1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7777-J081-205
Study Protocol Title:	A Phase 2 study of E7777 in patients with relapsed or refractory peripheral T-cell lymphoma and cutaneous T-cell lymphoma
Sponsor:	Eisai Co., Ltd. 4-6-10 Koishikawa, Bunkyo-Ku, Tokyo 112-8088, Japan
Investigational Product Name:	E7777/denileukin diftitox
Indication:	Patients with relapsed or refractory peripheral T-cell lymphoma and cutaneous T-cell lymphoma
Phase:	2
Approval Date:	V2.0 19 Feb 2016
GCP Statement:	This study is to be performed in full compliance with Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7777

Name of Active Ingredient: denileukin diftitox

Study Protocol Title

A Phase 2 study of E7777 in patients with relapsed or refractory peripheral T-cell lymphoma and cutaneous T-cell lymphoma

Investigator(s)

Shown in the Attachment

Sites

Approximately 18 sites in Japan

Study Period and Phase of Development

Study period: 32 months (planned)

Phase of development: Phase 2

Objectives

Primary objective:

To evaluate the efficacy of E7777 with objective response rate (ORR) in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL).

Secondary objectives:

1. To evaluate the efficacy of E7777 below.
   - Progression-free survival (PFS)
   - Duration of response (DOR)
   - Time to response (TTR)
   - Complete response (CR) rate
   - Overall survival (OS)
2. To evaluate the safety of E7777.
3. To evaluate the pharmacokinetics (PK) and immunogenicity (anti-E7777 antibody, anti-IL-2 antibody and neutralizing activity of anti-E7777 antibody) of E7777.

Exploratory objectives:

To preliminarily explore the biomarkers in the tumor and blood below.

1. To measure the rate of CD25+ cells in tumor by immunohistochemistry (IHC).
2. To measure the serum soluble IL-2 receptor (sIL-2) and LDH levels.
3. To measure the T-cell subsets in the peripheral blood.

Study Design

This is a multicenter, single-arm, open-label, Phase 2 study to evaluate efficacy, safety, PK, and immunogenicity of E7777 in patients with relapsed or refractory PTCL and CTCL. This study will consist of the following 3 periods: Pretreatment, Treatment, and Follow-up Phases.

The Pretreatment Phase will include informed consent, screening, registration, and baseline assessments. Informed consent will be obtained within 28 days before the start of study drug administration. Subjects who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be entered to this study. Baseline assessments will be performed within 7 days before the study drug administration. Subjects will be confirmed to meet all of the inclusion criteria and not to meet any of the exclusion criteria prior to proceed to the Treatment Phase.

The Treatment Phase will start from the study drug administration on Cycle 1 Day 1 and will last until meeting any of the discontinuation criteria for an individual subject (discontinuation) or Cycle 8 Day 21 (completion), as 3 weeks per cycle. The evaluations at the discontinuation (completion) will be performed within 7 days after the discontinuation (completion).

Tumor evaluation:

In the Treatment Phase, tumor evaluation (nodal/extranodal lesion, liver/spleen enlargement, skin lesion, and peripheral blood lesion) will be performed on screening, Days 15 to 22 (if postponed the beginning of next cycle, by the beginning of next cycle or within 7 days at the time of completion of Cycle 8) of Cycles 2, 4, 6, 8, and at discontinuation. PET scan will be performed on screening, and if positive, Days 15 to 22 (if postponed the beginning of next cycle, by the beginning of next cycle, or within 7 days at the time of completion of Cycle 8) of Cycles 4 and 8, and at discontinuation as possible. Tumor evaluation will be performed in shorter period at confirmation of efficacy or if clinically indicated.

To evaluate bone marrow infiltration, bone marrow biopsy will be performed (if it is difficult, bone marrow aspiration can be performed instead) at screening. If the result is positive or unconfirmed, or bone marrow biopsy is not performed (ie, bone marrow aspiration is performed instead) at screening, bone marrow biopsy will be performed when to confirm CR as best overall response. In addition, bone marrow biopsy can be performed in any subject when clinically indicated.

B symptoms (fever of >38 °C with unknown reason, night sweat [requiring to change bedding], and >10% decrease of bodyweight with unknown reason within 6 months) will be evaluated at the same timepoints with tumor evaluations.

The subjects who discontinued or completed the study drug administration will proceed to the Follow-up Phase. In the Follow-up Phase, the final observation will be performed on 30 days after the last dose of the study drug. Tumor evaluations (except PET and color photography of the skin lesion) will be performed on every 6 to 8 weeks (except the case of discontinuation by disease progression or starting treatment of a next antitumor drug) and survival investigations on every 12 to 16 weeks from the discontinuation (or completion) of the study drug, unless the subject withdrew the informed consent or the sponsor decided to stop the investigation. In the Follow-up Phase, the information about next antitumor drugs/therapies (dosage period and best overall response of the treatment) will be collected as much as possible.

In all registered subjects, PK and immunogenicity (anti-E7777 antibody, anti-IL-2 antibody, and neutralizing activity of anti-E7777 antibody) will be evaluated and blood samples for the measurement of serum sIL-2R, LDH and T-cell subsets in the peripheral blood will be collected according to the specified schedule below.

The disease diagnosis by a central pathologist, and central evaluation of the rate of CD25+ cells in

tumor and CCR4 expression will be performed.

Pharmacokinetics:

Blood samples for non-compartment analysis will be collected at the following timepoints until 6 subjects continued the treatment for at least 5 cycles.

Day 1 of Cycles 1, 3, and 5;
predose (within 180 minutes), 30 minutes after the start of infusion (±5 minutes), immediately after the end of infusion (within 5 minutes), and 30 (±5), 60 (±5), 90 (±5), 120 (±10), and *240 (±10) minutes after the end of infusion. [*Only collected in Cycle 1]

As to subjects who start administrations of the study drug after 6 subjects continued the treatment for at least 5 cycles, blood samples for population PK analysis will be collected at the following timepoints.

Day 1 of Cycles 1, 3, 5, and 8;
predose (within 180 minutes), immediately after the end of infusion (within 5 minutes), 60 to 180 minutes after the end of infusion.

Immunogenicity (anti-E7777 antibody, anti-IL-2 antibody, and neutralizing activity of anti-E7777 antibody):

Blood samples (3 samples each timepoint) will be collected at the following timepoints.

Day 1 of Cycles 1, 2, 3, 5, and 8; predose (within 180 minutes).

At the discontinuation or completion of the study drug.

Serum sIL-2R and LDH:

Blood samples will be collected at the following timepoints.

Day 1 of Cycles 1, 2, 3, 5, and 8; predose (within 180 minutes).

At the discontinuation or completion of the study drug.

T-cell subsets:

Blood samples will be collected at the following timepoints.

Cycles 1 and 2; predose (within 180 minutes) on Day 1, and on Days 8 and 15,

Cycles 3, 5, and 8; predose (within 180 minutes) on Day 1.

At the discontinuation or completion of the study drug.

Central disease diagnosis, the rate of CD25+ cells in tumor, and CCR4 expression by IHC:

For the evaluation of disease diagnosis by a central pathologist, measurement of the rate of CD25+ cells in tumor, and confirmation of CCR4 expression, tumor samples (fixed with formalin and embedded with paraffin) collected before the study drug administration will be submitted to the central measurement laboratory by the last observation. The submitted tumor samples may be used for the development of the diagnostic agent of E7777.

The disease diagnosis judged by the central pathological diagnosis committee will have priority, when it is different from the result of the investigational site.

Number of Subjects

Total of 35 patients with relapsed or refractory PTCL and CTCL (at least 6 patients in CTCL).

Inclusion Criteria

1. Patient with histological diagnosis of PTCL or CTCL as follows.
   - Peripheral T-cell lymphoma-not otherwise specified (PTCL-NOS)
   - Angioimmunoblastic T-cell lymphoma (AITL)
   - Anaplastic large cell lymphoma, ALK positive (ALCL-ALK+)
   - Anaplastic large cell lymphoma, ALK negative (ALCL-ALK–)
   - Enteropathy-associated T-cell lymphoma (EATL)
   - Hepatosplenic T-cell lymphoma (HSTL)
   - Mycosis fungoides (MF)
   - Sézary syndrome (SS)
   - Primary cutaneous CD30＋T-cell lymphoproliferative disorders
   - Subcutaneous panniculitis-like T-cell lymphoma
   - Primary cutaneous γδT-cell lymphoma
   - Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
   - Primary cutaneous CD4+ small/medium T-cell lymphoma
2. Patient who has measurable lesion.

   a. As to patients with PTCL, who have the lesion as all of below
      - Lymph node or extranodal lesion diagnosed as lymphoma by CT scan.
      - Clearly measurable in 2 orthogonal ways by CT scan.
      - ≥1.5 cm in long axis or >1.0 cm in short axis, when long axis were <1.5 cm by CT scan.

   b. As to patients with CTCL, who have the disease as skin lesion (patch, plaque, or tumor)
3. Patient who has previous systemic chemotherapy (except monotherapy of corticosteroid, psoralen and ultraviolet A [PUVA] therapy, interferon, and retinoid).
4. As to patient with CD30+ anaplastic large cell lymphoma, who has received previous therapy of brentuximab vedotin or inappropriate for the drug.
5. Patient who was PD or did not respond (CR or PR) during systemic chemotherapy, or who relapsed or progressed after systemic chemotherapy.
6. Patient who can provide tumor samples for central review of disease diagnosis and CD25+ cell expression.
7. Patient with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.
8. Patient with life expectancy of ≥3 months from starting study drug.
9. Patient with no carry-over of adverse events with ≥Grade 2 of the prior treatment that may affect the safety evaluation of the investigational drug (excluding alopecia).
10. Patient with adequate renal function as below:
    - Serum creatinine ≤1.5×upper limit of normal (ULN).
11. Patient with adequate liver function as below:
    - Total bilirubin ≤1.5×ULN
    - Serum albumin ≥3.0 g/dL (confirm 2 weeks later from dosage of albumin product)

- AST or ALT ≤3.0×ULN

12. Patient with adequate bone marrow function as below:
(confirm 2 weeks or later from last administration of granulocyte colony-stimulating factor [G-CSF] and blood transfusion)
    - Absolute neutrophil count ≥1.5×10^3/μL (1.5×10^9/L)
    - Platelet count ≥7.5×10^4/μL
    - Hemoglobin ≥8.0 g/dL
13. Patient who can be hospitalized from Days 1 to 8 of Cycle 1.
14. Male and female patient ≥20 years of age at the time of informed consent.
15. Patient who has provided written consent to participate in the study.

Exclusion Criteria

1. Patient with central nerves invasion with clinical symptoms or which requires treatment.
2. Patient with active infection requiring treatment.
3. Patient with history of treatment with denileukin diftitox.
4. Patient with history or plan to perform treatment below by starting study drug treatment.
    a. Blood transfusion, albumin product, G-CSF: within 2 weeks
    b. Chemotherapy including corticosteroid use (except continuous use of low amount [as equal as prednisolone 10 mg/day or low] before informed consent) as antitumor therapy, radiotherapy, electron beam therapy, photochemotherapy, systemic retinoid, interferon and histone deacetylase (HDAC) inhibitor: within 4 weeks
    c. Antibody therapy as antitumor therapy: within 12 weeks
5. Patient who participates in other clinical study or ≤4 weeks from last administration of study drug (≤12 weeks in case of antibody).
6. Patient with serious complications or histories as below:
    a. History of myocardial infarction within 6 months before informed consent.
    b. Concurrent cardiac diseases require the treatment, such as ischemic heart disease and arrhythmias etc.
    c. Complications of hepatic cirrhosis.
    d. Complications of interstitial pneumonia or pulmonary fibrosis.
    e. Complications of clinically significant bleeding events (eg, cerebral hemorrhage) or thrombotic events (eg, pulmonary embolism).
7. Patient who has clinical abnormality in electrocardiography such as remarkable prolongation of QT/QTc (eg, more than 500 ms in repeated measurements).
8. Patient with history of hypersensitivity to protein therapeutics.
9. Patient who is positive for HIV antibody, HCV antibody, or HBs antigen. Patient who is positive for HBs or HBc antibody and showing DNA more than sensitivity in HBV-DNA assay.
10. Patient with malignancy of activity other than PTCL or CTCL within 36 months before informed consent (except treated non-invasive melanoma, basal cell carcinoma of the skin or squamous cell carcinoma, intraepithelial carcinoma such as uterine cervix).
11. Woman of childbearing potential or man of impregnate potential who do not agree to use a medically effective method for contraception for periods from before informed consent to during the clinical trial and 30 days later from last administration of study drug.

12. Woman with pregnant or breastfeeding.
13. Patient with allogeneic stem cell transplantation.
14. Patient with ≤6 months from autologous stem cell transplantation by starting study drug treatment.
15. Patient who was decided as inappropriate to participate in the study by the investigator or subinvestigator

Study Treatment(s)

E7777 (9 μg/kg/day) will be intravenously infused in 60 minutes (±10 minutes) once daily from Days 1 through 5 of each cycle in maximum of 8 cycles. Every cycle consists of 3 weeks.

Premedication:

The following premedication will be provided within approximately 120 minutes (within approximately 30 to 60 minutes for oral drugs) before infusion of E7777.

The premedication must be provided in Cycles 1 to 3, but premedication in Cycle 4 and subsequent cycles may be omitted at the discretion of the investigator or subinvestigator.

Investigator or subinvestigator may use appropriate usage or dose, if they consider the same effect to be expected. If adverse events occurred, the premedication regimen can be changed appropriately (eg. increase the dose, change drugs).

