to assess liver, spleen, lymph nodes, and skin. Include medical photography with ruler measurements for documentation of any skin lesions.

3. Local laboratory: Collect blood for LDH.

4. If the patient's screening bone marrow biopsy/aspirate results are positive or indeterminate and the patient has a confirmed CR by imaging, the repeat core bone marrow biopsy slides need to be submitted to Central Pathology Review for confirmation of response. If bone marrow aspirate flow cytometry has been performed, send result reports to the central pathology reviewer. Once a patient's bone marrow is negative for lymphoma, the bone marrow biopsy will be repeated only when clinically indicated unless it is the patient's only site of disease.

5. A tumor biopsy may be performed and the slides should be sent to central pathology reviewer to confirm a response evaluation.
6. If peripheral blood flow cytometry has been performed, send result reports to the central pathology reviewer.

All treatment responses will be eventually evaluated by the Independent Central Review Committees as described in the Study Charters.

All radiographic images and digital photographs for subjects with cutaneous disease will be sent to the Independent Central Imaging Laboratory for the independent Central Radiology Review. The details will be described in the Site Imaging Manual and Independent Radiology Review Charter.

If applicable, all slides of tumor biopsies, core bone marrow biopsies or bone marrow aspirate, and results of peripheral blood flow cytometry will be collected for Central Pathology Review as confirmation as described in Site Pathology manual and Independent Pathology Review Charter.

Independent Central Oncology Review will be conducted by utilizing International Working Group Criteria (IWC, see appendix 18.4). The final response review will be performed by combining relevant clinical evidences (e.g., physical examination findings of liver and spleen etc.), Laboratory results (e.g., LDH), central radiology review results and central pathology review results. The details will be described in the Central Oncology Reviewer Charter.

Detailed description and measurement of tumor burden and eventual evaluation of the treatment response, will be reported through the Independent Response Central Review. However, the investigators will also assess response according to the IWC but will only report their overall response evaluation on the CRF.

9.2.5.2. Subsequent Cycles, Dose 1

Dose 1 of subsequent cycles can be delayed due to an AE for no more than 3 weeks after the last dose of pralatrexate. If > 3 weeks lapse between pralatrexate doses, the patient must discontinue study treatment.

9.2.5.2.1. Within 7 Days Prior to the Projected Dose 1

1. Perform a physical examination.
2. Record weight in kg and calculate BSA.
3. Assess and record ECOG Performance Status.
4. Local laboratory: Collect urine for β-hCG pregnancy test for women who are not postmenopausal or surgically sterile (within 72 hours prior to cycle 1, dose 1). The result must be negative.

9.2.5.2.2. Dose 1

The following evaluations or procedures should be completed within 1 day prior to dose 1 of subsequent cycles:

1. Record concomitant medications.
2. Record AEs and attribution.
3. Review the patient's diary of folic acid administration. Review dosing procedures with patient and re-supply if needed.
4. Review date of previous vitamin B12 injection. Administer vitamin B12 1 mg IM q 8-10 weeks.
5. Local laboratory: Collect blood for hematology and chemistry (including LDH) within1 day prior to pralatrexate dose.
6. If the patient is not experiencing any AEs that warrant treatment modification, administer pralatrexate IV push over 3-5 minutes.

9.2.5.2.3. Subsequent Cycles, Weeks 2–6

The following evaluations or procedures should be completed within 1 day prior to day of dosing:

1. Record AEs and attribution.
2. Record concomitant medications.
3. Review the patient's diary of folic acid administration to ensure protocol compliance.
4. Review date of previous vitamin B12 injection. Administer vitamin B12 1 mg IM q 8-10 weeks.
5. Local laboratory: Collect blood for hematology within1 day prior to each pralatrexate dose. Within 1 day prior to the fourth dose of each subsequent cycle, collect blood for hematology and chemistry.

6. If the patient is not experiencing any AEs that warrant treatment modification, administer pralatrexate IV push over 3-5 minutes.

9.2.6 Early Study Termination Visit

The procedures outlined below 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.

1. Complete the response evaluation procedures in Section 9.2.5.1 if the following occurs:
   - The patient terminates in cycle 1 and has received at least 1 dose of pralatrexate.
   - The patient terminates during any cycle of pralatrexate and it has been $\geqslant$ 10 weeks since protocol-required response assessments are obtained (prior to cycle 2-4 and every even cycle thereafter during the treatment phase or every 3 months in the follow-up phase), and subsequent treatment for T-cell lymphoma has not been initiated.
2. Record concomitant medications.
3. Record AEs and attribution.
4. Review and collect the patient's diary of folic acid administration.
5. Perform a physical examination.
6. Assess and record ECOG Performance Status.
7. Local laboratory: Collect blood for hematology and chemistry (including LDH).

9.2.7 Safety Follow-up Visit

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. The following procedures and evaluations should be performed:

1. Record concomitant medications.
2. Record AEs and attribution.
3. Review and collect the patient's diary of folic acid administration.
4. Instruct patient to discontinue folic acid.
5. Perform a physical examination.
6. Assess and record ECOG Performance Status.
7. Local laboratory: Collect blood for hematology and chemistry.
8. If disease progression has not been previously documented, and subsequent treatment for T-cell lymphoma has not been initiated, complete the response evaluation procedures (see Section 10.2.5.1) if:

- The patient terminates in cycle 1 and has received at least 1 dose of pralatrexate.
- It has been ⩾ 10 weeks since protocol-required response assessments are obtained (prior to every even cycle during the treatment phase).

9. Record subsequent treatment for T-cell lymphoma, if applicable.

9.2.8 Routine Follow-up Visit

After the Safety Follow-up Visit, routine follow-up visits will be based on standard clinical care. All subjects who received at least 1 dose of pralatrexate are to attend routine follow-up visits, which will occur every 3 months (+/-2 weeks) after the safety follow-up visit till two years after the last dose of pralatrexate to collect the information of progression of disease or subsequent treatment for T-cell lymphoma initiation, as well as survival.

The frequency of response assessments for those subjects who sustain a CR for at least 1 year will be based on the institution's standard of care and will no longer be required every 3 months.

Once progression of disease has been documented or subsequent treatment for T-cell lymphoma has been initiated, routine follow-up visits contacted by telephone for information of survival will be required. Subjects who achieve a CR and proceed to stem cell transplant will continue to be followed for subsequent therapy, and survival. The following procedures/evaluations should be performed at each routine follow-up visit.

1. Record study treatment related AEs.
2. Evaluation of response (see Section 9.2.5.1, item 1 for tests and procedures).
3. Record all subsequent treatment for T-cell lymphoma.
4. If applicable, record date of death.

10 Study treatments and concomitant therapies

10.1 Study Treatments

The start of study treatment is defined as the initiation of pralatrexate. The eligible subjects begin to administrate vitamin supplementation at screening phase.

10.1.1 Vitamin Administration [(Non-Investigational Medicinal Product (NIMP)]

Vitamin supplementation should be initiated at least 10 days prior to the study treatment. Vitamin supplementation will consist of vitamin B12 1 mg intramuscular (IM) q 8-10 weeks and folic acid 1.2mg by mouth (PO) once a day (QD). Once the patient is on-study, the dosing of vitamin supplementation must adhere to the schedule defined by the protocol. If a patient vomits within 15 minutes of taking the folic acid tablet, another dose should be taken the same day.

Once pralatrexate is permanently discontinued, vitamin supplementation will continue for at least 1 month after the last pralatrexate dose, or longer at the discretion of the investigator.

Vitamin B12 and folic acid will be supplied by the study sponsor. Treatment administration will be documented and records maintained by the study staff. Patients will be asked to record self-administration of folic acid in a diary to be reviewed by study staff during the course of the study.

10.1.2 Pralatrexate Administration [Investigational Medicinal Product (IMP)]

Pralatrexate will be administered via IV push over 3-5 minutes into a patient IV line containing normal saline (0.9% sodium chloride [NaCl]).

Pralatrexate will be administered at a dose of 30 mg/m^2/week for 6 weeks followed by 1 week of rest in a 7-week cycle. Pralatrexate administration occurs once a week during week 1 through week 6 of each cycle.

Dose omissions and/or reductions will be allowed according to the criteria described in Section 10.5.

10.2 Identity of Investigational Medicinal Product(s)

10.2.1 Pralatrexate Formulation

The pralatrexate drug product will be supplied by the sponsor and will have been tested and released according to established specifications. Pralatrexate is formulated as a sterile solution for injection and will be supplied in single-use glass vials containing an isotonic parenteral solution at a concentration of 20 mg/mL of pralatrexate. The osmolality of pralatrexate injection is 280~300 mOsmol/kg. The formulation is a clear yellow solution.