- Acetaminophen: 500 mg, orally
- Diphenhydramine: 20 mg, d-chlorpheniramine 5 mg, or chlorpheniramine 10 mg, intravenously
- Dexamethasone: 4 to 8 mg, intravenously
- An antiemetic agent according to the clinical practice of each investigational site.

Also, following procedures will be provided before and after E7777 administration.

- Before and after each infusion of E7777, 250 to 500 mL of physiological saline (or an intravenous fluid preparation selected by the investigator or subinvestigator) will be intravenously infused.
- For patients at risk for tumor lysis syndrome, prophylactic treatment (treatment of allopurinol or rasburicase and intravenous fluids, etc.) should be considered.

Dose interruption criteria:

Administration of E7777 will be skipped on that day if ≥Grade 3 toxicity related to drug (except lymphopenia, Grade 3 abnormal electrolyte, or other abnormal clinical test result judged as not clinically significant) is observed before E7777 administration during Days 2 to 5. E7777 administration may be interrupted if judged to be appropriate by investigator or subinvestigator.

To resume the E7777 administration at a later date, the tests related to the reason of dose-skipping should be performed and recovery to ≤Grade 2 must be confirmed. Same dosage is allowed to resume administration in such case.

Criteria for initiating next cycle:

If any of the toxicities related to the study drug in below is observed, initiation of the next cycle must be postponed.

- Serum albumin <3.0 g/dL
- AST or ALT >3.0×ULN

- Total bilirubin >1.5×ULN
- ≥ Grade 3 toxicity (except lymphopenia, Grade 3 abnormal electrolyte, or the other abnormal clinical test result judged as not clinically significant)

Investigator or subinvestigator may postpone the initiation of next cycle by their own discretion. The initiation of the next cycle can be postponed for a maximum of 21 days after the planned date of administration.

Dose reduction criteria:

If a subject meets any of the criteria below, the dosage of E7777 must be decreased to 6 μg/kg/day. Dose increase is not allowed after the reduction.

- Could not start next cycle at planned schedule (in principle, Day 22 of the previous cycle) in 2 consequent cycles by the toxicity related to the study drug.
- Investigator or subinvestigator considers that the dose reduction is needed.

The treatment will be discontinued if the subject meets the criteria above after the dose reduction. However, the continuous administrations of 6 μg/kg/day will be allowed, if the response is observed in the treatment period and the investigator or subinvestigator judges that the continuation of study drug treatment is possible and clinically valuable.

Duration of the Study

Pretreatment Phase:

Informed consent and screening: within 28 days before starting the study drug administration

Baseline: within 7 days before starting the study drug administration

Treatment Phase:

Until meeting any of "Discontinuation criteria for each subject" or completion of Cycle 8 (ie, Cycle 8 Day 21).

The evaluations at discontinuation (or completion) will be performed within 7 days after discontinuation or completion of study treatment.

Follow-up Phase:

The final observation will be performed on 30 days (+7 days) after the last dose of E7777.

In the case of starting treatment of other antitumor drug before the final observation, the data collected within 7 days before starting the next antitumor drug can be used as the final observation data. Tumor evaluation (except the case of discontinuation by disease progression and starting treatment of next antitumor drug) and survival investigations will be continued, unless the subject withdraws the informed consent or the sponsor determines to stop the investigation.

Discontinuation criteria for each subject:

1. Disease progression (PD) is observed.
2. A life-threatening, serious adverse event is observed.
3. The study treatment cannot be resumed within 21 days after the scheduled date of administration of E7777 (in principle, Day 22 of the previous cycle).
4. The subject meets the discontinuation criterion specified in the dose reduction criteria. However, the continuous administrations of 6 μg/kg/day will be allowed, if the response is observed in the treatment period and the investigator or subinvestigator judges that the continuation of study drug treatment is possible and clinically valuable.

5. The subject becomes pregnant or the partner of male subject desires pregnancy.
6. The subject ascertained as inappropriate after the registration (possibilities of continuation of treatment will be discussed with the sponsor as needed).
7. The subject wishes to decline participation in the study or withdraws consent.
8. The subject cannot comply with the protocol-specified procedures, and the investigator or subinvestigator judges inappropriate to continue the study to maintain safety for the subject.
9. The investigator or subinvestigator judges appropriate to discontinue the study for the subject by any other reason.

Concomitant Drug/Therapy

Concomitant use of chemotherapies (including corticosteroids), immunotherapies, radiotherapies, and other antitumor therapies are prohibited.

However, the use of topical corticosteroid (external use) or systemic use of low amount corticosteroid (equivalent to ≤ 10 mg/day prednisolone) is allowed, if it has been contentiously used before the study treatment and where the investigator or subinvestigator judged necessary to continue the drug. It is allowed to use drugs (other than antitumor drugs) intended to alleviate skin symptoms.

Concomitant use of any other study drug is prohibited.

Assessments

Efficacy:

For antitumor activity, investigator or subinvestigator will evaluate overall response and best overall response (the best response among all timepoints) from the result of tumor lymph node (nodal lesion), non-lymph node tumor in viscera (extranodal lesion), liver/spleen enlargement, and bone marrow infiltration according to "Revised response criteria for malignant lymphoma (Cheson, et al., 2007)", and skin lesion, peripheral blood lesion according to "Clinical endpoints and response criteria in mycosis fungoides and Sézary syndrome (Olsen, et al., 2011)". Central review will be conducted by the Imaging Review Committee for nodal and extranodal lesions. In addition, overall responses and the best overall response will be determined by the Efficacy and Safety Evaluation Committee based on the nodal and extranodal lesions reviewed by the Imaging Review Committee and responses on liver/spleen enlargement, bone marrow infiltration, skin lesion, and peripheral blood lesion evaluated by the investigator or subinvestigator.

Primary endpoint of the study is ORR (rate of subjects whose best overall response is CR or PR) judged by the Efficacy and Safety Evaluation Committee.

The items below judged by efficacy judgement committee (except OS) are the secondary endpoint.

- PFS:
  Defined as the term between the date of administration of the first dose of the study drug and the date of the first event (PD or death whatever the reason is). The detail of the censoring rule for PFS will be described in the statistical analysis plan (SAP).
- DOR:
  Defined as the term between the date of confirmation of the first response and the date of confirmation of the PD. The detail of the censoring rule for DOR will be described in the SAP.
- TTR:
  Defined as the term between the date of administration of the first dose of the study drug and the date of confirmation of the first response.

- CR rate:
  Defined as the rate of subjects whose best overall response is CR.
- OS:
  Defined as the term between the date of administration of the first dose of the study drug and the date of death whatever the reason is. The subject who is not confirmed to die will be censored at the early date of either last confirmation of alive or at the cut-off date of the study.

Addition to the evaluation of the overall response described above, the efficacy according to "Revised response criteria for malignant lymphoma" for PTCL and "Clinical endpoints and response criteria in mycosis fungoides and Sézary syndrome" for CTCL will be evaluated and summarized.

Pharmacokinetics (PK):

E7777 PK profile will be evaluated by serum concentration-time curves.

Immunogenicity:

Anti-E7777 antibody, anti-IL-2 antibody, and neutralizing activity of anti-E7777 antibody in serum will be evaluated by qualitative analyses.

Pharmacodynamics (PD):

Serum sIL-2R and LDH will be explored.

PK/PD:

Not applicable.

Safety:

Safety evaluations will include: all adverse events (AEs), serious adverse events (SAEs), the results of hematological and biochemical examinations and urinalysis, ophthalmological test, vital signs, and electrocardiographic (ECG) findings obtained on a regular basis. Safety will be evaluated in accordance with the CTCAE v4.03.

IHC:

The CD25 positive cell rate and CCR4 expression in tumor will be measured for subjects with tumor tissue to be available.

T-cell subsets:

Subsets of T-cells in peripheral blood will be measured (actual counts and ratios of T-cells with CD4+, CD4+/CD25+, CD4+/CD25+/Foxp3+, CD4+/CD7–*, CD4+/CD26–*).
*Only for MF and SS

Bioanalytical Methods

Serum concentrations of E7777 will be measured by using a validated bioanalytical method. Anti-E7777 antibodies, anti-IL-2 antibodies, and neutralizing activities of anti-E7777 antibody will be detected.

Statistical Methods

The cut-off date of the study analyses will be the earlier date of either all subjects have discontinued or completed Cycle 8 of the study, or the best overall response of all subjects on treatments are confirmed to be PR or better. All statistical analyses will be performed after the database is locked and released.

Analysis sets:

Full Analysis Set (FAS):

Defined as the group of subjects who registered in this study and received at least 1 dose of study drug. This group will be the population for the evaluation of efficacy.

Safety Analysis Set:

Defined as the group of subjects who received at least 1 dose of study drug and had at least 1 evaluable post-baseline safety data. This group will be the population for the evaluation of safety.

Pharmacokinetics Analysis Set:

Defined as the group of subjects who received at least 1 dose of study drug and had at least 1 evaluable serum concentration data.

Pharmacodynamics Analysis Set:

Defined as the group of subjects who received at least 1 dose of study drug and had at least 1 each of evaluable pre- and post-baseline PD data.

Efficacy Analyses:

FAS will be the primary analysis population. All efficacy results will be summarized for each disease (PTCL, CTCL) and overall.

Primary Efficacy Analyses:

The rate of subjects whose best overall response is CR or PR is calculated as ORR, and its corresponding 2-sided exact 95% CI is also calculated.

Secondary Efficacy Analyses:

- Analysis of PFS
  PFS will be summarized by Kaplan-Meier method using median with 95%CI.
- Analysis of DOR
  DOR will be summarized by Kaplan-Meier method using median with 95% CI in responders.
- Analysis of TTR
  TTR will be summarized by Kaplan-Meier method using median with 95% CI in responders.
- Analysis of CR rate
  The number and percentage of subjects whose best overall response and its corresponding 2-sided exact 95% CI will be provided.
- Analysis of OS
  OS will be summarized by Kaplan-Meier method using median with 95%CI.

Pharmacokinetic/Pharmacodynamic Analyses:

Pharmacokinetic Analyses:

Plots of E7777 serum concentration versus actual time will be displayed for those samples collected for non-compartmental analysis. PK parameters (including but not limited to the followings) will be derived by non-compartmental analysis of the serum concentration data;

Maximum observed concentration (C_{max}), time at which the highest drug concentration occurs (t_{max}), area under the concentration-time curve (AUC), terminal elimination phase half-life ($t_{1/2}$), volume of distribution at terminal phase (V_z), and total clearance (CL)

E7777 serum concentrations for population PK analyses will be listed.

Serum E7777 concentration data from this study and other studies will be integrated and used to build PK models to explain the observed concentration data using population approach. Additionally, the models may be used to explore the relationship between PK and select demographic variables. The relationship between PK parameters and efficacy/AE endpoints will also be investigated through population PK/PD modeling. For population PK and PK/PD analysis, the details will be described in the separately prepared analysis plan and its report, and the results will not be included in the clinical study report.

Immunogenicity:

The measurement value will be listed for anti-E7777 antibody, anti-IL-2 antibody, and neutralizing activity of anti-E7777 antibody in the Safety Analysis Set.

Pharmacodynamics:

The measurement value (and the change from baseline, if necessary) for each evaluation period will be summarized using the number of subjects, mean, SD, median, minimum and maximum for each disease (PTCL, CTCL) and overall. In addition, the individual plot over time will be prepared by subject.

Immunohistochemistry:

Frequency and percentage of the classified CD25 + cells rate will be calculated for each disease (PTCL, CTCL) and overall in subjects who submitted the tumor sample.

Safety Analysis:

All safety analyses will be performed on the Safety Analysis Set. The TEAEs will be summarized for each disease (PTCL, CTCL) and overall. TEAEs will also be summarized by system organ class (SOC) / preferred term (PT), causality, and severity. With respect to laboratory values, vital signs, and ECG parameters measured at each time point and changes from baseline in these parameters, the summary statistics, frequency, and incidence will be summarized for each disease (PTCL, CTCL) and overall.

Interim Analyses

No interim analysis is planned for this study.

Sample Size Rationale

Thirty-five patients are required to detect lower limit of the 95% confidence interval (CI) that exceed the 5% threshold in ORR, which is the primary endpoint of the study, with the expected ORR is 25% with a statistical power of 90%. In CTCL, 6 or more patient is targeted to evaluate the safety as specific disease.

3 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ADP	adenosine diphosphate
AE	adverse event
AITL	angioimmunoblastic T-cell lymphoma
Ala	alanine
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the serum concentration-time curve
BUN	blood urea nitrogen
Ca	calcium
CCR4	CC chemokine receptor 4
CD122	β-chain, subunit of the IL-2R
CD132	γ-chain, subunit of the IL-2R
CD25	α-chain, subunit of the IL-2R
CHOP	CHOP therapy
CI	confidence interval
CL	total clearance
Cl	chloride
C_{max}	maximum observed serum concentration
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	cutaneous T-cell lymphoma
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
HBc	hepatitis B virus core
HBs	hepatitis B virus surface
HBV	hepatitis B virus
HCV	hepatitis C virus
His	histidine
HIV	human immunodeficiency virus
HL	Hodgkin’s lymphoma

Abbreviation	Term
ICH	International Conference on Harmonisation
IL-2(R)	interleukin-2 (receptor)
K	potassium
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
Met	methionine
MF	mycosis fungoides
Na	sodium
NHL	non-Hodgkin's lymphoma
ORR	objective response rate
OS	overall survival
PET	positron emission tomography
PFS	progression-free survival
PR	partial response
PS	performance status
PT	preferred term
PTCL	peripheral T-cell lymphoma
QTc(F)	QT interval corrected for heart rate (using Fridericia's formula)
SAE	serious adverse event
SAS	statistical analysis system
SD	stable disease
sIL-2R	soluble interleukin-2 receptor
SOC	system organ class
SOP	standard operating procedures
SS	Sézary syndrome
$t_{1/2}$	terminal phase half-life
TEAEs	treatment-emergent adverse events
Thr	threonine
t_{max}	time at which the highest drug concentration occurs
Treg	regulatory T-cell
TTR	time to response
ULN	upper limit of normal
V_Z	volume of distribution at terminal phase
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) constituted and functioning in accordance with Good Clinical Practice (GCP). Any protocol amendment or revision to the ICF will be resubmitted to the IRB for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in CRA[s], change of telephone number[s]). Documentation of IRB compliance with the GCP regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB chairman must be sent to the head of the medical institution with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee. If the IRB decides to suspend or terminate the study, the head of the medical institution will immediately send the notice of study suspension or termination by the IRB to the sponsor.

Study progress is to be reported to IRBs annually (or as required) by the investigator via the head of the medical institution according to GCP. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the investigator and the relevant IRB via the head of the medical institution of any reportable adverse events (AEs) per GCP guidelines and local IRB standards of practice. Upon completion of the study, the investigator will provide the IRB and sponsor via the head of the medical institution with a brief report of the outcome of the study.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects)
- GCP

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, 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.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. It will be confirmed that the subject has signed an informed consent before any tests or assessments relating to the study are performed (ie, before starting the screening). No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB-approved ICF must be prepared in accordance with GCP and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the investigator or subinvestigator (and clinical research coordinator, if needed). The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsor at approximately 18 investigational sites in Japan.

The name and telephone and fax numbers of the sponsor are listed in the Attachment.

7 INTRODUCTION

7.1 Epidemiology and Treatment of the Cutaneous T-cell Lymphoma and Peripheral T-cell Lymphoma

7.1.1 Epidemiology of the Malignant Lymphoma

According to the Ministry of Health, Labor and Welfare Ministry's 2011 patient survey, the total number of patients with malignant lymphoma in Japan was about 55000 per year. According to the "Monitoring of Cancer Incidence in Japan (2011)" of the National Cancer Center, Center for Cancer Control and Information Services, the number of incidence was reported to be about 24000 per year.

Malignant lymphoma is classified into various diseases depending on the surface antigen and morphological characteristics of tumor cells, and prognosis prediction and treatment method are different between the segmented diseases. Malignant lymphoma is classified into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). Cutaneous T-cell lymphoma (CTCL) and peripheral T-cell lymphoma (PTCL), the targets of E7777, are very rare diseases classified as the NHL (Vose, et al., 2008).

7.1.2 Epidemiology of the Cutaneous T-cell Lymphoma (CTCL)

CTCL is a T-cell derived NHL with the main lesion in skin and includes Mycosis fungoides (MF) and Sézary syndrome (SS) as major diseases. The most frequent disease is MF, according to the Ministry of Health, Labor and Welfare Ministry's 2011 patient survey, the number of patients with MF (as C84.0: Mycosis fungoides) was about 1000. The number of patients with SS (as C84.1: Sézary syndrome) was reported to be less than 1000. Also, according to a report on domestic frequencies of malignant lymphoma by disease classification, the proportion of MF and SS in malignant lymphoma was about 0.5% to 1% (Lymphoma Study Group of Japanese Pathologists, 2000； Aoki, et al., 2008), the total number of patients is from 275 to 500, and the number of incidence is considered to be 110 to 220 per year. Furthermore, according to "the results of case survey for skin lymphoma in 2013", the cumulative number of patients registered as MF or SS for 7 years was 1138 patients (163 patients per year) (the Japanese Skin Cancer Society, 2013). Based on these reports, the number of CTCL patients is estimated to be about 1500 at the maximum and the number of incidence is less than 300 per year.

The prognosis of patients with MF and SS, the major diseases of CTCL, varies with stage. The 5-year survival rate was reported to be 94% and 84% in IA and IB (erythema stage), respectively, 78% and 47% in IIA and IIB (squamous infiltration stage), respectively, 47% and 40% in IIIA and IIIB (tumor stage), and 37%, 18%, and 18% in IVA1, IVA2, and IVV (visceral infiltration stage), respectively, and the prognosis of CTCL with IIB or later stage was reported to be particularly poor (Agar, et al., 2010). Thus delaying disease progression by treatment is clinically meaningful. As CTCL often shows symptoms of pain and/or pruritus, treatment not only improves prognosis but also improves quality of life is important.

7.1.3 Treatment of the Cutaneous T-cell Lymphoma (CTCL)

Different treatment option is chosen depending on the stage of CTCL (Japanese Skin Cancer Society and Japanese Dermatological Association, 2010). For early stages of MF (stage IA, IB, or IIA), local therapy such as external use of steroids, ultraviolet irradiation therapy, local radiation therapy, etc. is performed, however if it does not respond to local therapy, biological response modifiers (BRM) treatment including etretinate (not approved for CTCL in Japan) and interferon and chemotherapy are considered. For later stages of MF (stage IIB or later), electron beam irradiation therapy, radiation therapy, BRM treatment, and/or chemotherapy is selected.

Chemotherapy for CTCL is selected from drugs with indications of malignant lymphoma, but their effects are limited. The duration of response of the combination therapy including doxorubicin was reported to be within 6 months in later stage of MF (Grozea, et al., 1979) and that of the recurrent or refractory MF or T-cell lymphoma with skin infiltration was reported to be within 15 months (Zinzani, et al., 2000). Also, the molecular targeted drugs that have indications for CTCL are only vorinostat (histone deacetylase inhibitor) and mogamulizumab (anti-CCR4 antibody) in Japan, and the indication of mogamulizumab is limited to CCR4-positive CTCL.

In the National Comprehensive Cancer Network (NCCN) guidelines in the United States (US), treatment methods similar to those in Japan are generally recommended. Interferon, retinoid, and deacetylase inhibitors are recommended as systemic drug treatment, although IFN-α, bexaroten, and romidepsin have not been approved in Japan.

Denileukin diftitox was recommended for drug treatment of CTCL (NCCN, 2012), but the description of denileukin diftitox has been deleted from V.1.2013 (NCCN, 2013) after it stopped marketing of denileukin diftitox (ONTAK®) in the US.*

As described above, the outcome of treatment for CTCL is not sufficient and the treatment options are limited in Japan compared with the US, so development of a new treatment method is required.

*Since the manufacturing company Lonza's Hopkinson factory (Massachusetts, the US) was closed after GMP warning letter was issued from the FDA to the factory.

7.1.4 Epidemiology of the Peripheral T-cell Lymphoma (PTCL)

PTCL is classified in NHLs, which derived from rear thymus originated T-cell. According to the Ministry of Health, Labor and Welfare Ministry's 2011 patient survey, the number of patients was reported to be less than 1000 and about 1000 in C84.4 (peripheral T-cell lymphoma) and C84.5 (other/unknown T-cell lymphoma), respectively.

Also, according to a report on domestic frequencies of malignant lymphoma by disease classification, the proportion of PTCL-not otherwise specified（PTCL-nos), angioimmunoblastic T-cell lymphoma（AITL), and anaplastic large cell lymphoma

（ALCL) in malignant lymphoma is about 10% to 11% (Lymphoma Study Group of Japanese Pathologists, 2000； Aoki, et al., 2008). According to Section 7.1.1 "Epidemiology of the Malignant Lymphoma" and these reports, the total number of PTCL patients (excluding adult T-cell leukemia/lymphoma) is estimated to be about 5500 to 6000, and the number of incidence is estimated to be about 2200 to 2400 patients per year.

The 5-year survival rate of PTCL is 32% for the major disease of PTCL nos and AITL, and 49% for ALK negative (ALK–) ALCL. It is reported that the prognosis of PTCL is generally poor, except 70% for ALK positive (ALK+) ALCL (Vose, et al., 2008).

7.1.5 Treatment of the Peripheral T-cell Lymphoma (PTCL)

In Japan, clinical practice guideline for hematologic malignancies including PTCL are issued (the Japanese Society of Hematology, 2013) according to NCCN guidelines etc. in the US. The standard primary treatment of PTCL is combination chemotherapy including CHOP therapy (cyclophosphamide, doxorubicin, vincristine, and prednisolone) for both B-cell and T-cell NHL in Japan and other countries (Fisher, et al., 1993)

Primary combination therapy including anthracycline (such as CHOP therapy) respond to about 50% of PTCL patients (AbouYabis, et al., 2011), but for patients with relapsing or refractory after the first therapy, secondary and subsequent standard treatment have not been established.

Hematopoietic stem cell transplantation will be considered for eligible patients, and treatment outcome of autologous hematopoietic stem cell transplantation after chemotherapy for PTCL (excluding ALK+ALCL) has been reported as 5-year survival rate of 51% (Yared and Kimball, 2013). There is not enough evidence for allogeneic hematopoietic stem cell transplantation and its usefulness is not clear. As other treatments, combination chemotherapies such as ICE therapy (ifosfamide, carboplatin, and etoposide) and GDP therapy (gemcitabine, dexamethasone, and cisplatin) and monotherapies as salvage chemotherapy are recommended. However, progression free survival and overall survival of patients with relapsed or refractory PTCL were reported to be 3.7 months (median) and 6.5 month (median), respectively, and it was reported that any treatment did not show superiority (Mak, et al., 2013).

Recently, molecular targeted therapy is also considered, but molecular targeted drugs that have indications for relapsed or refractory PTCL are only brentuximab vedotin (limited to CD30 positive ALCL) and mogamulizumab (limited to CCR4 positive PTCL) in Japan.

In the NCCN guidelines in the US, in addition to brentuximab vedotin, other molecular targeted drugs (pralatrexate, romidepsin, and belinostat) are recommended as second-line therapy for relapsed or refractory PTCL (NCCN, 2015), although those drugs have not been approved in Japan.

Denileukin diftitox was recommended for second-line therapy of PTCL which is not indicated for hematopoietic stem cell transplantation in the guideline V.3.2012

(NCCN, 2012), but the description of denileukin diftitox has been deleted from V.1.2013 (NCCN, 2013) after it stopped marketing of denileukin diftitox (ONTAK®) in the US.

As described above, the outcome of treatment for PTCL is not sufficient and the treatment options are limited in Japan compared with the US, so development of a new treatment option is required.

7.2 Denileukin diftitox（E7777，E7272）

Denileukin diftitox (E7777 and E7272) is a recombinant cytotoxic fusion protein composed of the amino acid sequences for diphtheria toxin fragments A and B (Met1-Thr387)-His and for human interleukin-2 (Ala1-Thr133).

Denileukin diftitox thought to have antitumor activities through specific binding to IL-2 receptor (IL-2R) on malignant cells. Once bound to the cell surface, the fusion protein is internalized by receptor-mediated endocytosis into an endosomal vesicle where it is cleaved by the serine endoprotease furin resulting in release of the diphtheria toxin enzymatic and translocation domains from the IL-2 domain. Upon further cleavage, the enzymatic domain separates from the translocation domain, and moves into the cytoplasm, where it catalyzes the covalent linkage of ADP-ribose to elongation factor-2, resulting in the inhibition of protein synthesis and ultimately cell death (VanderSpek, et al., 1993).

T-cell activation and cellular immune responses are modulated by IL-2 through binding to its corresponding cell surface receptor. These receptors are composed of up to three subunits α (CD25), β (CD122), and γ (CD132). The high affinity receptor is a heterotrimer composed of α, β, and γ subunits, the intermidiate affinity receptor is a heterodimer composed of β and γ subunits, and the low affinity receptor is a monomer only composed of α subunit.

Antitumor activities of denileukin diftitox are expected on malignant cells with or without CD25 expression, since the α subunit is known to upregulate receptor sensitivity to IL2, while dimer of β and γ subunits mainly mediates internalization. Mechanism of action for E7777 and E7272 is shown in Figure 1.

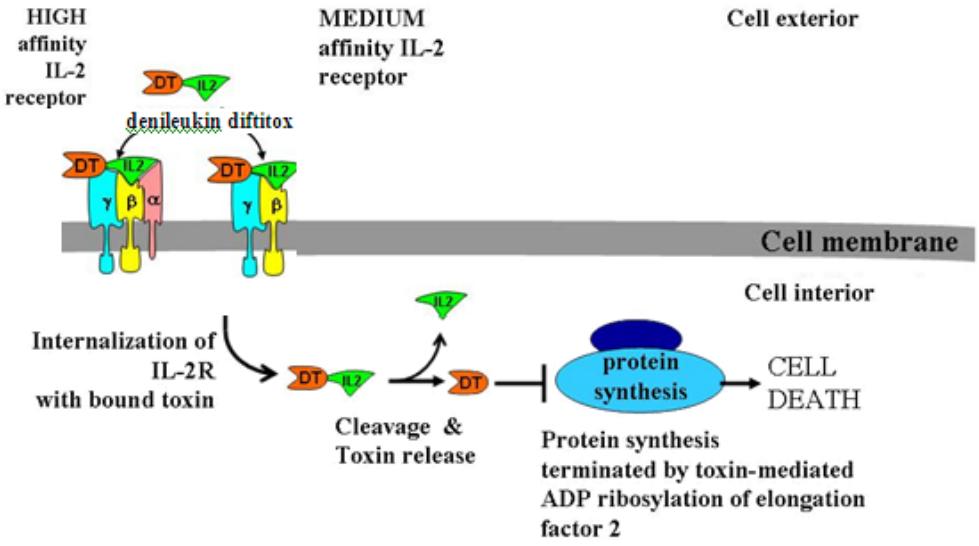

Figure 1 Mechanism of Action for E7777 and E7272

ADP = adenosine diphosphate, DT = diphtheria toxin, IL2 and IL-2 = interleukin 2, and IL-2R = interleukin 2 receptor.