10.2.2 Storage and Handling

Pralatrexate is a cytotoxic agent. The institutional, local, and all applicable policies and procedures should be followed for proper handling and disposal of chemotherapy drugs.

Pralatrexate should be stored refrigerated at 2-8°C (36-46°F) and protected from light. Pralatrexate contains no bacteriostatic agent; each vial is for single-use only. Vials of pralatrexate should be stored under secured conditions with access limited to authorized study personnel only.

10.2.3 Packaging/Labeling

The contents of the label will be in accordance with all applicable regulatory requirements. Each vial of pralatrexate used in this study will have a label with the following information: generic name, strength of test drug, storage requirements, caution statement regarding new drug for investigational use only, statement specifying vial is for single-use only, lot number, and the name and address of the sponsor and its manufacturer.

10.3 Dosage and Administration

10.3.1 Preparation and Dose Calculation

Caution should be exercised in the handling, preparing, and administering of the solution. The use of gloves and other protective clothing is recommended. If pralatrexate comes in contact with the skin, immediately and thoroughly wash with soap and water. If pralatrexate comes in contact with mucous membranes, flush thoroughly with water.

The stock pralatrexate solution should be infused at the original concentration of 20 mg/mL.

The BSA will be calculated based on the patient's weight obtained within 3 days prior to the first pralatrexate dose of each cycle (refer to Section 18.5). The patient will receive the same pralatrexate dose throughout the 6 weeks of treatment within a cycle unless the patient experiences a $\geqslant$10% change in weight. The volume to be infused will be based on the following calculation:

$$\text{Volume (mL)} = \frac{\text{(Patient BSA [m}^2\text{]) x (pralatrexate dose [mg/m}^2\text{])}}{\text{20 mg/mL (pralatrexate concentration)}}$$

Subjects with a BSA > 2 m^2 can be treated either at actual BSA or at BSA = 2 m^2, at the discretion of the investigator.

10.3.2 Administration of Study Drug

Pralatrexate is supplied as a preservative free, sterile, isotonic, nonpyrogenic clear yellow aqueous solution contained in a single-use clear glass vial for IV administration. Before administration, pralatrexate vials should be inspected for abnormalities such as cracks, sediments, crystals, turbidity, articulate matter or discoloration etc. If any abnormalities are noted, the sponsor should be notified and the vial should not be used. Appropriate procedures for cytotoxic agents should be followed for administration of pralatrexate.

Pralatrexate will be administered as an intravenous push over 3-5 minutes via the side port of a free-flowing 0.9% Sodium Chloride Injection, intravenous line. The calculated dose of Pralatrexate should be aseptically withdrawn into a syringe for immediate use. If the pralatrexate injection is interrupted or delayed, the administration should be restarted as soon as possible. When available, the 2-part, lot-number sticker should be removed from the pralatrexate vial and placed on the patient's source documents for each vial of pralatrexate used.

10.4 Treatment Duration

Pralatrexate administration will continue until 24 months of pralatrexate have been administrated, or the patient experiences any of the following:

- Development of disease progression

- Initiation of radiotherapy or systemic therapy for T-cell lymphoma
- Development of an AE indicating intolerance of the lowest study dose allowed (20 mg/m^2/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 patient's participation
- Investigator decision to withdraw the subject
- Subject withdraws consent
- Pregnancy of the subject
- Noncompliance with trial treatment or procedure requirements
- Administrative reasons

All subjects will be followed for at least 30 days after their last dose of pralatrexate for safety. Subjects who discontinue pralatrexate and have received at least 1 dose of pralatrexate are to attend the Safety Follow-up Visit and complete the Routine Follow-up Visit procedures.

10.5 Treatment Modifications of Pralatrexate

Management of severe or intolerable adverse reactions may require dose omission, reduction, or interruption of pralatrexate administration. Dose omissions and/or reductions will be allowed according to the criteria outlined below in Table 2, Table 3, and Table 4.

Complete blood cell counts and severity of mucositis should be monitored weekly. Serum chemistry tests including renal and hepatic function, should be performed prior to the start of the first and fourth dose of a given cycle.

The following conditions must to meet prior to administering any dose of pralatrexate:

- Mucositis should be $\leqslant$ Grade 1
- Platelet count should be $\geqslant$ 100,000/μL (or 100 $\times$ 10^9/L) for first dose and $\geqslant$ 50,000/μL (or 50 $\times$ 10^9/L) for all subsequent doses
- Absolute neutrophil count (ANC) should be $\geqslant$ 1,000/μL (or 1 $\times$ 10^9/L)

The dose of pralatrexate will be 30 mg/m^2/week, which can be reduced to 20 mg/m^2/week in the event of a treatment-related AE. No further dose reductions are allowed. If the patient develops an AE indicating intolerance of this lowest dose of 20 mg/m^2/week, the patient will be discontinued from study treatment. There will not be re-escalation of the pralatrexate dose once a dose reduction has occurred.

Pralatrexate administration occurs once a week during week 1 through week 6 of each cycle. If an AE occurs that prevents the administration of pralatrexate on the scheduled dosing day (+/- 2 days), the dose will be omitted that week and the patient will be reassessed the following

week to proceed to the next dose of the cycle. Omitted doses will not be made up at the end of the cycle.

If pralatrexate administration is delayed for more than 2 days within a week (eg, administration on a Thursday instead of Monday) due to administrative reasons (eg, vacation, holiday, etc.) the dosing schedule for the subsequent weeks should be adapted to continue on the new administration day within the week (eg, on Thursdays rather than on Mondays).

Once pralatrexate is permanently discontinued, vitamin supplementation will continue for at least 1 month after the last pralatrexate dose, or longer at the discretion of the investigator.

All treatment-emergent AEs will be managed per the investigator's judgment or the site's clinical standard of care.

Subjects will be monitored for safety throughout the study and at specific time points. If safety concerns arise, the pralatrexate dose administered to subjects will be revisited.

10.5.1 Hematological Toxicities

Treatment modification for hematological toxicities is as follows:

Table 2 Pralatrexate Treatment Modifications for Hematological Toxicities

Hematological Parameter	Duration of Toxicity	Action	Dose upon Restart
Platelets < 50,000/μL (or 50 × 10^9/L) on day of treatment	1 week	Omit dose	Continue prior dose
	2 weeks	Omit dose	20 mg/m^2
	3 weeks	Treatment discontinuation	
ANC 500~1,000 /μL (or 0.5-1 × 10^9/L) and no fever	1 week	Omit dose	Continue prior dose
ANC 500~1,000 /μL (or 0.5-1 × 10^9/L) with fever or ANC < 500/μL (or 0.5 × 10^9/L)	1 week	Omit dose, give G-CSF or GM-CSF support	Continue prior dose with G-CSF or GM-CSF support
	2 weeks or recurrence	Omit dose, give G-CSF or GM-CSF support	20 mg/m^2 with G-CSF or GM-CSF support
	3 weeks or 2nd recurrence	Treatment discontinuation	

ANC: absolute neutrophil count

10.5.2 Non-Hematological Toxicities

For all instances of mucositis, dose adjustments will be made as follows:

Table 3 Pralatrexate Treatment Modifications for Mucositis

Mucositis Grade[a] on Day of Treatment	Action	Dose upon Recovery to ⩽ Grade 1
Grade 2	Omit dose	Continue prior dose
Grade 2 recurrence	Omit dose	20 mg/m^2
Grade 3	Omit dose	20 mg/m^2
Grade 4	Treatment discontinuation	

a: Per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 4.03)

For all other non-hematological toxicities excluding nausea/vomiting, dose adjustments will be made as follows:

Table 4 Pralatrexate Treatment Modifications for All Other Non-hematological Treatment-related Toxicities

Toxicity Grade[a] on Day of Treatment	Action	Dose upon Recovery to ⩽ Grade 2
Grade 0-2	No change in pralatrexate dose	—
Grade 3	Omit dose	20 mg/m^2
Grade 4	Treatment discontinuation	—

a: Per National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 4.03)

10.6 Response Evaluation

10.6.1 Timing of Response Evaluations

All assessment techniques documenting disease status at screening must be repeated at every protocol-required time point for response evaluation.

Response evaluation will occur at the following study time points:

- Treatment Phase: 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).

- Safety Follow-up Visit (collect under the following conditions provided that subsequent treatment for T-cell lymphoma has not been initiated):

  - The patient discontinues in cycle 1 and has received at least 1 dose of pralatrexate.

  - The patient discontinues during any subsequent cycle of pralatrexate and it has been ⩾10 weeks since protocol-required response assessments are obtained.

- Routine Follow-up Visit: Every 3 months (+/-2 weeks) after the safety follow-up visit until progression of disease has been determined or subsequent treatment for T-cell lymphoma has been initiated.

- Early Termination Visit:

  - The patient terminates the study in cycle 1 and has received at least 1 dose of pralatrexate.

  - The patient terminates the study during any subsequent cycle of pralatrexate or during routine follow-up visits, and it has been ⩾10 weeks since protocol-required response assessments are obtained, and subsequent treatment for T-cell lymphoma has not been initiated.

10.6.2 Required Procedures/Scans/Tests

The following procedures/tests are to be performed for evaluation of response:

1. Radiographic imaging:

   a. Contrasted-enhangced CT of chest, neck, abdomen, and pelvis. For detailed technical requirements, please refer to the site imaging manual issued by central imaging lab.

   b. Other imaging techniques documenting disease site other than chest, neck, abdomen, or pelvis, if applicable.

   c Unscheduled imaging exams at the discretion of physician, which may impact the response evaluation.

2. Physical examination to assess liver, spleen, lymph nodes, and skin. Include medical photography with ruler measurements for documentation of any skin lesions.

3. Local laboratory: Collect blood for LDH.

4. If the patient's screening bone marrow biopsy/aspirate results were positive or indeterminate and the patient has a confirmed CR by imaging, a repeat bone marrow biopsy and aspirate assessment must be performed and the slides should be submitted for central pathology review. If bone marrow aspirate flow cytometry has been performed, send result reports for central pathology review. Once a patient's bone marrow is negative for lymphoma, the bone marrow biopsy will be repeated only when clinically indicated unless it is the patient's only site of disease.

5. A tumor biopsy may be performed if needed to confirm a response evaluation.

6. If peripheral blood flow cytometry has been performed, send result reports to the central pathology review.

10.6.3 Review of Response

Response will be assessed according to the IWC (Appendix 18.4).

All treatment responses will be eventually evaluated by the Independent Central Review Committees as described in the Study Charters.

All radiographic images and digital photographs for subjects with cutaneous disease will be sent to the Independent Central Imaging Laboratory for the independent Central Radiology Review. The details will be described in the Site Imaging Manual and Independent Radiology Review Charter.

If applicable, all slides of tumor biopsies, core bone marrow biopsies or bone marrow aspirate, and results of peripheral blood flow cytometry will be collected for Central Pathology Review as confirmation as described in Site Pathology manual and Independent Pathology Review Charter.

Independent Central Oncology Review will be conducted by utilizing International Working Group Criteria (IWC, see appendix 18.4). The final response review will be performed by combining relevant clinical evidences (e.g., physical examination findings of liver and spleen etc.), Laboratory results (e.g., LDH), central radiology review results and central pathology review results. The details will be described in the Central Oncology Reviewer Charter.

Detailed description and measurement of tumor burden and eventual evaluation of the treatment response, will be reported through the Independent Response Central Review. However, the investigators will also assess response according to the IWC but will only report their overall response evaluation on the CRF.

10.6.4 Disease Progression

PD should be documented according to the site's standard procedures. If objective PD has been clearly documented, a confirmatory assessment is not required.

Once PD has been documented or subsequent treatment for T-cell lymphoma has been initiated, response assessments will no longer be collected.

10.7 Treatment Compliance/Drug Accountability

The Investigator and study staff will be responsible for the accountability and record maintenance of all clinical supplies (dispensing, inventory, and returns) following Sponsor instructions and will adhere to GCP guidelines as well as applicable China specific regulations. At each visit the Investigator must check and document subjects' compliance with taking study treatment(s).

Under no circumstances will the Investigator allow the study treatment(s) to be used other than as directed by this protocol. Clinical supplies will not be dispensed to any individual who is not enrolled and currently participating in the study.

10.8 Concomitant Medications

All medications administered from signing the informed consent form through the Safety Follow-up Visit will be recorded on the CRF. Additions, deletions, or changes of dosage of medications will also be noted.

10.8.1 Antiemetic Therapy

There is no data evidence to expect drug-drug interactions between pralatrexate and standard antiemetic therapy and no specific antiemetic therapy has yet been proven to be superior over others in the setting of pralatrexate administration. Therefore, prophylaxis and treatment of nausea and vomiting can be administered according to the standard of care within the institution, however administration is not recommended prior to first dose because of the low emetogenity of pralatrexate. Steroids are not allowed for prophylaxis or treatment.

10.8.2 Hematopoietic Growth Factors

Erythropoietin will be allowed if it is judged by the investigator to be in the best interest of the patient (e.g, for subjects with underlying anemia or unacceptable hematologic toxicity). Other hematopoietic growth factors (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF]), with the exception of pegfilgrastim (Neulasta®), are to be administered in accordance with the instructions for treatment modification for hematological toxicities in Section 10.5.1.

10.8.3 Other Supportive Care Medications

The administration of appetite stimulating hormones (eg, megestrol acetate) is allowed to control anorexia and cachexia.

Use of prophylactic antibiotics is allowed and may be administered at the discretion of the investigator.

Transfusions are allowed per the discretion of the investigator.

10.8.4 Radiotherapy, Cytotoxic Therapy, and Biologic or Immune Response Modifiers

No radiotherapy, other cytotoxic agents, biologic, or immune response modifiers (especially thymosin) are to be administered to subjects until study treatment has been discontinued.

10.8.5 Subsequent Treatment

All subsequent treatment data for T-cell lymphoma will be collected until completion of the study. Additional treatment for T-cell lymphoma should not be administered during treatment with pralatrexate.

10.8.6 Therapies Not Permitted

The prior therapies that are not allowed are described in the Exclusion Criteria.

Any form of additional therapy for T-cell lymphoma will not be permitted during treatment with pralatrexate, including radiation therapy, other cytotoxic agents, biologic, immune response modifiers, and herbal products.

While on treatment with pralatrexate, steroids are not allowed for prophylaxis or treatment except:

- As continuation of prior systemic steroid treatment at stable of no more than 10 mg/day or equivalent dose of prednisone
- As continuation of local or Inhaled or intranasal steroids as used prior to study entry
- For treatment of possible Addison's crisis in patients with prior history of steroid use

11 Plasma Pharmacokinetics

Collection of plasma to determine the full PK profile of R-pralatrexate and S-pralatrexate will be performed in 15 subjects at pre-selected sites. Participation in the pharmacokinetic assessment portion of the protocol will be limited to sites with appropriately trained staff and adequate equipment for procuring and processing the specimens.

Plasma will be frozen for subsequent PK analysis. The concentration of R-pralatrexate and S-pralatrexate at each time-point will be determined by liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) methodology using a previous validated assay. See Study Manuals provided by the sponsor for detailed guidance regarding the collection, processing, and shipment of samples.

The collection times for full pralatrexate PK (15 subjects) 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.

12 REFERENCE VALUES

12.1 Physical/Vital Sign Assessments

Vital signs (e.g. blood pressure [systolic blood pressure, diastolic blood pressure], pulse rate, respiration rate and temperature (axillary) will be obtained at the visits designated on the Schedule of Visits and Procedures (Table 1). Blood pressure and pulse rate will be measured after the subject has been sitting for 3 minutes.

Each clinically notable vital sign abnormality has to be recorded on the AE section of the EDC. Table 5 in Appendix 18.2.1 describes parameters for clinically notable vital signs. Additionally, if the change in vital signs qualifies as a SAE it has to be reported to the CRO/Sponsor using the SAE data form (Section 13.2).

12.2 Laboratory Assessments

All scheduled clinical laboratory tests will be performed by local laboratories. Local laboratories will perform tests to qualify subjects for entry into the study and relative safety assessment. Laboratory certification will be included in the clinical study report for this protocol as appendix. The Schedule of Visits and Procedures (Section 9.1) shows the time points at which blood and urine samples will be collected for clinical laboratory tests. Table 6 in Appendix 18.2.2 presents the clinical laboratory tests to be performed.

A laboratory abnormality may qualify as an AE or SAE as described in Section 13.1. Additionally, if the abnormality qualifies as a SAE it must be reported to the Sponsor using the SAE data form (Section 13.2). Table 7 in Appendix 18.2.2 presents the criteria (i.e. upper limit, lower limit criteria for each laboratory parameter) that will be used to identify subjects with markedly abnormal laboratory values.

Values out of the lower normal range do not automatically lead to an exclusion of the subject from the study. The decision to discontinue a subject from the study due to bilirubin or creatinine levels below the lower limit of normal should be based on the medical judgement of the Investigator. Microscopic urinalysis will only be performed when certain parameters of the macroscopic urinalysis show abnormal results.

12.3 Additional Assessments Reference Ranges

Not applicable.