Denileukin diftitox is suggested to target and suppress CD4+CD25+Foxp3+ regulatory T cells (Treg) in nonclinical and clinical studies (Litzinger, et al., 2007, Morse, et al., 2008).

Tregs are immunosuppressive and when present in the tumor microenvironment can contribute to tumor escape from host tumor immune surveillance（Curiel, et al., 2004）. Thus suppression of Tregs is also considered to be a potential mechanism of antitumor activities of denileukin diftitox.

Efficacy of denileukin diftitox has been shown in 3 Phase 3 studies on CTCL and a Phase 1 study of PTCL in foreign countries (Olsen, et al., 2001, Prince, et al., 2010, Prince, et al., 2013, Dang, et al., 2007).

7.3 Origin/History of Development and Future Development Plan

E7272 (ONTAK®) was approved in 1999 by the FDA under the accelerated drug approval program for treatment of patients with persistent or recurrent cutaneous T-cell lymphoma (CTCL) whose malignant cells express the CD25 component of the IL-2 receptor at the dose of 9 or 18 µg/kg/day for 5 consecutive days every 21 days, based on Phase 1/2 study (92-04-01) in CTCL, the other NHL and HL, and Phase 3 study (93-04-10) in CTCL patients with CD25 positive. At the time of approval, it is mentioned that granting of this approval is contingent upon completion of the placebo-controlled Phase 3 study and submission of the results and upon improvement of the purity of the drug product.

In October 2008, E7272 was fully approved by the FDA based on the results of the placebo-controlled Phase 3 study (L4389-11) in CTCL patients with CD25 positive and another Phase 3 study (L4389-14) in CTCL patients who are not eligible to the L4389-11 study (includes CTCL patients with CD25 negative). However, the issue of low drug purity had not been solved yet, E7777, improved purity denileukin diftitox, was to be developed and manufactured.

E7777, improved purity denileukin diftitox, has an improved manufacturing process and therefore has a higher proportion of active monomer and a lower proportion of protein aggregates and misfolded proteins.

Currently, in order to replace E7272 with E7777, single-arm Phase 1/3 study (E7777-G000-302) of E7777 in persistent or recurrent CTCL patients with CD25 positive is ongoing in the United States and Australia. The clinically recommended dose of E7777 in CTCL patients was determined to be 9 μg/kg/day for 5 consecutive days every 3 weeks based on the Lead-in part (Phase 1 part) of the study.

In Japan, Phase 1 study (E7777-J081-101) in CTCL and PTCL patients was completed on August 4, 2015, and the recommended dose of E7777 was determined to be 9 μg/kg/day for 5 consecutive days every 3 weeks, which is the same as above.

7.4 Study Rationale

Since denileukin diftitox had an indication for CD25 positive CTCL in the US, development request for persistent or recurrent CTCL with CD25 (a component of IL-2R) positive malignant cells was issued in May 2010 from the Ministry of Health, Labor and Welfare based on the recommendation as an unapproved and highly required drug in Japan at the 3rd conference of evaluation committee on unapproved or off-labeled drugs with high medical needs (April 2010). Also, E7777 has received orphan drug designation for treatment of PTCL (June 2011) and CTCL (July 2013) in the US.

Since recommended dosage and dose of E7777 in Japanese patients were determined in the domestic Phase 1 study (E7777-J081-101), domestic Phase 2 study in patients with CTCL and PTCL (E7777-J081-205) was planned.

No second-line or subsequent treatment has been established as showing prolongation of PFS or OS in CTCL or PTCL. In addition, with the response to the drug, it is expected to lead to improve associated symptoms such as pain and pruritus with skin lesions in CTCL (Olsen, et al., 2011) and to recovery of B symptoms (fever, night sweat, weight decrease) and to improve the results of posttreatment therapy including transplantation of hematopoietic stem cell (Gouill, et al., 2008). Thus the response itself is thought to be clinically meaningful, and primary endpoint of this study was determined to be objective response rate (ORR).

The evaluation criteria of this study is the overall response of lesions based on “Revised response criteria for malignant lymphoma (Cheson, et al., 2007)” which is the international evaluation criteria on NHL including PTCL and “Clinical endpoints and response criteria in mycosis fungoides and Sézary syndrome (Olsen, et al., 2011)” which is the international

evaluation criteria on CTCL. By using this criteria, the efficacy on both PTCL and CTCL patients is thought to be evaluable within the single study.

Both CTCL and PTCL are malignant lymphomas derived from mature T-cells, and expression of IL-2R has been reported in mature T-cells. Since denileukin diftitox specifically binds to IL-2R and exerts cytotoxic effects, from the viewpoint of the mechanism of action, denileukin diftitox may also be effective in PTCL which is categorized as NHL as same as CTCL.

In addition, it is considered that the efficacy of this drug is not limited to CD25 positive cells from the viewpoint of the mechanism of action, and certain responses were observed also in CD25 negative patients in a foreign clinical study of E7272 (L4389-14) on CTCL patients including CD 25 negative ones and a foreign doctor-initiated study in PTCL patients (Dang, et al., 2007). Thus patients with CD25 positive or negative PTCL and CTCL were to be eligible for this study.

As the patients eligible to this study are extremely few and standard second-line or later therapy has not been established yet, a single-arm clinical study without a control group is considered to be sufficient if the treatment group exceeds the 5% threshold in ORR. Thirty-five patients are required to detect lower limit of the 95% confidence interval (CI) that exceed the 5% threshold in ORR, which is the primary endpoint of the study, with the expected ORR is 25% with a statistical power of 90%. For CTCL, 6 or more patients are minimally required to evaluate the safety as specific disease.

With the above reasons, it is reasonable to conduct the planned Phase 2 study (E7777-J081-205) which is designed to investigate the efficacy, safety, pharmacokinetics, and immunogenicity of E7777 in patients with relapsed or refractory PTCL and CTCL.

8 STUDY OBJECTIVES

8.1 Primary Objective

To evaluate the efficacy of E7777 with objective response rate (ORR) in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL).

8.2 Secondary Objectives

1. To evaluate the efficacy of E7777 below.
   - Progression-free survival (PFS)
   - Duration of response (DOR)
   - Time to response (TTR)
   - Complete response (CR) rate
   - Overall survival (OS)
2. To evaluate the safety of E7777.
3. To evaluate the pharmacokinetics (PK) and immunogenicity (anti-E7777 antibody, anti-IL-2 antibody and neutralizing activity of anti-E7777 antibody) of E7777.

8.3 Exploratory Objectives

To preliminarily explore the biomarkers in the tumor and blood below.

1. To measure the rate of CD25+ cells in tumor by immunohistochemistry (IHC).
2. To measure the serum soluble IL-2 receptor (sIL-2) and LDH levels.
3. To measure the T-cell subsets in the peripheral blood.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

E7777-J081-205 study is a multicenter, single arm, Phase 2 study to evaluate efficacy, safety, PK, and immunogenicity of E7777 in patients with relapsed or refractory PTCL and CTCL.

Study design of this study is shown in Figure 2.

This study will consist of the following 3 phases: Pretreatment, Treatment, and Follow-up Phases.

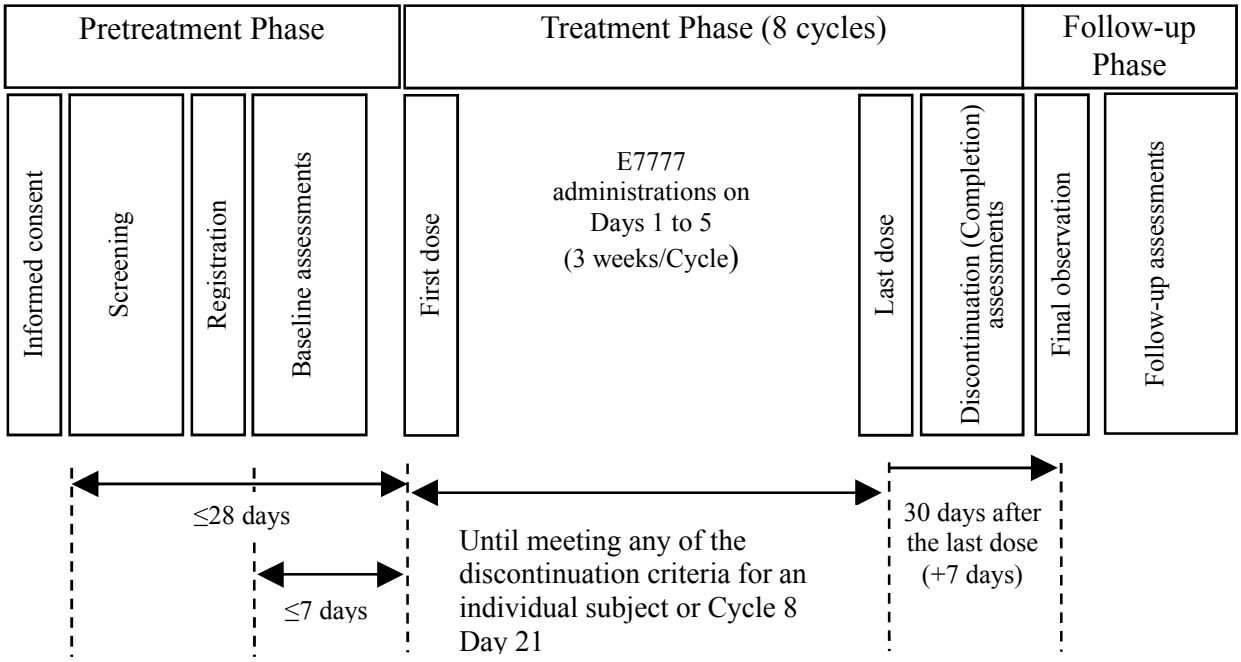

Figure 2 Outline of the Study Design

9.1.1 Pretreatment Phase

The Pretreatment Phase will include informed consent, screening, registration, and baseline assessments.

9.1.1.1 Informed Consent, Screening, and Registration

Informed consent will be obtained within 28 days before the start of study drug administration. Screening assessments will be performed on subject who submitted written informed consent to enroll this study. Subjects who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be registered to this study.

9.1.1.2 Baseline Assessments

Baseline assessments will be performed within 7 days before the study drug administration. Subjects will be confirmed to meet all of the inclusion criteria and not to meet any of the exclusion criteria prior to proceed to the Treatment Phase.

9.1.2 Treatment Phase

The Treatment Phase will start from the study drug administration on Cycle 1 Day 1 and will last until meeting any of the discontinuation criteria for an individual subject (discontinuation) or Cycle 8 Day 21 (completion), as 3 weeks per cycle.

The evaluations at the discontinuation (completion) will be performed within 7 days after the last dose of the study drug. Subjects who discontinued or completed the study drug administration will be proceeded to the Follow-up Phase. Subjects will be in hospitalized during Days 1 to 8 in Cycle 1.

9.1.3 Follow-up Phase

The final observation will be performed on 30 days (+7 days) after the last dose of the study drug. If a subject start receiving a next anti-tumor therapy, etc. before that, any data collected within 7 days before starting such therapy can be considered as the final observation. If the evaluations at the discontinuation is to be performed after 30 days of the last dose of the study drug, the data can be used as the final observation data.

Tumor evaluations (except PET) will be performed on every 6 to 8 weeks (except the case of discontinuation by disease progression or starting treatment of a next antitumor drug) and survival investigations on every 12 to 16 weeks from the discontinuation (or completion) of the study drug, except where a subject withdraws consent or the sponsor chooses to discontinue the survival investigations. In the Follow-up Phase, the information about next antitumor drugs/therapies (dosage period and best overall response of the treatment) will be collected as much as possible.

9.2 Discussion of Study Design, Including Choice of Control Groups

This study has no control groups. This study was designed based on domestic Phase 1 study and “The Guidelines for Clinical Evaluation of Anticancer Drug in Japan (Notification No. 1101001 issued on November 1, 2005)”.

9.3 Selection of Study Population

Total of 35 patients with relapsed or refractory PTCL and CTCL (at least 6 patients in CTCL) will be included in this study. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Patient with histological diagnosis of PTCL or CTCL as follows.
   - Peripheral T-cell lymphoma-not otherwise specified (PTCL NOS)
   - Angioimmunoblastic T-cell lymphoma (AITL)
   - Anaplastic large cell lymphoma, ALK positive (ALCL ALK+)
   - Anaplastic large cell lymphoma, ALK negative (ALCL ALK –)
   - Enteropathy-associated T-cell lymphoma (EATL)
   - Hepatosplenic T-cell lymphoma (HSTL)
   - Mycosis fungoides (MF)
   - Sézary syndrome (SS)
   - Primary cutaneous CD30+ T-cell lymphoproliferative disorders
   - Subcutaneous panniculitis-like T-cell lymphoma
   - Primary cutaneous γδT-cell lymphoma
   - Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
   - Primary cutaneous CD4+ small/medium T-cell lymphoma
2. Patient who has measurable lesion.
   a. As to patients with PTCL, who have the lesion as all of below
      - Lymph node or extranodal lesion diagnosed as lymphoma by CT scan.
      - Clearly measurable in 2 orthogonal ways by CT scan.
      - ≥1.5 cm in long axis or >1.0 cm in short axis, when long axis were <1.5 cm by CT scan.
   b. As to patients with CTCL, who have the disease as skin lesion (patch, plaque, or tumor)
3. Patient who has previous systemic chemotherapy (except monotherapy of corticosteroid, psoralen and ultraviolet A [PUVA] therapy, interferon, and retinoid).
4. As to patient with CD30+ anaplastic large cell lymphoma, who has received previous therapy of vedotin or inappropriate for the drug.
5. Patient who was PD or did not respond (CR or PR) during systemic chemotherapy, or who relapsed or progressed after systemic chemotherapy.
6. Patient who can provide tumor samples for central review of disease diagnosis and CD25+ cell expression.
7. Patient with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0 or 1.
8. Patient with life expectancy of ≥3 months from starting study drug.
9. Patient with no carry-over of adverse events with ≥Grade 2 of the prior treatment that may affect the safety evaluation of the investigational drug (excluding alopecia).
10. Patient with adequate renal function as below:

- Serum creatinine ≤1.5×upper limit of normal (ULN).