13 SAFETY ASSESSMENTS

Safety assessments will be recorded from the point at which the Informed Consent is signed. These will consist of:

- Monitoring and recording all adverse events (AEs) and serious adverse events (SAEs), observed or volunteered, regardless of suspected causal relationship to the IMP. This includes reactions, interactions, accidents, illnesses, misuse and abuse. Please refer to table 1 section 10.1 for schedule visit arrangement including AE collection.
- Events will be graded for severity according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, 2010.

The obligations and responsibilities with regards to collection, distribution and onward reporting of adverse events and reactions to the appropriate regulatory bodies, committees and other investigators will be carried out in accordance with local and international regulations and are documented in a separate Safety Management Plan.

13.1 Adverse Events (AEs) and Serious Adverse Events (SAEs)

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can be:

- Any unfavourable and unintended sign (including reactions from overdose, abuse, incorrect use of any treatment, or interaction)
- Any new disease or exacerbation of an existing disease (e.g. increase in frequency or worsening in nature)
- Any deterioration in measurements of laboratory values or other clinical tests (e.g. ECG, vital signs or X-ray) that results in symptoms, a change in treatment, or discontinuation from the IMP
- Recurrence of an intermittent medical condition (e.g. headache) not present at baseline
- Other medical events regardless of their relationship to the IMP, such as accidents, falls and any injuries resulting from them.

A Serious Adverse Event (SAE) is any AE that:

- results in death
- is life-threatening (i.e. the subject is at immediate risk of death from the AE as it occurred)
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect (in the child of a subject who is exposed to the IMP)
- is a medically important event or reaction.

Assessment of medically important events:

The Investigator **must** check the list of Important Medical Events (supplied in the Investigator Site File) to determine whether criteria for a SAE is met. Additionally, any event not on this list, but that the Investigator determines is medically important (e.g. if it jeopardises the patient or requires intervention to prevent a serious outcome) should be reported as an SAE.

Grade 4 events from the investigations system organ class, or from another system organ class (SOC) if used synonymously to an investigation result where grading is based mainly on the numerical result of a laboratory test without immediate serious threat to the patient (e.g. SOC Investigation: Neutrophil count decreased or SOC Blood and lympathic system organ class: Neutropenia) should only be reported as a SAE if they fulfil the seriousness criteria per definition given above or the investigator considers the event serious (medically significant). All clinical diagnosis or symptom grade 4 toxicity should normally result in seriousness classification and be reported as an SAE.

Events specific to this protocol that may not require immediate reporting include:

Disease Progression – Natural progression or deterioration of the malignancy under study will be recorded as part of the efficacy evaluation and should not be recorded as an AE/SAE. Signs and symptoms should not be reported as AEs/SAEs if they are clearly related to a relapse or an expected change or progression of the baseline malignant disease.

A SAE must be reported *immediately* (within 24 hours), independent of the circumstances or suspected cause, if it occurs or comes to the attention of the Investigator at any time during the study period. Any SAE with a suspected causal relationship to the IMP occurring at any time after completion of the study must be promptly reported.

The following **mandatory information** must be provided to the Sponsor pharmacovigilance contact within 24 hours for each SAE:

- Protocol number

- Site number
- Subject number
- AE
- IMP(s)
- Investigator's name and contact details

Causality assessment should be completed as soon as possible.

A succinct medical summary narrative should be provided as soon as possible.

Follow-up information should be actively sought until the SAE has resolved or sequelae have stabilised. Additional information e.g. hospital reports or death certificates, may be requested by the Sponsor and should be anonymised/pseudonymised before transmission and subsequently filed in the Investigator Site File.

The medical safety of the subject is of paramount importance when discussing study continuation. Not all SAEs will require the subject to be discontinued from the study.

13.2 Reporting of Adverse Events

See also Figure 2, Appendix Section 18.1.

Reporting period – Events will be recorded from the point at which the Informed Consent is signed until 30 (± 5) days after the last dose of pralatrexate. This includes new AEs that are reported in the 30 (± 5) days following the subject's last dose of pralatrexate. Any AE that is still on-going after 30 (± 5) days after the completion / discontinuation visit will have an outcome of 'on-going' in the CRF, however the Investigator will continue to follow up on-going AEs and record information in the source documents. SAEs will be followed until the event resolves or the event or sequelae stabilise and this information will be reported to the Sponsor using the SAE Data Form.

Medical conditions that are diagnosed at the screening visit will *only* be documented as adverse events if they are known to have started or are suspected to have started after the subject has signed the informed consent form. All other medical findings at the medical examination at the screening visit will be documented as medical history. Medical judgement should be exercised to estimate if a condition is likely to have started between the signing of the informed consent and the date/time of the physical examination.

If the Investigator becomes aware of a SAE after the completion of the study, which may have been caused by an IMP or NIMP used in the study, they should report it to the Sponsor by phone, fax or e-mail.

Screen failures - For subjects who are screen failures, AEs will be recorded on the EDC.

For subjects who receive at least one dose of study medication - All AEs will be collected on the AE section of the EDC. In addition, a note should be made in the source documentation of the subject.

SAEs - All SAEs will be collected on the AE section of the EDC and flagged as serious. A separate paper SAE Data Form should be completed and reported to sponsor within 24 hours since getting SAE information by investigator.

Reporting term - A cluster of signs and symptoms that results from a single cause or that could form a diagnosis should be reported as a single AE (e.g. fever, elevated WBC, cough, abnormal chest x-ray, etc. can all be reported as “pneumonia.”).

Contact - The sponsor drug safety contact phone number/fax number and email address will be stored in the Investigator Site File. Questions relating to Drug Safety and Pharmacovigilance should be addressed to this number or e-mailed.

13.3 Causality Assessment

The question of the relationship of an AE to the IMP should be determined by the Investigator after thorough consideration of all facts that are available.

Assessment of causality is based on considering associative connections (time or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, underlying conditions in the study population, exclusion of other causes, and/or absence of alternative explanations.

The Investigator will be asked if a **reasonable possibility of a causal relationship** to the IMP is suspected**.**

- “Yes” should be selected if there are facts (evidence) or arguments to suggest a causal relationship.
- “No” should be selected if there are no facts (evidence) or arguments to suggest a causal relationship.

Please note that causality assessment of adverse events in the CRF only relates to the IMP(s) named in Section 13.3.

If an AE is related to a non-investigational medicinal product e.g. concomitant therapy only, and not an interaction or effect of the IMP, or to a study procedure, the causality assessment will be “No” (no reasonable possibility of a causal relationship to IMP). The suspected drug or procedure should be indicated in the narrative in such cases.

13.4 Severity Assessment

The Investigator (or medically qualified designee) will evaluate the comments of the subject and the response to treatment to judge the severity of the AE. All adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version [4.03] criteria. Where a specific definition of the severity of an event is not given in the CTCAE grading criteria, the following definitions will be used:

CTCAE Grade	Severity	Description
Grade 1	**Mild**	▫ Minor ▫ Mild symptoms and intervention not indicated ▫ Non-prescription intervention indicated ▫ No specific medical intervention ▫ Asymptomatic laboratory finding only ▫ Radiographic finding only ▫ Marginal clinical relevance
Grade 2	**Moderate**	▫ Intervention indicated ▫ Minimal, local, non-invasive intervention (e.g. packing, cautery) ▫ Limiting instrumental activities of daily living (e.g. shopping; laundry; transportation; conduct finances)
Grade 3	**Severe**	▫ Medically significant but not life-threatening ▫ Inpatient or prolongation of hospitalisation indicated ▫ Important medical event that does not result in hospitalisation but may jeopardise the patient or may require intervention either: • to prevent hospitalisation or • to prevent the AE from becoming life-threatening or potentially resulting in death ▫ Disabling - results in persistent or significant disability or incapacity ▫ Limiting self-care activities of daily living (e.g. getting in and out of bed; dressing; eating; getting around inside; bathing; using the toilet)
Grade 4	**Life threatening**	▫ Life-threatening consequences ▫ Urgent intervention indicated ▫ Urgent operative intervention indicated ▫ Patient is at risk of death **at the time of the event** if immediate intervention is not undertaken
Grade 5	**Death related to AE**	

Source: http://evs.nci.nih.gov/ftp1/CTCAE/Documentation/CTCAE_Governance_2010-03-11.pdf
AEs with CTCAE grade 5 are always serious, and must be reported according to Section 13.1. Special attention should be given to Grade 3 and 4 events and seriousness on numeric values considered as per the guidance in section 13.1.

Any medication necessary for the treatment of an adverse event must be recorded on the Concomitant Therapy Section of the EDC and, if applicable, on the SAE Data Form.

13.5 Pregnancy

Pregnancy occurring in a subject or a male subject's female partner during a clinical study must be reported to the Sponsor using the Pregnancy Notification Form. The CRO/Sponsor will contact the investigator to confirm significant pregnancy information i.e. AEs during pregnancy, the pregnancy outcome, and any events to 3 months post-partum. Female subject will be terminated from the study if pregnancy is confirmed and continues. If the subject or the spouse of a male subject get pregnant, they need to be followed up until at least 3-months post-partum.

13.6 Laboratory Abnormalities

Abnormalities in laboratory test values should only be reported as AEs if any of the following apply:

- **They result in a change in IMP schedule of administration** (change in dosage, delay in administration, IMP discontinuation, **or other medical or treatment intervention** (e.g. anaemia requiring transfusions or hyperglycaemia requiring potassium supplement))
- They are considered as **clinically significant** by the Investigator.

Where possible, the AE description should be the diagnosis rather than the abnormal laboratory value. The same is true if abnormal values reflect a worsening of an underlying condition. Abnormal laboratory values that are present at Screening are not AEs (unless they are a consequence of a Screening procedure). Where an Investigator does not deem an abnormal (or markedly abnormal, see **Table 7** in section 18.2.2) laboratory value to be clinically significant, the reason must be clearly document in the source notes (e.g. normal fluctuation of the disease).

13.7 Vital Signs and Physical Examinations

AEs from vital sign or physical examination assessments include any changes, values or findings (abnormalities):

- which result in medical intervention
- and/or is deemed by the Investigator as **clinically significant**
- and/or meets the clinically notable abnormal criteria (see Table 5 in section 18.2.1).

13.8 ECG Adverse Events

A simultaneous 12-lead resting ECG will be obtained at screening and will be performed during study only if clinically indicated. For consistency, the same physician should read all ECGs from one subject whenever possible. Abnormal test findings as judged by the Investigator as clinically significant should be recorded as AEs.

13.9 Other Safety Considerations/Risk Management

Preventable medication administration errors with an IMP are a potential safety issue and must be reported immediately to the Sponsor/CRO as a protocol deviation. Examples of these include:

- Overdose - This must always be reported, and may additionally (but not always) meet the criteria for an AE/SAE. No specific information is available on the treatment of overdosage of pralatrexate. If an overdose occurs, general supportive measures should be instituted as deemed necessary by the treating physician. Based on pralatrexate's mechanism of action, consider the prompt administration of leucovorin.
- Drug Abuse - Defined as intentional excessive and persistent or sporadic use of a medicinal product which is accompanied by harmful physical or psychological effects. Drug abuse is always a medically important event and subject to immediate SAE reporting.
- Drug Diversion - Defined as study treatment that is sold or given to other persons either deliberately or accidentally. This may include accidental misdirection of study supply into mainstream hospital supplies. Adverse events in persons other than the subject after drug diversion will be processed in the Sponsor's drug safety database.

Any packaging or labelling that has been identified as causing potential risk (e.g. due to similarity with other products or unclear instruction) must be immediately reported to the Sponsor.

14 Statistical Analyses

All data analyses will be performed by the Sponsor or a designated CRO after the study is completed and the database is locked. Statistical programming and analyses will be performed using SAS and/or other validated statistical software as required.

14.1 Statistical Methodology and Analytical Plans

The statistical analyses described in this section will be performed as further outlined in the Statistical Analysis Plan (SAP), which will be finalised prior to database lock and will be included in the clinical study report for this protocol. The final SAP will take into account any amendment to the protocol.

14.2 Statistical Considerations

In general, continuous data will be summarised using the following descriptive statistics: n, mean, standard deviation, median, minimum and maximum. Categorical data will be summarised as the number and percentage of subjects in each category.

Further details of statistical methods and analyses will be documented in the SAP.

14.3 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:

- The absence of any major protocol violations
- The completion of a minimal 3 doses of exposure to the treatment regimen of one treatment cycle

Major protocol violations 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.

14.4 Protocol Violations and Deviations

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

1) Failure to comply with the major inclusion/exclusion criteria.
2) Being non-compliant with study treatments.
3) Taking any prohibited concomitant therapies.

Additional factors excluding subjects from inclusion in the PPP may be included in the SAP for the study. Major protocol violations will be agreed at the data review meeting prior to database lock. Further details will be documented in the SAP.

14.5 Sample Size and Power Considerations

Based on the PROPEL study 29 out of 32 responses (91%) occurred within the first five cycles of treatment. Consequently the data cut-off date for the primary analysis will be defined once all subjects have been treated for 5 cycles.

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.

14.6 Primary Efficacy Variable(s)

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 test for single proportion at two-sided significance level of 5%. The hypotheses under test will be H_0: ORR<15% vs. H_1: 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.

Response rate by International Working Criteria :

Response rate is defined as number of responders divided by number of subjects, where a subject is considered a responder if she/he has obtained a CR, CRu or a PR.

The following procedures/tests will be included in the evaluation of response:

1. Radiographic imaging (use same imaging techniques as screening).
   - CT of chest, neck, abdomen, and pelvis
   - Other imaging documenting disease site other than chest, neck, abdomen, or pelvis, if applicable
2. Physical examination to assess liver, spleen, lymph nodes, and skin. Include medical photography and ruler measurements of any skin lesions. A sum of the longest diameter (LD) for all skin lesions will be calculated.
3. LDH level determination.
4. Bone marrow biopsy and aspirate should be performed and assessed by flow cytometry if the subject had bone marrow involvement with lymphoma prior to treatment and the subject has a confirmed CR by imaging and physical examination.

5. A tumor biopsy could be performed if needed to confirm a response evaluation.
6. Results of peripheral blood flow cytometry if applicable.

Response and progression of disease will be evaluated by using:

1. The IWC proposed by the NCI sponsored International Working Group
2. Bone marrow biopsies should be scored as follows:
   - Negative = no aggregates or only a few well circumscribed lymphoid aggregates and $\leqslant$ 3% blasts.
   - Positive = unequivocally cytologic or architectural evidence of malignancy (percentage of invasion and the lymphoma subtype should be indicated).
   - Indeterminate = increased number or size of aggregates without cytologic or architectural atypia.
3. Measurements of each cutaneous lesions utilizing medical photography and ruler:
   - A sum of the LD for all cutaneous lesions will be calculated and reported as the baseline sum LD and will be used as reference for tumor response
   - Response and progression of cutaneous disease will be evaluated using the following definitions:
     - CR = disappearance of all evidence of disease for at least 4 weeks.
     - PR = 50% or greater decrease in the sum of the LD of each lesion for at least 4 weeks.
     - PD = increase of $\geqslant$ 25% of the LD of any lesion or appearance of new lesions.
     - SD = less than a PR but does not meet criteria for PD.

If it is difficult to distinguish residual disease from normal tissue and confirmation of CR depends on this determination, it is recommended that the residual lesion be investigated (biopsy or fine needle aspirate) before confirming CR status.

If progression is determined at a time point or by a method not defined in the protocol, those data will be sent to central review.

14.7 Secondary Efficacy Variable(s)

Secondary efficacy endpoints are

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

Duration of Response:

Duration of response will be measured from first day of documented response to disease progression or death, whatever comes first. Subjects receiving subsequent therapy, including transplant before PD is documented, will be censored at that time, with a note indicating censoring occurrence, along with reason.

Time to Response:

Time to response will be measured from first day of treatment to the first date of documented response.

Progression Free Survival:

PFS will be measured from treatment day 1 until event or censoring. An event is defined as the earliest of the following: death from any cause or disease progression. Subjects undergoing transplant or any other subsequent therapy prior to documentation of PD will be censored at that time.

Overall Survival:

OS will be measured from treatment day 1 until death or censoring.

It is recognized that the product-limit estimate for PFS may, in fact, lie above that for OS due to censoring PFS at transplant and not censoring OS at transplant. This will be understood as a consequence of the way in which transplant is handled in the statistical analysis of these data.

Secondary time-to-event endpoints (e.g. duration of response, time to 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]). Censoring rules will be detailed in the SAP.

Secondary endpoints based on tumor assessments (e.g. duration of response, time to response and PFS) will be analysed twice, once using the independent review data and once using the investigator assessment data.

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

14.8 Exploratory Efficacy Variables

Not applicable.

14.9 Subject Disposition

The number and percentage of subjects enrolled and the primary reason for screen failure will be summarised for subjects in the enrolled population.

The number and percentage of subjects in each population and the reasons for exclusion from the PPP will be summarised for subjects in the safety population.

The number and percentage of subjects that discontinue the study and the primary reason for discontinuation will be summarised for subjects in the safety population.

The number and percentage of subjects enrolled from each site will be summarised for subjects in the safety population.

14.10 Demographic/Baseline Analyses

Demographic and baseline variables will be summarised for subjects in the safety population.