11. Patient with adequate liver function as below:
    - Total bilirubin ≤1.5×ULN
    - Serum albumin ≥3.0 g/dL (confirm 2 weeks later from dosage of albumin product)
    - AST or ALT ≤3.0×ULN
12. Patient with adequate bone marrow function as below:
    (confirm 2 weeks or later from last administration of granulocyte colony-stimulating factor [G-CSF] and blood transfusion)
    - Absolute neutrophil count $\geq 1.5\times10^3/\mu L$ ($1.5\times10^9/L$)
    - Platelet count $\geq 7.5\times10^4/\mu L$
    - Hemoglobin ≥8.0 g/dL
13. Patient who can be hospitalized from Days 1 to 8 of Cycle 1.
14. Male and female patient ≥20 years of age at the time of informed consent.
15. Patient who has provided written consent to participate in the study.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Patient with central nerves invasion with clinical symptoms or which requires treatment.
2. Patient with active infection requiring treatment.
3. Patient with history of treatment with E7777.
4. Patient with history or plan to perform treatment below by starting study drug treatment.
   a. Blood transfusion, albumin product, G-CSF: within 2 weeks
   b. Chemotherapy including corticosteroid use (except continuous use of low amount [as equal as prednisolone 10 mg/day or low] before informed consent) as antitumor therapy, radiotherapy, electron beam therapy, photochemotherapy, systemic retinoid, interferon and histone deacetylase (HDAC) inhibitor: within 4 weeks
   c. Antibody therapy as antitumor therapy: within 12 weeks
5. Patient who participates in other clinical study or ≤4 weeks from last administration of study drug (≤12 weeks in case of antibody).
6. Patient with serious complications or histories as below:
   a. History of myocardial infarction within 6 months before informed consent.
   b. Concurrent cardiac diseases require the treatment, such as ischemic heart disease and arrhythmias etc.
   c. Complications of hepatic cirrhosis.
   d. Complications of interstitial pneumonia or pulmonary fibrosis.
   e. Complications of clinically significant bleeding events (eg, cerebral hemorrhage) or thrombotic events (eg, pulmonary embolism).
7. Patient who has clinical abnormality in electrocardiography such as remarkable prolongation of QT/QTc (eg, more than 500 ms in repeated measurements).

8. Patient with history of hypersensitivity to protein therapeutics.
9. Patient who is positive for HIV antibody, HCV antibody, or HBs antigen. Patient who is positive for HBs or HBc antibody and showing DNA more than sensitivity in HBV-DNA assay.
10. Patient with malignancy of activity other than PTCL or CTCL within 36 months before informed consent (except treated non-invasive melanoma, basal cell carcinoma of the skin or squamous cell carcinoma, intraepithelial carcinoma such as uterine cervix).
11. Woman of childbearing potential or man of impregnate potential who do not agree to use a medically effective method* for contraception for periods from before informed consent to during the clinical trial and 30 days later from last administration of study drug.
    *Condom, contraceptive sponge, foam, jelly, diaphragm, intrauterine device (IUD), or use of oral contraception from at least 90 days before starting the study treatment
12. Woman with pregnant or breastfeeding.
13. Patient with allogeneic stem cell transplantation.
14. Patient with ≤6 months from autologous stem cell transplantation by starting study drug treatment.
15. Patient who was decided as inappropriate to participate in the study by the investigator or subinvestigator

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator or subinvestigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. If a subject discontinues study treatment, the subject will enter the Follow-up Phase and complete protocol-specified assessments, and survival investigations unless the subject withdraws consent. If a subject withdraws consent, the date will be documented in the source documents. The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be reported on the CRF. In addition, the date of last dose of study drug will be documented on the CRF.

Subjects who have discontinued or completed the study treatment without progression should have disease assessments (same assessments as the Follow-up Phase) every 6 to 8 weeks from the date of the discontinuation of completion until disease progression is documented or another antitumor therapy is initiated.

All subjects will be followed for survival until death, except where a subject withdraws consent or the sponsor chooses to discontinue the survival investigations, every 12 to 16 weeks from the date of the discontinuation of completion.

9.3.3.1 Discontinuation Criteria for Each Subject:

1. Disease progression (PD) is observed.
2. A life-threatening, serious adverse event is observed.

3. The study treatment cannot be resumed within 21 days after the scheduled date of administration of E7777 (in principle, Day 22 of the previous cycle).
4. The subject meets the discontinuation criterion specified in the dose reduction criteria. However, the continuous administrations of 6 μg/kg/day will be allowed, if the response is observed in the treatment period and the investigator or subinvestigator judges that the continuation of study drug treatment is possible and clinically valuable.
5. The subject becomes pregnant or the partner of male subject desires pregnancy.
6. The subject ascertained as inappropriate after the registration (possibilities of continuation of treatment will be discussed with the sponsor as needed).
7. The subject wishes to decline participation in the study or withdraws consent.
8. The subject cannot comply with the protocol-specified procedures, and the investigator or subinvestigator judges inappropriate to continue the study to maintain safety for the subject.
9. The investigator or subinvestigator judges appropriate to discontinue the study for the subject by any other reason.

9.4 Treatments

9.4.1 Treatments Administered

9.4.1.1 Dose, Dosing Method, and Duration of Dose

E7777 (9 μg/kg/day) will be intravenously infused in 60 minutes (±10 minutes) once daily from Days 1 through 5 of each cycle in maximum of 8 cycles. Every cycle consists of 3 weeks.

The same dose applied within a cycle. Dose recalculation (μg/body) associated with body weight decrease will be allowed before initiating each cycle at the discretion of the investigator or subinvestigator.

9.4.1.2 Premedication:

The following premedication will be provided within approximately 120 minutes (within approximately 30 to 60 minutes for oral drugs) before infusion of E7777.

The premedication must be provided in Cycles 1 to 3, but premedication in Cycle 4 and subsequent cycles may be omitted at the discretion of the investigator or subinvestigator.

Investigator or subinvestigator may use appropriate usage or dose, if they consider the same effect to be expected. If adverse events occurred, the premedication regimen can be changed appropriately (eg. increase the dose, change drugs).

- Acetaminophen: 500 mg, orally
- Diphenhydramine: 20 mg, d-chlorpheniramine 5 mg, or chlorpheniramine 10 mg, intravenously
- Dexamethasone: 4 to 8 mg, intravenously

- An antiemetic agent according to the clinical practice of each investigational site.

Also, following procedures will be provided before and after E7777 administration.

- Before and after each infusion of E7777, 250 to 500 mL of physiological saline (or an intravenous fluid preparation selected by the investigator or subinvestigator) will be intravenously infused.
- For patients at risk for tumor lysis syndrome, prophylactic treatment (treatment of allopurinol or rasburicase and intravenous fluids, etc.) should be considered.

9.4.1.3 Preparation and Administration of the Study Drug

- Water for injection (2.1 mL) will be gently poured into the vial along its wall. ·Mix the solution by gentle swirling (be careful not to foam the contents) until completely resolved to get 2.2 mL of E7777 solution (0.15 mg/mL).
- When using multiple vials, E7777 will be completely resolved to the water in each vial before mixing the solution of multiple vials.
- Haze due to microbubbles may be observed during dissolving, it may disappear by standing. Use only if the solution is clear. If the solution is not clear, colorless, or without visible particulate matter, the solution cannot be used. Use of inline filter is prohibited.
- Administer prepared solutions of E7777 immediately (within 24 hours at room temperature at the latest).
- The E7777 solution can be diluted up to 50 times (3 μg/mL) by saline at room temperature. However, it is not allowed to use a solution diluted to less than 15 μg/mL (10-fold dilution) in plastic syringes. For details of the materials of the equipment that can be used for preparation or administration and acceptable concentrations of E7777, refer to the study drug handling manual.
- E7777 will be intravenously infused in 60 minutes (±10 minutes) once daily from Days 1 through 5 of each cycle.
- Do not mix or simultaneously administer E7777 with other drugs.
- Do not administer as bolus injection.
- Discard unused portions of E7777 immediately

9.4.1.4 Control of Infusion Reactions During the Administration

E7777 can be cause infusion reactions during or after the administration. Therefore, E7777 will be administered under preparations of drugs and equipment, such as adrenaline antipyretic analgestics, antihistamine, corticosteroids, antiemetics, or other medical preparation per local institutional guidelines, which can be used for emergencies.

In the event an infusion reaction is suspected, the investigator or subinvestigator can decide to interrupt the administration of E7777. Administration of E7777 can be resumed if the event returns to baseline under the judgment or investigator or subinvestigator.

9.4.1.5 Dose Interruption Criteria

Administration of E7777 will be skipped on that day if ≥Grade 3 toxicity related to drug (except lymphopenia, Grade 3 abnormal electrolyte, or other abnormal clinical test result judged as not clinically significant) is observed before E7777 administration during Days 2 to 5. E7777 administration may be interrupted if judged to be appropriate by investigator or subinvestigator.

To resume the E7777 administration at a later date, the tests related to the reason of dose-skipping should be performed and recovery to ≤Grade 2 must be confirmed. Same dosage is allowed to resume administration in such case.

9.4.1.6 Criteria for Initiating Next Cycle

If any of the toxicities related to the study drug in below is observed, initiation of the next cycle must be postponed.

- Serum albumin <3.0 g/dL
- AST or ALT >3.0×ULN
- Total bilirubin >1.5×ULN
- ≥ Grade 3 toxicity (except lymphopenia, Grade 3 abnormal electrolyte, or the other abnormal clinical test result judged as not clinically significant)

Investigator or subinvestigator may postpone the initiation of next cycle by their own discretion. The initiation of the next cycle can be postponed for a maximum of 21 days after the planned date of administration.

9.4.1.7 Dose Reduction Criteria

If a subject meets any of the criteria below, the dosage of E7777 must be decreased to 6 μg/kg/day. Dose increase is not allowed after the reduction.

- Could not start next cycle at planned schedule (in principle, Day 22 of the previous cycle) in 2 consequent cycles by the toxicity related to the study drug.
- Investigator or subinvestigator considers that the dose reduction is needed.

The treatment will be discontinued if the subject meets the criteria above after the dose reduction. However, the continuous administrations of 6 μg/kg/day will be allowed, if the response is observed in the treatment period and the investigator or subinvestigator judges that the continuation of study drug treatment is possible and clinically valuable.

9.4.2 Identity of Investigational Product

Study drug will be supplied by the sponsor in labeled containers.

9.4.2.1 Chemical Name, Structural Formula of E7777

- Test drug code: E7777

- Generic name: denileukin diftitox
- Chemical name: 1-388-Toxin (Corynebacterium diphtheriae strain C7), *N*-L-methionyl-387-L-histidine-388-L5 alanine-, (388→2')-protein with 2-133-interleukin 2 (human clone pTIL2-21a)
- Formulation: freeze-dried formulation
- Composition: a vial contains 300 μg of E7777

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

The following information has to be provided. Detailed information on the labeling and packaging of study drug will be included in an Attachment.

- For clinical study use only
- Name and address of the sponsor
- Drug identifier
- Lot number/batch number
- Storage conditions

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. The assigned pharmacist or designee is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained by using either an in-house acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will receive E7777. There is no randomization in this study. Procedure of the study registration is described below.

1. The investigator, subinvestigator, or clinical research coordinator will issue the Subject ID Number to individual subjects who provide signed informed consent for enrollment and record it in “Subject Screening Log.”
2. The investigator, subinvestigator, or clinical research coordinator will screen the subjects and determine subject eligibility based on the inclusion and exclusion criteria. The investigator, subinvestigator, or clinical research coordinator will record the decision on the subject eligibility in the “Subject Screening Log.”

3. For the eligible subjects, the investigator or subinvestigator will record the screening data and subject demography to the Subject Registration Form (an Attachment) and will inform the sponsor.

9.4.4 Selection of Doses in the Study

Currently, single-arm Phase 1/3 study (E7777-G000-302) of E7777 in CTCL patients with CD25 positive is ongoing in abroad. The clinically recommended dose of E7777 in CTCL patients was determined to be 9 μg/kg/day for 5 consecutive days every 3 weeks based on the Lead-in part (Phase 1 part) of the study.

In Japan, Phase 1 study (E7777-J081-101) in CTCL and PTCL patients was conducted and the recommended dose of E7777 was determined to be 9 μg/kg/day for 5 consecutive days every 3 weeks, which is the same as above.

Therefore, the above recommended dose which determined in the E7777-J081-101 study as well as the E7777-G000-302 study will be selected in this study. Administrations of E7777 at 6 μg/kg/day also seems to have efficacies in clinical studies conducted in Japan or other countries, dose reduction to 6 μg/kg/day is allowed in this study.

9.4.5 Selection and Timing of Dose for Each Subject

The selection and timing of the dose for each subject are provided in Section 9.4.1 Treatments Administered.