Age, weight, height, and body mass index will be summarised as continuous data. Gender and race will be summarised as categorical data.

Current medical conditions will be summarised by System Organ Class and Preferred Term.

14.11 IMP Analyses

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

- Number of infusions
- Duration of treatment (weeks) = [(Date of last dose – date of first dose) + 7] ÷ 7
- 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

For subjects who did not receive any amount of a compound, the dose exposure parameters for that treatment (number of infusions, duration of treatment, cumulative dose, dose intensity, relative dose intensity) will be set to 0.

All these variables will be summarised as continuous data. Additionally, the relative dose intensity will be summarised categorised (ie, number and percentage of subjects with relative dose intensity of <60%, 60-<80%, 80-<90%, 90-<110%, ≥110%). Moreover, the number and percentage of subjects with any dose delay and with any dose reduction will be presented.

The number and percentage of subjects treated by cycle as well as the number of cycles received by patient will be presented.

14.12 Concomitant Medications Analyses

Concomitant medications will be assigned an 11-digit code using the World Health Organisation Drug Dictionary (WHO-DD) drug codes. Concomitant medications will be further

coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification.

The number and percentage of subjects taking concomitant medications will be summarised by ATC anatomical class, pharmacological class, pharmacological sub-class and treatment group for subjects in the safety population.

14.13 Safety Analyses/Adverse Outcomes

Safety data that will be evaluated includes adverse events (AEs), laboratory values, and vital signs. Safety data will be summarised for subjects in the safety population. All safety data will be listed.

14.14 Analysis of Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system to give a System Organ Class (SOC) and preferred term for each event.

Only treatment emergent AEs will be summarised. 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.

The number and percentage of subjects reporting any AE will be summarised by the 'preferred term' nested within the SOC. In addition, the number of reported AEs will be summarised.

AEs will be summarised by worst severity and relationship to IMP. In addition, severe AEs, AEs leading to death, serious AEs, AEs leading to discontinuation from study, AEs requiring additional therapy, AEs leading to dose reduction, and AEs leading to dose interruption will be summarised.

14.15 Laboratory Values

Clinical laboratory data to be summarised includes haematology, blood chemistry, and urinalysis. Appendix Section 18.2.2 Table 7 lists the ranges applied for this study.

Clinical laboratory results recorded at each visit and change from baseline to each visit will be summarised as continuous data for each parameter. 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 summarised 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. The number and percentage of subjects reporting markedly abnormal values will be

summarised for each parameter. Each subject can be counted once in the parameter high and the parameter low categories, as applicable. 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.

14.16 Vital Signs

Vital sign parameters to be summarised 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 summarised as continuous data for each parameter. Appendix Section 18.2.1 Table 5 lists the abnormal ranges applied for this study.

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 summarised using shift tables to evaluate categorical changes from baseline to end of study with respect to reference range values (lower than, within, higher than).

Vital sign values after first dose of IMP will be evaluated for clinically notable abnormalities. The number and percentage of subjects reporting clinically notable abnormalities will be summarised for each parameter by treatment group. Each subject can be counted once in the parameter high and the parameter low categories, as applicable.

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.

14.17 ECG

If applicable, ECG results recorded at each visit and change from baseline to each visit will be summarised as continuous data for each parameter.

Clinically significant ECG findings as determined by the Investigator will be reported.

14.18 Other Special Tests

None planned. All analyses, including any further analyses not yet described in this study protocol, will be pre-specified and described in the SAP.

14.19 Pharmacokinetic Measurements and Analysis

14.19.1 Drug Concentration Measurements and Analysis

Plasma concentrations of R-pralatrexate and S-pralatrexate will be quantified by liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) methodology using a previously validated assay.

14.19.2 Pharmacokinetic Measurements and Analysis

Plasma concentrations will be listed by analyte (R-pralatrexate and S-pralatrexate) for the subjects in the PK population.

Plasma concentrations for each analyte will be summarised descriptively by nominal time-point and treatment as continuous data (i.e. n, mean, standard deviation, standard error, median, minimum and maximum) for subjects in the PK population.

The plasma concentration data for each analyte for subjects in the PK population will be presented graphically in a number of ways using both a linear and a log-linear scale:

- The mean plasma concentration data will be plotted over time
- For each subject, the individual plasma concentration data will be plotted over time

Pharmacokinetic parameters (AUCt, AUCINF, Cmax, Ctrough, tmax, LambdaZ, t1/2Z, CLss, Vdss) will be listed by analyte for subjects in the PK population, if data permit. Data excluded from the PK analysis will be flagged with an asterisk.

Pharmacokinetic parameters (AUCt, AUCINF, Cmax, Ctrough, tmax, LambdaZ, t1/2Z, CLss, Vdss) for R-pralatrexate and S-pralatrexate will be derived using noncompartmental analysis (NCA) method (WinNonlin® Version 6.3, Pharsight Corporation, St. Louis, MO, USA). Concentration values below the lower limit of quantitation (LLOQ) will be set to zero prior to the first quantifiable concentration and as missing thereafter. The log linear trapezoid rule will be used in AUC calculations. To derive the extrapolated AUC (%AUCextra), the last observed concentration value above the LLOQ will be used for the calculation. If the %AUCextra is greater than 20% of AUCINF, the value of AUCINF will be reported as “Not Available” (NA). LambdaZ, t1/2 as well as any PK parameters derived from LambdaZ will not be reported if the adjusted R^2 in LambdaZ estimation is less than 0.8. Accumulation in exposure at steady state will also be reported.

Pharmacokinetic parameters (AUCt, AUCINF, Cmax, Ctrough, tmax, LambdaZ, t1/2Z, CLss, Vdss) 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 (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. tmax will be summarized by minimum, maximum and median.

14.20 Interim Analysis

There will be no formal interim analysis.

The primary analysis will be performed based on a data cut-off date defined after all subjects have been treated for 5 cycles. The study report based on the cut-off data will be prepared and used for NDA submission. However, the study will continue till the protocol defined termination criteria.

15 Ethics & Regulatory

15.1 Declaration of Ethical Conduct

This study will be conducted in accordance with the standard operating practices of the Sponsor and CRO, which are designed to ensure adherence to Good Clinical Practice (GCP) guidelines as required by the following:

1. Declaration of Helsinki, 1964 (“Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects”), and all its accepted amendments to date concerning medical research in humans.
2. ICH E6 Guideline for GCP and subsequent notes for guidance (CPMP/ICH/135/95) European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use. (Note for Guidance on Good Clinical Practice, 2002).
3. European Union (EU) Clinical Trials Directive 2001/20/EC on the regulation of clinical trials in the EU and the implementation of GCP.
4. GCP Directive 2005/28/EC

This study will be conducted in accordance with national and local laws of the countries where study sites are located.

The Investigator agrees, when signing the protocol, to adhere to the instructions and procedures described in the protocol and to adhere to the principles of ICH Good Clinical Practice to which the protocol conforms as well as all governing local regulations and principles for medical research.

15.2 Ethical and Regulatory Review

The protocol, any protocol amendments, the patient information sheet (PIS), informed consent form (ICF) and any study related information or documents issued to subjects for recruitment, data recording etc., will be reviewed and approved along with other required documents by the Ethics Committee (EC) and each study site’s local EC before subjects are screened for entry.

The ECs should be constituted and functioning in accordance with ICH E6, Section 3.2, and any local regulations. A list of the EC(s) that provided a positive opinion for this study will be included in the clinical study report for this protocol.

A signed letter of positive opinion regarding the study from the EC Chairman must be sent to the Investigator. The Sponsor/CRO must be provided with a copy prior to study start and the release of any study treatment to the site by the Sponsor or its designee (ICH E6). The Investigators or Sponsor will submit, depending on local regulations, periodic reports and inform the EC of any reportable adverse events (AEs) per ICH guidelines and local EC standards of practice.

SAEs should be reported to the EC in accordance with local regulatory requirements.

In the case of early termination/temporary halt of the study, the Investigator should notify the EC and CA within 15 days and a detailed written explanation of the reasons for the termination/halt should be given. If the EC decides to suspend or terminate the study, the Investigator will immediately send the notice of study suspension or termination by the EC to the Sponsor/CRO.

At the end of the study, the Sponsor should notify the EC and CA within 90 days. The end of the study will be the date of the last scheduled study visit for the last subject in the study. The Sponsor will always also provide the EC/CA with a summary of the study's outcome.

15.3 Subject Information and Consent

Informed consent should be obtained by means of a PIS and Informed Consent Form (ICF), prepared in accordance with ICH E6 Section 4.8.10 and applicable local regulations, written in non-technical language. All subjects and/or their guardians/legally authorised representatives will be provided with oral and written information describing the nature and duration of the study and the procedures to be performed. The subject will be asked to sign and date an ICF prior to any study-specific procedures being performed. No subject can enter the study before his/her informed consent has been obtained. A sample subject ICF used in the study will be included in the clinical study report for this protocol.