9.4.6 Blinding

The study will not be blinded.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject during the study (starting at the date of informed consent and until the final observation) will be recorded. The adverse event or medical condition for which the concomitant medication or therapy was administered will be recorded. Drugs used for other than treatments (such as contrast mediums, diagnostic agents, antiseptics, and infusion solution for flushing) will be excepted.

9.4.7.1 Drug-Drug Interactions

No clinical study for drug-drug interaction has been conducted for E7777.

9.4.7.2 Prohibited Concomitant Therapies and Drugs

Concomitant use of other antitumor therapies for the primary disease such as chemotherapy (including corticosteroids), immunotherapy, and radiotherapy is not allowed.

However, the use of topical corticosteroid (external use) or systemic use of low amount corticosteroid (equivalent to ≤ 10 mg/day prednisolone) is allowed, if it has been contentiously used before the study treatment and where the investigator or subinvestigator judged necessary to continue the drug. In such a case, the concomitant steroid medication is allowed as long as the type of steroid, and steroid dose remain the same as what the subject had been receiving for the prolonged period (dose increase is not allowed). It is allowed to use drugs (other than antitumor drugs) intended to alleviate skin symptoms. Concomitant use of any other study drug is prohibited.

9.4.8 Treatment Compliance

The investigator, subinvestigator, or clinical research coordinator will instruct subjects to follow appropriate use of study drug and record the treatment compliance. The CRA will review the treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

The assigned pharmacist (or the designee) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions "Instructions for Handling of Investigational Products and Trial-related Materials" and adherence to GCP guidelines as well as other requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The assigned pharmacist (or the designee) must maintain an accurate and timely record of the following: receipt of all study drugs, administered study drugs to the subject, and return of reconciled study drugs to the sponsor. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs administered/reconciliation log, (c) study drugs accountability log, and (d) documentation of returns to the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority. Upon completion of drug accountability and reconciliation procedures by the assigned pharmacist (or the designee) and documentation of study drugs return with the sponsor, all unused study drugs will be returned to the sponsor. Unused study drugs that are returned from the site are hand-delivered to CRAs and to be returned to the sponsor's designated depot.

Drug accountability will be reviewed by the CRA throughout the study during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the screening. Demography information includes Subject ID Number, date of written informed consent, date of birth (or age), sex, race/ethnicity.

The following information on primary disease and its prior therapies will be collected at Screening and recorded on the CRF.

1. Primary disease
   - Diagnosis (WHO classification)
   - Date of diagnosis
   - Disease stage at the screening
     PTCL: Ann Arbor staging (Carbone, et al., 1971)
     MF/SS: TNMB classification (Olsen, et al., 2007)
     CTCL (except MF/SS): TNM classification (Kim, et al., 2007); TNMB classification will be employed for disease stage.
   - CCR4 expression (positive or negative)
     (A tumor biopsy sample collected before study drug administration will be sent to the central laboratory until the last observation. Results of IHC obtained in the past can be used.)
2. Prior therapies for primary disease
   - Anti-tumor therapy (name of therapy/drug, best overall response, start date, and end date)

9.5.1.2 Assessments in the Pretreatment Phase

9.5.1.2.1 Medical History and Physical Examinations

Medical and surgical history and current medical conditions will be recorded at the screening. All medical history that is considered to have effects on safety, efficacy, or PK by the investigator or subinvestigator and medical conditions that are identified at Screening must be recorded on the CRF.

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 7). Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the screening will be recorded on the CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the CRF.

9.5.1.3 Efficacy Assessments

For anti-tumor activity, investigator or subinvestigator will evaluate overall response and best overall response (the best response among all timepoints) from the result of tumor lymph node (nodal lesion), non-lymph node tumor in viscera (extranodal lesion), liver/spleen enlargement, and bone marrow infiltration according to "Revised response criteria for malignant lymphoma (Cheson, et al., 2007)", and skin lesion, peripheral blood lesion according to "Clinical endpoints and response criteria in mycosis fungoides and Sézary syndrome (Olsen, et al., 2011)" (see an Appendix "Overall Response Evaluation Criteria"). Central review will be conducted by the Imaging Review Committee for nodal and extranodal lesions. In addition, overall responses and the best overall response will be determined by the Efficacy and Safety Evaluation Committee based on the nodal and extranodal lesions reviewed by the Imaging Review Committee and responses on liver/spleen enlargement, bone marrow infiltration, skin lesion, and peripheral blood lesion evaluated by the investigator or subinvestigator.

Primary endpoint of the study is ORR (rate of subjects whose best overall response is CR or PR) judged by Efficacy and Safety Evaluation Committee.

The items below judged by efficacy judgement committee (except OS) are the secondary endpoint.

- PFS:
  Defined as the term between the date of administration of the first dose of the study drug and the date of the first event (PD or death whatever the reason is). The detail of the censoring rule for PFS will be described in the statistical analysis plan (SAP).
- DOR:
  Defined as the term between the date of confirmation of the first response and the date of confirmation of the PD. The detail of the censoring rule for DOR will be described in the SAP.
- TTR:
  Defined as the term between the date of administration of the first dose of the study drug and the date of confirmation of the first response.
- CR rate:
  Defined as the rate of subjects whose best overall response is CR.
- OS:
  Defined as the term between the date of administration of the first dose of the study drug and the date of death whatever the reason is. The subject who is not confirmed to die will be censored at the early date of either last confirmation of alive or at the cut-off date of the study.

Addition to the evaluation of the overall response described above, the efficacy according to "Revised response criteria for malignant lymphoma" for PTCL and "Clinical endpoints and response criteria in mycosis fungoides and Sézary syndrome" for CTCL will be evaluated and summarized.

Tumor evaluation

Tumor evaluations of nodal/extranodal lesion (except skin lesion), imaging of liver/spleen enlargement (CT and PET [^{18}F-FDG PET]), skin lesion (visual examination; color photograph will be taken if there are skin lesions), and lesion in the peripheral blood (count and percent of abnormal lymphocytes [lymphoma cells] among lymphocytes). If astrointesitinal lesions are suspected, endoscopy (and biopsy, if necessary) will be performed
◦

Tumor evaluation (nodal/extranodal lesion, liver/spleen enlargement, skin lesion, and peripheral blood lesion) will be performed on screening, Days 15 to 22 (if postponed the beginning of next cycle, by the beginning of next cycle or within 7 days at the time of completion of Cycle 8) of Cycles 2, 4, 6, 8, and at discontinuation. PET scan will be performed on screening, and if positive, Days 15 to 22 (if postponed the beginning of next cycle, by the beginning of next cycle, or within 7 days at the time of completion of Cycle 8) of Cycles 4 and 8, and at discontinuation as possible. Tumor evaluation will be performed in shorter period at confirmation of efficacy or if clinically indicated.

Tumor evaluations (except PET and color photography of the skin lesion) will be performed on every 6 to 8 weeks (except the case of discontinuation by disease progression or starting treatment of a next anti-tumor drug) from the discontinuation (or completion) of the study drug, unless the subject withdrew the informed consent or the sponsor decided to stop the investigation.

Bone marrow biopsy

To evaluate bone marrow infiltration, bone marrow biopsy will be performed (if it is difficult, bone marrow aspiration can be performed instead) at screening. If the result is positive or unconfirmed, or bone marrow biopsy is not performed (ie, bone marrow aspiration is performed instead) at screening, bone marrow biopsy will be performed when to confirm CR as best overall response. In addition, bone marrow biopsy can be performed in any subject when clinically indicated.

B symptoms

B symptoms (fever of >38 °C with unknown reason, night sweat [requiring to change bedding], and >10% decrease of bodyweight with unknown reason within 6 months) will be evaluated at the same timepoints with tumor evaluations.

Items and methods for efficacy evaluation is provided in an Attachment ”Overall Response Evaluation Criteria”.

Survival investigations

Survival investigations on every 12 to 16 weeks from the discontinuation (or completion) of the study drug, unless the subject withdrew the informed consent or the sponsor decided to stop the investigation.

Storage and provision of data

In order to carry out central review, CT/MRI images, PET images, and color photographic images taken at the screening and tumor evaluations will be stored at the medical institution and provided to the sponsor as electronic data after masking personal information of the subject.

Regarding the evaluation of the skin lesions, a copy of the judgment record of the medical institution will be provided to the sponsor.

Submit the blood smear sample for evaluation of peripheral blood lesion and bone marrow sample (biopsy or puncture; if required), and a copy of the diagnosis report will be submitted to the central review committee.

Refer to the procedure manual (defined separately) for the provision of data and collection, handling, and transport procedures of samples.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

In all registered subjects, PK and immunogenicity (anti-E7777 antibody, anti-IL-2 antibody, and neutralizing activity of anti-E7777 antibody) will be evaluated and blood samples for the measurement of serum sIL-2R, LDH and T-cell subsets (actual counts and ratios of T-cells with CD4+, CD4+/CD25+, CD4+/CD25+/Foxp3+, CD4+/CD7–*, CD4+/CD26–*; *Only for MF and SS) in the peripheral blood will be collected.

Pathological diagnosis of the primary disease and measurement of CD25 positive rate in the tumor cells will be conducted centrally.

9.5.1.4.1 Measurements of Drug Concentrations

Blood samples (6 mL each) will be collected for non-compartment analysis at the timepoints in Table 1 until 6 subjects continued the treatment for at least 5 cycles.

Table 1 Timepoints for Drug Concentration Measurements (For until 6 Subjects Continued at Least 5 Cycles)

Cycle	Day	Blood Collection Timepoint	Allowance (approximately)
Cycles 1, 3, and 5	Day 1	Predose	Within 180 minutes to administration
		30 minutes after the start of infusion	± 5 minutes
		Immediately after the end of infusion	Within 5 minutes after the end of infusion
		30 minutes after the end of infusion	± 5 minutes
		60 minutes after the end of infusion	± 5 minutes
		90 minutes after the end of infusion	± 5 minutes
		120 minutes after the end of infusion	± 10 minutes
		240 minutes after the end of infusion *	± 10 minutes

*Cycle 1 only

Blood samples (6 mL each) will be collected in sparse sampling for pharmacokinetic analysis at the timepoints in Table 2 after 6 subjects continued the treatment for at least 5 cycles.

Table 2 Timepoints for Drug Concentration Measurements (For after 6 Subjects Continued at Least 5 Cycles)

Cycle	Day	Blood Collection Timepoint	Allowance (approximately)
Cycles 1, 3, 5,and 8	Day 1	Predose	Within 180 minutes to administration
		Immediately after the end of infusion	Within 5 minutes after the end of infusion
		30 to 180 minutes after the end of infusion	–

Refer to the procedure manual (defined separately) for collection, handling, and transport procedures of PK samples.

For samples collected from the treated subjects, serum concentrations of E7777 will be determined by a validated analytical method. The pharmacokinetic parameters for E7777 including the followings will be calculated: maximum observed concentration (C_{max}), time at which the highest drug concentration occurs (t_{max}), area under the concentration-time curve (AUC), terminal elimination phase half-life ($t_{1/2}$), volume of distribution at terminal phase (V_z), and total clearance (CL).

9.5.1.4.2 IMMUNOGENICITY (ANTI-E7777 ANTIBODY, ANTI-IL-2 ANTIBODY AND NEUTRALIZING ACTIVITY OF ANTI-E7777 ANTIBODY)

Blood samples (4 mL of peripheral blood × 3 samples per each timepoint) will be collected at the timepoints in Table 3.

Table 3 Timepoints for Serum Antibodies and Neutralizing Activities

Cycle	Day	Blood Collection Timepoint	Allowance (approximately)
Cycles 1, 2, 3, 5, and 8	Day 1	Predose	Within 180 minutes to administration
Discontinuation or completion of the study*			Date of discontinuation or completion + 7 days

*Perform depend on the subject's condition, etc.

Refer to the procedure manual (defined separately) for collection, handling, and transport procedures of samples for immunogenicity assessments.

9.5.1.4.3 MEASUREMENTS OF PHARMACODYNAMICS AND OTHER BIOMARKERS

Serum sIL-2R and LDH levels

Blood samples (3 mL of peripheral blood for each timepoint) for sIL-2R and LDH measurements will be collected at the timepoints in Table 4.

Table 4 Timepoints for sIL-2R and LDH Measurements

Cycle	Day	Blood Collection Timepoint	Allowance (approximately)
Cycles 1, 2, 3, 5, and 8	Day 1	Predose	Within 180 minutes to administration
Discontinuation or completion of the study*			Date of discontinuation or completion + 7 days

*Perform depend on the subject's condition, etc.

Refer to the procedure manual (defined separately) for collection, handling, and transport procedures of samples for sIL-2R and LDH measurements.

T-cell subsets

Blood samples (4 mL of peripheral blood for each timepoint) will be collected at the timepoints in Table 5.

Table 5 Timepoints for T-cell Subsets Measurements

Cycle	Day	Blood Collection Timepoint	Allowance (approximately)
Cycles 1 and 2	Day 1	Predose	Within 180 minutes to administration
	Day 8	–	+ 3 days
	Day 15	–	± 3 days
Cycles 3, 5, and 8	Day 1	Predose	Within 180 minutes to administration
Discontinuation or completion of the study*			Date of discontinuation or completion + 7 days

*Perform depend on the subject's condition, etc.

Refer to the procedure manual (defined separately) for collection, handling, and transport procedures of peripheral blood samples for T-cell subset measurements

Central pathological diagnosis, CD25 positive rate in tumor cells by immunohistochemical staining, and CCR4 expression:

For central pathological diagnosis of the primary disease, measurement of CD25 positive rate in the tumor cells, and CCR4 expression, tumor samples (formalin-fixed paraffin-embedded tissue sample) before study drug administration will be collected and submitted to the central laboratory prior to the last observation. The submitted tumor samples may also be used for development of diagnostic agent for E7777.