As part of administering the informed consent document, the Investigator must explain to each subject and/or their guardian/legally authorised representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any potential discomfort. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The subject should understand the PIS and ICF before signing and dating the ICF. The Investigator or person obtaining consent must also sign and date the form. Each subject will be given a copy of the signed informed consent and written information.

The original signed ICF for each subject will be verified by the Sponsor/CRO monitors and kept in the study centre investigational site files.

15.4 Data Protection and Human Tissue Sampling

Data protection will be carried out in accordance with the Principles of the Data Protection Act (1998) 95/46/EC. This will apply to all study data in whatever format it is collected and recorded.

Any scan data, imaging, ECGs etc., collected for the trial will be retained in the subject's medical notes held with the Investigator.

Samples collected for the purpose of safety analysis will not be retained after analysis.

15.5 Quality Assurance & Inspection Requirements

This study will be organised, performed, and reported in compliance with the protocol, Standard Operating Procedures (SOPs) of the Sponsor and CRO. ICH E6 defines Quality Assurance (QA) as 'all those planned and systemic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded) and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements'. Sponsor QA activity will be undertaken as outlined in the study audit plan. Section 5.19.3(b) of ICH E6 states that the audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to competent authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects and any identified problem(s). QA activities may be outsourced to CROs or independent consultants. The investigator is required to support audit activities, to be available to the auditors upon request and to permit the auditor direct access to source data/documents.

A competent authority (CA) /authorised third party may also wish to conduct an inspection (during the study or after its completion). If an inspection is requested by a CA, the Investigator must inform the Sponsor immediately that this request has been made.

16 Study management Records & Publication

16.1 Protocol Amendments

The Investigator should not implement any deviation from, or changes to the protocol without agreement by the Sponsor and prior review and documented approval from the EC (ICH E6 4.5.2).

Any change to the protocol requires a written substantial or non-substantial protocol amendment. Substantial protocol amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require approval by the

applicable ECs of all sites. These requirements should in no way prevent any immediate action from being taken by the Investigator, or by the Sponsor, in the interest of preserving the safety of all subjects included in the study. If an immediate change to the protocol is felt by the Investigator to be necessary for safety reasons, the Sponsor designee must be notified promptly and the EC for the site must be informed in accordance with the policy of the EC approving the study, local regulations and policies. Changes affecting only administrative aspects of the study do not require substantial protocol amendments or EC approval, but the EC must be kept informed of such changes. In these cases, the Sponsor will send a letter to the EC detailing such changes.

16.2 Record Maintenance and Retention

In order to provide the Sponsor with accurate, complete, and legible case reports, the following criteria are to be maintained in all study related and source documentation:

- All entries are to be typed or printed using a ballpoint pen.
- There are to be no erasures, write-overs, use of correction fluid or tape, and the original entry must remain legible.
- Errors are to be corrected by placing one line through the error. The correct entry should appear next to the error, dated, and initialled by the responsible person making the change. The name of anyone making corrections must appear on the Site Signature Log collected at the beginning of the study and as study assignments change throughout the conduct of the study. Each error is to be corrected separately.
- The Investigator (Principal Investigator or Sub Investigator) must sign and date the CRF where noted. A signature stamp may not be used.
- Changes to any study document that has been previously signed by the Investigator must be initialled and dated by the Investigator after the change is made. Changes made to CRFs via data clarification forms issued by the Sponsor must likewise be signed by the Investigator.

Neither a subject's name nor initials are to appear on documents transmitted to the Sponsor in order to maintain confidentiality. Additional anonymisation/pseudonymisation laws as applicable by country will also be adhered to.

In order to provide the Sponsor/CRO with accurate, complete, and legible data, the following criteria are to be maintained:

- Source documents will be completed according to a source document agreement outlining all the data that is to be collected in the source documents throughout the study.
- EDC entries should be made as close to the visit of the subject as possible.

The circumstances of completion or termination of the study notwithstanding, the Investigator has the responsibility to retain all study documents, including but not limited to the protocol,

copies of EDC, Investigator's Brochure, regulatory agency registration documents, ICFs, and EC correspondence.

The site should plan on retaining study documents for approximately 15 years after completion of the study. This will include copies of the EDC.

It is requested that at the completion of the required retention period, or should the Investigator retire or relocate, the Investigator contact the Sponsor, allowing the Sponsor the option of permanently retaining the study records. Records retained will be stored independently of the Sponsor, and the Sponsor will not be permitted direct access to this data.

16.3 Adherence to the Protocol

The Investigator will conduct the study in strict accordance with the protocol, which has been written to enable the Investigator's compliance with ICH E6, Section 4.

There are to be no waivers to the Inclusion/Exclusion criteria and no Investigator-led deviations from the schedules and procedures set out within this protocol. Any subject whose treatment deviates from the protocol or who is not qualified for study participation may be ineligible for analysis and may compromise the study.

Any unintentional deviation or violation that is discovered should be reported to the Sponsor/CRO immediately. Any deviation of violation that may have an impact upon subject's safety or suitability for the study should be reported to, and discussed with the Medical Monitor.

Subjects who have not signed an IRB/EC approved ICF cannot receive study medication.

The Investigator and research team must comply with the 13 principles of ICH GCP and all applicable local regulatory laws and regulations.

16.4 Discontinuation of Study

The Sponsor reserves the right to discontinue the study for medical or administrative reasons at any time, however not without good cause. Reimbursement for expenses covering subjects, use of live-in facilities, laboratory tests, and other professional fees will be made. The Investigator will refund the excess of payments made in advance.

The Investigator reserves the right to discontinue the study should his/her judgement so dictate. In such an event, final settlement of the grant-in-aid will be adjusted pro rata, and the Investigator will refund the excess of payments made in advance. The Investigator will notify the EC in case of study discontinuation. Study records must be retained as noted above.

16.5 Registration and Publication of Study Summary and Results

If a study design is of the type required for registration in a public database as detailed in the guidance on www.clinicaltrial.gov or www.ClinicalTrialResults.org the study will be registered on a public database according to the Sponsor's SOPs. If required by local legislation the study will also be registered in other public databases.

Following the end of the study the results should be published within a year of product approval for newly registered products, or within a year of completion of the clinical study report (CSR) if the product is already approved. If results are intended for publication in a peer review scientific journal, no detailed results will be published on a public database beforehand.

The site may publish or present the results of this protocol subject to the protection of any patentable rights of the Sponsor or its nominee(s) and subject to the protection of the Sponsor's confidential information. The Sponsor will be furnished with a copy of any proposed publication or presentation at least 60 days prior to submission for review of confidential or patentable information. Upon notice by the Sponsor, however, that the Sponsor reasonably believes that a patent application claiming an invention relating to the IMP(s) made during the performance of the study will be filed prior to such publication, such publication may be delayed for an additional 30 days or until any patent application or applications have been filed, whichever will first occur.

For multi-site studies, it is mandatory that the first publication be based on data obtained from all analysed subjects; therefore Investigators participating in multi-site studies must agree not to present data gathered individually or by a subgroup of sites prior to the full, initial publication, unless this has been agreed to by all other Investigators and the Sponsor. Publication of clinical trial results may include the presentation of such work at national and international congresses, symposia, professional meetings, peer-reviewed journals, and via other appropriate channels. Named authors and contributors to such publications shall be determined by the Sponsor in accordance with both the Company Publication Policy and the criteria as outlined by standard authorship guidelines. Selected Investigators, Consultants and Scientific Advisors may be invited to be named authors on such publications by the Sponsor. If the Investigator/Consultant/Scientific Advisor agrees to participate in the publication as an author, they will be asked to participate in the creation of all versions of the document(s) in question prior to submission or public dissemination. The Sponsor will ensure that any reasonable comments made by the invited author will be incorporated into the publication and that the named author will consent to the publication of the final version of the document. The copyright associated with any publication will be and shall remain the sole property of the Sponsor, unless or until the copyright of the document is transferred to the scientific peer-reviewed journal prior to and as part of the publication process.

17 REFERENCE LIST

Copies of all references will be held in the trial master file.

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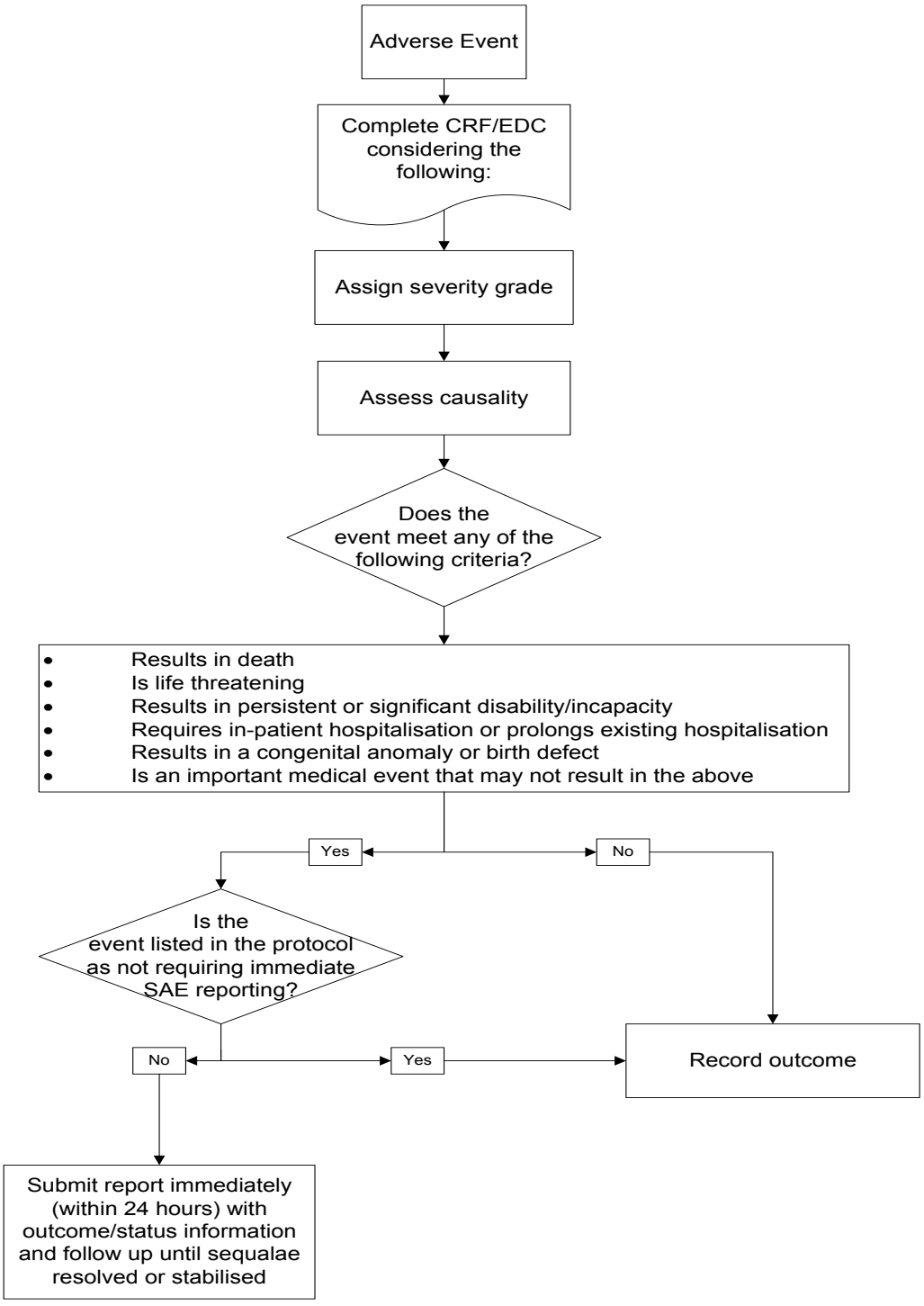
18 APPENDICES

18.1 Adverse Event Reporting Process

Figure 2 Flow diagram for AE reporting



18.2 REFERENCE VALUES

18.2.1 Physical/Vital Sign Assessments

Table 5 describes parameters for clinically notable vital signs.

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.

18.2.2 Laboratory Assessments

Table 6 presents the clinical laboratory tests to be performed.

Table 6 Clinical Laboratory Tests

Category	Parameters
Haematology	RBC, haemoglobin, haematocrit, platelets, and WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Chemistry	
Electrolytes	sodium, potassium, chloride, bicarbonate (HCO_3^-)
Liver function tests	alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl-transferase (GGT), total bilirubin, direct bilirubin
Renal function parameters	blood urea, creatinine
Other	glucose, calcium, albumin, cholesterol, triglycerides, phosphorus (inorganic phosphate), lactate dehydrogenase (LDH), total protein, globulin, uric acid

Table 7 presents the criteria (i.e. upper limit, lower limit criteria for each laboratory parameter) that will be used to identify subjects with markedly abnormal laboratory values. Identification of markedly abnormal lab values not covered by table 7 are subject to the clinical judgement of the investigator.

Table 7 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	$<75.0 \times 10^9$/L or <75000/mm^3	——
Leukocytes	$<3.0 \times 10^9$/L or <3000/mm^3	——
Lymphocytes	$<1.0 \times 10^9$/L or <1000/mm^3	——
Neutrophils	$<1.5 \times 10^9$/L or <1500/mm^3	——
Clinical Chemistry		
Electrolytes		
Sodium	< LLN	>150 mmol/L
Potassium	< LLN	>5.5 mmol/L
Bicarbonate (HCO_3^-)	≤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	——

18.3 ECOG Performance Scale

ECOG Grade	Performance
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 cable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

18.4 The International Workshop Criteria (IWC)

The following criteria are considered anatomic definitions (Table 8). In the future, as additional radiographic, laboratory, and functional studies become more widely available and clearly demonstrate predictive value, they may be recommended as well.

CR requires the following:

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities (e.g., lactate dehydrogenase [LDH]) definitely assignable to NHL.
2. All lymph nodes and nodal masses must have regressed to normal size (≤1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).
3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. For instance, spleens thought to be of normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes. The determination of splenic volume or splenic index by CT scan are cumbersome and not widely used. Any macroscopic nodules in any organs detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.
4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow aspirate and biopsy of the same site. The sample on which this determination is made must be adequate (≥20 mm biopsy core). Flow cytometric, molecular, or cytogenetic studies are not considered part of routine assessment to document persistent disease at the present time. These studies should only be incorporated into trials examining important research questions.

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Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. J Clin Oncol 1999;17(4): 1244.

Table 8. Response Criteria for Non-Hodgkin's Lymphoma

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	> 75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥ 50% decrease	≥ 50% decrease	Irrelevant
	Decrease in liver/spleen	≥ 50% decrease	≥ 50% decrease	Irrelevant
Relapse/progression	Enlarging liver/spleen; new sites	New or increased	New or increased	Reappearance

CR/unconfirmed (CRu) includes those subjects who fulfill criteria 1 and 3 above, but with one or more of the following features:

1. A residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.
2. Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

PR requires the following:

1. ≥ 50% decrease in SPD of the six largest dominant nodes or nodal masses. These nodes or masses should be selected according to the following features: (a) they should be clearly measurable in at least two perpendicular dimensions, (b) they should be from as disparate regions of the body as possible, and (c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase in the size of the other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by at least 50% in the SPD.
4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease.
5. Bone marrow assessment is irrelevant for determination of a PR because it is assessable and not measurable disease; however, if positive, the cell type should be specified in the report, e.g., large-cell lymphoma or low-grade lymphoma (ie, small, lymphocytic small cleaved, or mixed small and large cells).
6. No new sites of disease.

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Stable disease is defined as less than a PR (see above) but is not progressive disease (see below).

Relapsed disease (CR, CRu) requires the following:

1. Appearance of any new lesion or increase by ≥ 50% in the size of previously involved sites.
2. ≥ 50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

Progressive disease (PR, nonresponders) requires the following:

1. ≥ 50% increase from nadir in the SPD of any previously identified abnormal node for PRs or nonresponders.
2. Appearance of any new lesion during or at the end of therapy.

Response Assessment

Response is currently assessed on the basis of clinical, radiologic, and pathologic (ie, bone marrow) criteria.

1. CT scans remain the standard for evaluation of nodal disease. Thoracic, abdominal, and pelvic CT scans are recommended even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL. Studies should be performed no later than 2 months after treatment has been completed to assess response. This interval may vary with the type of treatment, e.g, a longer period may be more appropriate for biologic agents where the anticipated time to response may be greater.
2. A bone marrow aspirate and biopsy should only be performed to confirm a CR if they were initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

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18.5 BSA Calculation Formula

Recommend use below formula to calculate the BSA (applicable to male and female)*:

S=0.0061×Height +0.0124×Weight-0.0099
(S: BSA, unit: M^2; Height, unit: cm; Weight, unit: kg)

*Hu YM, Wu XL, Hu ZH, Ren AH, Wei XQ, Wang XC, et al. Study of formula for calculating body surface areas of the Chinese adults. Sheng Li Xue Bao. 1999;51(1):45-48.