Central pathological diagnosis of the primary disease will be prioritized if it is different from that of the investigational site.

Refer to the procedure manual (defined separately) for handling and transport procedures of tumor samples.

9.5.1.5 Safety Assessments

Safety assessments are shown in Table 7 (Schedule of Procedures/Assessments).

Safety assessments will consist of monitoring and recording all AEs, including all Common Terminology Criteria for Adverse Events (CTCAE) v4.03 grades (for increasing severity), and SAEs; monitoring of hematology, blood chemistry, and urine values; measurement of vital signs and ECGs; and performance of ophthalmological and physical examinations.

9.5.1.5.1 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a subject. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E7777.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease found after the time of informed consent, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

All AEs observed during the study will be recorded on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the final observation visit. However, if other antitumor treatments should be implemented as soon as possible considering the deterioration of subject's physical condition, the last visit will be allowed within 30 days after the last dose (ie, before the start of other antitumor treatments). SAEs will be collected until the final observation visit. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure and its seriousness reported on the CRF.

Any laboratory abnormality considered to constitute an AE should be reported on the CRF. Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs must be followed until last visit for final observation or until resolution, whichever comes first. However, if other antitumor treatments should be implemented as soon as possible considering the deterioration of subject's physical condition, the last visit will be allowed within 30 days after the last dose (ie, before the start of other antitumor treatments). All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to Common Terminology Criteria for Adverse Event (CTCAE v4.03). Investigators will report CTCAE grades for all AEs (for increasing severity).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of

SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error (see Sections 9.5.4.2 and 9.5.4.3). These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations (not including natural childbirth) are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

9.5.1.5.3 INFUSION REACTIONS

In general, administration of a protein-derived drug has a possibility of causing an acute reaction called "infusion reactions".

For TEAEs developed on the day of administration of the study drug or on the day after administration, the investigator or subinvestigator judged whether it is an infusion reaction or not and recorded on the CRF.

For each AE judged to be an infusion reaction, the times of onset and outcome will be recorded on the CRF (record of the time of outcome will not be required if it is on or after 24 hours from the onset).

Examples of the infusion reactions include fatigue, nausea, vomiting, joint pain, muscle pain, fever, and chills.

9.5.1.5.4 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 6. The Schedule of Procedures/Assessments (Table 7) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 6 Clinical Laboratory Tests

Category	Parameters
Hematology	RBC count, hemoglobin, hematocrit, platelets, and WBC count with differential (neutrophils, lymphocytes, monocytes, basophils, eosinophils,)
Chemistry	
Liver function tests	Alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, total bilirubin, cholinesterase
Renal function tests	Blood urea nitrogen, creatinine
Other	Glucose, albumin, cholesterol, triglycerides, lactate dehydrogenase, amylase, lipase, total protein, uric acid, sodium, potassium, chloride, calcium, C-reactive protein
Urinalysis	Protein (qualitative), glucose (qualitative), occult blood

RBC = red blood cell, WBC = white blood cell.

All hematology, blood chemistry and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration at the beginning of each treatment cycle. When a clinically significant laboratory abnormality is observed and it is necessary to consider whether to continue the administration of study drug, refer to Dose Interruption Criteria (Section 9.4.1.5), Criteria for Initiating Next Cycle (Section 9.4.1.6), and Dose Reduction Criteria (Section 9.4.1.7).

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the CRF.

9.5.1.5.5 Vital Signs, Weight, and Height Measurements

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], body temperature [in centigrade]), and weight (kg) and height (cm) will be obtained at the visits designated in the Schedule of Procedures/Assessments (Table 7) by predetermined methods. Blood pressure and pulse will be measured after the subject has been resting.

9.5.1.5.6 Physical Examinations

Physical examinations will be performed as designated in the Schedule of Procedures/Assessments (Table 7). Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the CRF.

9.5.1.5.7 ECOG-PS

ECOG-PS will be evaluated by the method described in the Attachment as designated in the Schedule of Procedures/Assessments (Table 7).

9.5.1.5.8 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures/Assessments (Table 7). Complete, standardized, 12-lead ECG recordings are to be used. heart rate (bpm), QT (msec), and QTc (msec) will be recorded. Fridericia's correction (QTcF) will be employed for calculation of QTc.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1). In these instances, the AE corresponding to the ECG abnormality will be recorded on the CRF.

9.5.1.5.9 OPHTHALMOLOGICAL EXAMINATIONS

Ophthalmological examinations (visual test, color vision test as well as other tests judged to be necessary by the physician, such as visual field test, tonometry, and ophthalmoscopy) will be performed as designated in the Schedule of Procedures/Assessments (Table 7).

9.5.1.5.10 PREGNANCY TESTS

A serum or urine hCG test will be performed as designated in the Schedule of Procedures/Assessments (Table 7) for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months.

9.5.1.5.11 VIRAL TESTS

HBs antigen, HBs antibodies, HBc antibodies, HCV antibodies, and HIV antibodies will be measured at screening. In case the results of HBs antibodies or HBc antibodies are positive, HBV-DNA will be quantitatively measured.

9.5.1.6 Assessments on Treatment Compliance

Treatment compliance (date and time of administration, dose [reason for dose change if applicable]) will be collected and recorded on the CRF.

9.5.1.7 Assessments of Prior and Concomitant Therapy

Any medication or therapy administered to the subject during the study (between at the date of informed consent and the date of final observation) will be recorded. For all drugs/therapies, the name, reason for use, treatment start date, treatment end date will be collected and recorded on the CRF. Treatment by another physician will be also collected from the physician if it is required.

9.5.2 Schedule of Procedures/Assessments

Table 7 presents the schedule of procedures/assessments for the study.

Table 7 Schedule of Procedures/Assessments

Phase	Pretreatment Phase			Treatment Phase								Follow-up Phase	
Period	IC	Screening	Baseline [p]	Cycle 1 to 8							EOT	LO	FU
Day		–28 days	–7 days	1[q]	2	3	4	5	8 (+3)	15 (±3)	(+7)	30 (+7) days from last dose	
Informed consent	X												
Patient characteristic		X											
Inclusion/Exclusion criteria		X											
Registration		X											
Prior therapy		X											
Medical history/Complication		X											
Height		X											
Weight [a, b]		X	X	X									
Physical exam		X	X	X	X	X	X	X	X	X	X	X	
Vital signs [b]		X		X	X	X	X	X	X	X	X	X	
ECOG PS [a, b]		X	X	X							X	X	
Electrocardiogram (12-lead) [b, c]		X		X							X	X	
Pregnancy test (if required)		X									X		
Virus test													
Hematology test [a, b, d]		X	X	X					X	X	X	X	
Biochemistry test [a, b, e]		X	X	X					X	X	X	X	
Urinalysis [a, b]		X	X	X				X	X	X	X	X	
Ophthalmology test [f]		X								[X]	X	X	
E7777 administration				X	X	X	X	X					
Pharmacokinetics [g]				[X]									
Anti-E7777 antibody, anti-IL-2 antibody, neutralizing activity [h]				[X]							X		
Serum s-IL-2R and LDH [h]				[X]							X		
T-cell subsets [i]				[X]					[X]	[X]	X		
Tumor evaluation [j]		X								[X]	X		[X]
Bone marrow biopsy [k]		X		[X]									
B symptoms [l]		X								[X]	X		
Submission of tumor samples for central diagnosis, review of CD25 and CCR4 [q m]	Through all terms by the last observation												
Concomitant drugs/therapies [n]	Through all terms by the last observation												[X]
Adverse events	Through all terms by the last observation												
Survival investigations [o]													X

EOT: end of treatment (ie, discontinuation or completion), FU: follow-up, LO: last observation

Note：X indicates items to be perform on that timepoint, while [X] indicates items those may be performd on that timepoint.

a: Baseline data can be employed on Cycle 1 Day 1.

b: It will be conducted before the administration.

c: Perform immediately (approximately within 5 minutes) after the study drug administration on Cycle 1 Day 1.

d: Perform prior to the administration of study drug and confirm it meets the administration criteria (except differential white blood count).

e: Perform prior to the administration of study drug and confirm it meets the administration criteria (Data of AST, ALT, total bilirubin, and albumin are mandately. The other items will be also confirmed, if available).

f: Perform at screening, Day 15 of odd cycles, discontinuation (or completion) and the last observation. Able to use any data at discontinuation (or completion) and within 14 days from the last observation. Also perform when clinically indicated.

g: Blood samples will be collected for non-compartment analysis in schedule below (approximately) until 6 subjects continued the treatment for at least 5 cycles.
Day 1 in Cycles 1, 3, 5; at predose (within 180 minutes), 30 minutes after the start of infusion (±5 minutes), immediately after the end of infusion (within 5 minutes), 30 (±5), 60 (±5), 90 (±5), 120 (±10), and 240 (±10)* minutes after the end of infusion (* Cycle 1 only).
After 6 subjects continued the treatment for at least 5 cycles, blood samples will be collected in sparse sampling schedule below.
Day 1 in Cycles 1, 3, 5, 8; at predose (within 180 minutes), immediately after the end of infusion (within 5 minutes), and 60 to 180 minutes after the end of infusion.

h: Blood samples will be collected at predose (within 180 minutes) of Day 1 in Cycles 1, 2, 3, 5, 8, and at discontinuation (or completion).

i: Blood samples will be collected at predose (within 180 minutes) of Day 1, as well as Days 8 and 15 in Cycles 1 and 2, predose (within 180 min) of Cycles 3, 5, and 8, and at discontinuation (or completion).

j: The tumor evaluation data within 28 days before the informed consent can be used as screening data if it meets the requirement of the protocol. Tumor evaluation will be performed on screening, day 15-22 (if postponed the beginning of next cycle, by the beginning of next cycle) of cycle 2, 4, 6, 8 and discontinuation. PET scan will be performed on screening, and if positive, day 15-22 (if postponed the beginning of next cycle, by the beginning of next cycle) of cycle 4, 8 and discontinuation as possible. Perform tumor evaluation in short period at confirmation of efficacy or if clinically indicated. The data within 14 days can be used as discontinuation data. At the follow-up, tumor evaluation (except PET) will be performed on every 6-8 weeks (except the case of discontinuation by disease progression and starting treatment of next antitumor drug). To be intravenously administered 60 minutes (±10 minutes) from days 1 through 5 of each cycle.

k: The data of bone marrow biopsy (if it is difficult, bone marrow aspiration can be performed instead) within 28 days before IC can be used as screening data if it meets the requirement of the protocol. Bone marrow re-biopsy is required to confirm CR as best overall response, for the patients who were positive or unconfirmed for infiltration at screening or who did not perform bone marrow biopsy (who performed bone marrow aspiration). If clinically indicated, all patients are able to perform bone marrow re-biopsy.

l: Perform at the screening, Day 15 to 22 (if postponed the beginning of next cycle, by Day 42) of Cycles 2, 4, 6, and 8 and discontinuation.

m: Submit a tumor biopsy sample which collected before the study drug treatment to the central laboratory prior to the last observation. If there are immunohistochemical staining data on CCR4 expression, such data can be used for this study.

n: Only the antitumor drugs and therapies will be collected as concomitant drugs/therapies during the Follow-up Phase. Information of the duration of treatment and best overall response will be collected as long as possible.

o: Conduct on every 12 to 16 weeks from the discontinuation (or completion).

p: Data collected at the screening can be used as the baseline data if the data are collected within 7 days before the study drug administration.

q: From Cycle 2 or later, the next cycle can start on ±1 day from the planned date. The data collected 1 day before Day 1 can be used as those on Day 1 (except vital signs and 12-lead electrocardiogram data). Subjects will be hospitalized during Cycle 1 Days 1 to 8.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of malignant lymphoma.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, vital signs, body weight, physical examinations, ECOG PS, ECGs, ophthalmologic tests, and assessment of AEs are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event. The investigator must report SAEs to the sponsor promptly using the SAE report form. The detailed contact information for reporting of SAEs is provided in the Attachment of this protocol.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in a female subject in which the estimated date of conception is either before the last visit or within 30 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 30 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Attachment of this protocol. The Pregnancy Report Form (attached) must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported using the Pregnancy Outcome Report Form (attached) as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome. A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, or Medication Error

Adverse events associated with study drug overdose, misuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators, the head of the medical institution, and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis. For this reason, it is imperative that investigator or subinvestigator provide complete SAE information in the manner described in Section 9.5.4.1 "Reporting of Serious Adverse Events".

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 7).

The investigator or subinvestigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information.

Subjects who discontinue early from the study will be discontinued for 1 of primary reasons. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator, subinvestigator, or clinical research coordinator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator, subinvestigator, or clinical research coordinator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, subinvestigator, or clinical research coordinator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs. As defined by GCP, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of the sponsor and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of the sponsor or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

The cut-off date of the study analyses will be the earlier date of either all subjects have discontinued or completed Cycle 8 of the study, or the best overall response of all subjects on treatments are confirmed to be PR or better. All statistical analyses will be performed after the database is locked and released. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of the study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

Objective response rate (ORR) of the best overall response.

9.7.1.1.2 SECONDARY ENDPOINTS

- Progression-free survival (PFS)
- Duration of response (DOR)
- Time to response (TTR)
- Complete response (CR) rate

- Overall survival (OS)
- Safety endpoints (AEs, clinical laboratory parameters, vital signs, weight, ECOG PS, 12-lead ECGs results, and ophthalmologic test results)
- PK parameters
- Immunogenicity (anti-E7777 antibody, anti-IL-2 antibody, and neutralizing activity of anti-E7777 antibody)

9.7.1.1.3 EXPLORATORY ENDPOINTS

Biomarkers in the tumor and blood.

9.7.1.2 Definitions of Analysis Sets

Full Analysis Set (FAS) is the group of subjects who registered in this study and received at least 1 dose of study drug. This group will be the population for the evaluation of efficacy.

Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 evaluable post-baseline safety data. This group will be the population for the evaluation of safety.

Pharmacokinetics Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 evaluable serum concentration data.

Pharmacodynamics Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 each of evaluable pre- and post-baseline PD data.

9.7.1.3 Subject Disposition

The number of subjects signed informed consent, continued in the study after screening and screen failures will be provided and primary reasons for screening failure will be summarized. The number of subjects treated, untreated, completed the study, discontinued the study and the primary reasons for study discontinuation will be summarized. The number of subjects completed the study treatment, discontinued the study treatment and the primary reasons for discontinuation of the study treatment will also be summarized.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the FAS and the Safety Analysis Set will be summarized for each disease (PTCL, CTCL) and overall. Continuous demographic and baseline variables include age, height, and weight. Categorical variables include sex, age group, race, ethnicity, ECOG PS, and previous treatment for the primary disease (radiotherapy, chemotherapy, and other therapies).

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). Prior medications will be

defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the subject's last visit. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

All efficacy analyses will be performed on the FAS. All efficacy results will be summarized for each disease (PTCL, CTCL) and overall.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The rate of subjects whose best overall response is CR or PR is calculated as ORR, and its corresponding 2-sided exact 95% CI is also calculated.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

- Analysis of PFS
  PFS will be summarized by Kaplan-Meier method using median with 95%CI.

- Analysis of DOR
  DOR will be summarized by Kaplan-Meier method using median with 95% CI in responders.

- Analysis of TTR
  TTR will be summarized by Kaplan-Meier method using median with 95% CI in responders.

- Analysis of CR rate
  The number and percentage of subjects whose best overall response and its corresponding 2-sided exact 95% CI will be provided.

- Analysis of OS
  OS will be summarized by Kaplan-Meier method using median with 95%CI.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Not applicable.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

For the Pharmacokinetic Analysis Set, plots of E7777 serum concentration versus actual time will be displayed for those samples collected for non-compartmental analysis. PK parameters will be derived by non-compartmental analysis of the serum concentration data.

The following pharmacokinetic parameters for E7777 will be calculated: maximum observed concentration (C_{max}), time at which the highest drug concentration occurs (t_{max}), area under the concentration-time curve (AUC), terminal elimination phase half-life ($t_{1/2}$), volume of distribution at terminal phase (V_z), and total clearance (CL).

E7777 serum concentrations for population PK analyses will be listed for each subject by actual sampling time.

Serum E7777 concentration data will be used to build PK models to explain the observed concentration data using population approach. Additionally, the models may be used to explore the relationship between PK and select demographic variables. The relationship between PK parameters and efficacy/AE endpoints will also be investigated through population PK/PD modeling. For population PK and PK/PD analysis, the details will be described in the separately prepared analysis plan and its report, and the results will not be included in the clinical study report.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

Immunogenicity

The measurement value will be listed for anti-E7777 antibody, anti-IL-2 antibody, and neutralizing activity of anti-E7777 antibody in Safety Analysis Set.

Pharmacodynamics

The measurement value (and the change from baseline, if necessary) for each evaluation period will be summarized using the number of subjects, mean, SD, median, minimum and maximum for each disease (PTCL, CTCL) and overall. In addition, the individual plot over time will be prepared by subject.

Immunohistochemistry

Classified frequency and percentage of the CD25+ cells will be calculated for each disease (PTCL, CTCL) and overall in subjects who submitted the tumor sample.

9.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. All safety results will be summarized for each disease (PTCL, CTCL) and overall.

9.7.1.8.1 EXTENT OF EXPOSURE

Number of cycles received, duration of treatment, total number of doses, total doses and dose ratio (actual dose/planned dose) will be summarized.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities

(MedDRA). Adverse events will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment (baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized for each disease (PTCL, CTCL) and overall. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by highest CTCAE grade.

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-emergent serious adverse events (SAEs) will be summarized by MedDRA SOC and PT for each disease (PTCL, CTCL) and overall.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug, leading to dose reduction or leading to dose interruption will be summarized by MedDRA SOC and PT for each disease (PTCL, CTCL) and overall.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.4, the actual value and the change from baseline to each postbaseline visit and to the end of treatment will be summarized by visit for each disease (PTCL, CTCL) and overall using descriptive statistics. Qualitative parameters will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

In addition, CTCAE v4.03 will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs), if necessary.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, and temperature) and weight and changes from baseline will be presented by visit for each disease (PTCL, CTCL) and overall.

9.7.1.8.5 ELECTROCARDIOGRAMS

ECG assessments were performed at each visit. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit for each disease (PTCL, CTCL) and overall. Shift tables will present changes from baseline in ECG interpretation. In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Fridericia (QTcF) during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- QTcF interval >450 ms
- QTcF interval >480 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms

9.7.1.8.6 OTHER SAFETY ANALYSES

ECOG PS

ECOG-PS will be summarized by scale at each visit and by highest postbaseline scale.

9.7.2 Determination of Sample Size

Thirty-five patients were required to detect lower limit of the 95% confidence interval (CI) that exceed the 5% threshold in ORR, which is the primary endpoint of the study, with the expected ORR is 25% with a statistical power of 90%. In CTCL, 6 or more patients are targeted to evaluate the safety as specific disease.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

AbouYabis AN, Shenoy PJ, Sinha R, Flowers CR, Lechowicz MJ. A systematic review and meta-analysis of front-line anthracycline-based chemotherapy regimens for peripheral T-cell lymphoma. ISRN Hematol. 2011; Article ID 623924: 14 pages

Agar NS, Wedgeworth E, Crichton S, Mitchell TJ, Cox M, Ferreira S, et al. Survival outcomes and prognostic factors in mycosis fungoides/Sézary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal. J Clin Oncol. 2010; 28: 4730-9.

Aoki R, Karube K, Sugita Y, Nomura Y, Shimizu K, Kimura Y, et al. Distribution of malignant lymphoma in Japan: analysis of 2260 cases, 2001-2006. Pathol Int. 2008; 58: 174-182.

Carbone PP, Kaplan HS, Musshoff K, Smithers DW, Tubiana M. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res. 1971; 31: 1860-61.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007; 25: 579-86.

Clinical Practice Guideline of Hematological Malignancies. the Japanese Society of Hematology, 2013.

Curiel TJ, Coukos G, Zou L, Alvarez X, Cheng P, Mottram P, et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nature Med. 2004; 10: 942-9.

Dang NH, Pro B, Hagemeister FB, Samaniego F, Jones D, et al. Phase II trial of denileukin diftitox for relapsed/refractory T-cell non-Hodgkin lymphoma. Br J Haematol. 2007; 136: 439-47.

Fisher RI, Gaynor ER, Dahlberg S, Oken MM, Grogan TM, Mize EM, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-hodgkin’s lymphoma. NEJM. 1993; 328: 1002-6.

Grozea PN, Jones SE, McKelvey EM, Coltman CA Jr, Fisher R, et al. Combination chemotherapy for mycosis fungoides: a Southwest Oncology Group study. Cancer Treat Rep. 1979; 63: 647-53.

Gouill SL, Milpied N, Buzyn A, Latour RPD, Vernant JP, Mohty M, et al. Graft-versus-lymphoma effect for aggressive T-cell lymphomas in adults: a study by the Société Francaise de Greffe de Moëlle et de Thérapie Cellulaire. J Clin Oncol. 2008; 26: 2264-71.

Hamada T and Iwatsuki K. The results of case survey for skin lymphoma in 2013. The Japanese Skin Cancer Society. 2013

Kim YH, Willemze R, Pimpinelli N, Whittaker S, Olsen EA, Ranki A, et al. TNM classification system for primary cutaneous lymphomas other than mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007; 110: 479-84.

LeMaistre CF, Saleh MN, Kuzel TM, Foss F, Platanias LC, et al. Phase I trial of a ligand fusion-protein (DAB389IL-2) in lymphomas expressing the receptor for interkeukin-2. Blood. 1998; 91: 399 405.

Létourneau S, Krieg C, Pantaleo G, Boyman O. IL-2- and CD25-dependent immunoregulatory mechanisms in the homeostasis of T-cell subsets. J Allergy Clin Immunol. 2009; 123: 758-62.

Litzinger MT, Fernando R, Curiel TJ, Grosenbach DW, Schlom J, Palena C. IL-2 immunotoxin denileukin diftitox reduces regulatory T cells and enhances vaccine-mediated T-cell immunity. Blood. 2007; 110: 3192-3201.

Lymphoma Study Group of Japanese Pathologists. The world health organization classification of malignant lymphomas in Japan: incidence of recently recognized entities. Pathol Int. 2000; 50: 696 702.

Mak V, Hamm J, Chhanabhai M, Shenkier T, Klasa R, Sehn LH, et al. Survival of patients with peripheral T-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. J Clin Oncol. 2013; 31:1970-6.

Morris JC, Waldmann TA. Advances in interleukin 2 receptor targeted treatment. Ann Rheum Dis 2000; 59 (suppl I):i109-14.

Morse MA, Hobeika AC, Osada T, Serra D, Niedzwiecki D, Lyerly HK, et al. Depletion of human regulatory T cells specifically enhances antigen-specific immune responses to cancer vaccines. Blood. 2008; 112:610-8.

NCCN Clinical Practice Guidelines in Oncology non-Hodgkin’s Lymphomas. V.3.2012.

NCCN Clinical Practice Guidelines in Oncology non-Hodgkin’s Lymphomas. V.1.2013.

NCCN Clinical Practice Guidelines in Oncology non-Hodgkin’s Lymphomas. V.1.2015.

Olsen E, Duvic M, Frankel A, Kim Y, Martin A, Vonderheid E, et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. J Clin Oncol. 2001; 19: 376-88.

Olsen E, Vonderheid E, Pimpinelli N, Willemze R, Kim Y, Knobler R, et al. Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the cutaneous lymphoma task

force of the European Organization of Research and Treatment of Cancer (EORTC). Blood. 2007; 110: 1713-22.

Olsen EA, Whittaker S, Kim YH, Duvic M, Prince HM, Lessin SR, et al. Clinical End Points and Response Criteria in Mycosis Fungoides and Sézary Syndrome: A Consensus Statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol. 2011; 29: 2598-607.

Prince HM, Duvic M, Martin A, Sterry W, Assaf C, Sun Y, et al. Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. J Clin Oncol. 2010; 28:1870-7.

Prince HM, Martin AG, Olsen EA, Fivenson DP, Duvic M. Denileukin diftitox for the treatment of CD25 low-expression mycosis fungoides and Sézary syndrome. Leuk Lymphoma. 2013; 54: 69-75.

Scientific Evidence-Based Clinical Practice Guideline on Skin Malignancies II (1st edition). 2010

VanderSpek JC, Mindell JA, Finkelstein A, Murphy JR. Structure/function analysis of the transmembrane domain of DAB389-interleukin-2, an interleukin-2 receptor-targeted fusion toxin. J Biol Chem. 1993; 268: 12077-82.

Vose JM, Armitage J, Weisenburger D; International T-cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell Lymphoma study: pathology findings and clinical outcomes. J Clin Oncol. 2008; 26: 4124-30.

Yared J, Kimball A. The role of high dose chemotherapy and autologous stem-cell transplantation in peripheral T-cell lymphoma: A review of the literature and new perspectives. Cancer Treat Rev. 2013; 39: 51-9.

Zinzani PL, Baliva G, Magagnoli M, Bendandi M, Modugno G, et al. Gemcitabine treatment in pretreated cutaneous T-cell lymohoma: Experience in 44 patients. J Clin Oncol. 2000; 18: 2603-6.

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation.

Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs. 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 the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor, and the IRB for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to the IRB. In these cases, the sponsor may be required to send a letter to the head of the medical institution detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol.

11.3 Monitoring Procedures

The CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The head of the medical institution will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with GCP. All records at the site are subject to inspection by the local auditing agency and to IRB review.

In accordance with GCP, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IVRS/IWRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives

- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents. For the following items, the data recorded directly on the CRF are to be considered source data:

- Records of study drug administration (eg, reason for treatment discontinuation, reason for dose modification)
- Reasons for prior and concomitant therapy (including medications and therapies)
- Information on the discontinuation (eg, reason for discontinuation)
- Sampling date and time for PK analysis
- Sampling date for clinical laboratory tests
- Information on AEs (eg, grade, relationship to study drug, outcome)

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the head of the medical institution or the designated representative is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, ICFs and IRB correspondence).

The site should plan to retain study documents, as directed by the sponsor, for at least 3 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period the medical institution contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the GCP and all applicable local regulations. Government regulatory authority may request an inspection during the study or after its completion.

11.8 Handling of Study Drug

All study drug will be supplied to the assigned pharmacist (or designee) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The assigned pharmacist (or designee) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study, if required. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator or the assigned pharmacist (or designee) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the assigned pharmacist (or designee) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor, if required.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each head of the medical institution and the sponsor.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor and the head of the medical institution.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor and the head of the medical institution.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators, the head of the medical institution, and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/the head of the medical institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the head of the medical institution where applicable, and the investigator/ the head of the medical institution should promptly inform the sponsor and the IRB and provide the sponsor and the IRB with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.