REVISION HISTORY		
DATE	**Version Number**	**Highlights of Major Changes SECTION/CHANGE**
05 Sep 2012	**v1.0**	**Original protocol**
17 Apr 2013	**v2.0**	**Amendment 01:** • Addition of a non-formal interim analysis to ensure that an acceptably safe dose was established and at least one objective response was recorded in the Lead-In part before proceeding into the Main Study where larger numbers of subjects will be studied. • An addition to the text was made allowing subjects with visceral involvement into the Lead-In part of the study, to correct an error in the original protocol. • The process and data flow for the reviewing committee in Section 9.5.2.1 were clarified for comprehension. • The process for the mSWAT score, collection of data for skin lesion measurements for supplemental response assessment, and an addition of required photographic views in Section 9.5.2.2 for skin disease were explained in greater detail for comprehension. • The assessment of visceral involvement in Section 9.5.2.2 was explained in greater detail for comprehension. • The Schedule of Assessments (Table 4) was updated to clarify the flexibility in visit windows, to correct the timing of urine pregnancy testing, the duration of collection of adverse events and concomitant medications, lymph node biopsy processes, thyroid testing processes, and to confirm timing of confirmatory response assessments for improved comprehension and consistency among sites. • Appendix 4 was revised to describe assessments of mSWAT scoring and visceral disease measurements for greater comprehension and consistency among sites.

DATE	Version Number	Highlights of Major Changes SECTION/CHANGE
22 Apr 2014	**v3.0**	**Amendment 02:** • Dose limiting toxicity (DLT) definition for "serious infusion reaction" has been revised to allow an opportunity to assess if steroid premedication will be effective in managing Grade 3 infusion reaction. • Dose limiting toxicity (DLT) definition for "capillary leak syndrome" (CLS) has been changed to be based on CTCAE grading, to promote consistency in assessment of DLT, and to take into consideration current standard practices enabling medically managing this toxicity. • Investigator-assessed tumor responses will be used for decision-making on initiating the Main Study. • A longer time period of 8 weeks is now allowed from the time of signing informed consent to start of treatment, to enable central laboratory testing of CD25 expression (for Inclusion) to be performed within the Screening period. • Results obtained at Screening of from an archival skin biopsy can be used as long as the test was performed by the study-designated central laboratory. • Exclusion criterion "Need for treatment with a drug that contains a warning for hepatotoxicity or nephrotoxicity in its labeling." has been removed; it is a carry-over from a historical ONTAK protocol. • Instructions for premedication have been additionally clarified to be consistent with change in DLT definition for infusion reaction, and to allow more flexibility in timing and type of premedication as individual situations vary. • Dose interruption and dose modification instructions have been revised to be consistent with changes in DLT definitions. • Repeat procedures close in time are now not necessary, e.g. chemistry and hematology labs at Screening may count as Baseline assessments if they were performed within one week of start of treatment. • Addition of an analysis set in the Statistical section, "All enrolled subjects".

DATE	Version Number	Highlights of Major Changes SECTION/CHANGE
20 Apr 2016	**v4.0**	**Amendment 03:** • E7777 is no longer being referred to as "denileukin diftitox" as Sponsor may apply for a new proprietary name. • The dose of E7777 for the Main Study is now stated in the protocol, following completion of the Lead-In part. The Protocol Steering Committee has selected 9 μg/kg as the dose of E7777 to move forward with, in the Main Study. • CTCL disease stage for subject inclusion in the Main Study now allows Stage IVA_1 but excludes lymph node disease N_2, N_3; this is to align with subject population in the reference ONTAK study (L4389-11). • Pharmacokinetic sampling schedule revised and the number of samples taken has been reduced. • The Study Phases have been clarified such that Extension Phase occurs after data cutoff for primary analysis. • Drug administration instructions for a new lyophilized formulation is added. • Tumor assessment method description and schedules revised to align with changes in CTCL disease stage included

The table below describes revisions in Amendment 04 per the new protocol template (Nov 2016).

Revisions per Amendment 04 (Version 5.0)

Date: 26 Jun 2017

Change	Rationale	Affected Protocol Sections
Inclusion Criteria 4: CTCL disease stage for subject inclusion in the Main Study now allows Stage IA- IVA2 including lymph node disease N_2 and N_3.	Advised by Protocol Steering Committee to include N_2, N_3 patients as this patient population is expected to benefit from E7777, based on their clinical experience with ONTAK and E7777.	Synopsis – Inclusion Criteria Section 9.3.1
Inclusion Criteria 4: Removed exclusion of " known CTCL involvement of the bone marrow" from Main Study eligibility.	Bone marrow disease exclusion was following old ONTAK protocol (L4389-11). With updated ISCL/EORTC criteria, bone marrow involvement is considered as M1/ stage IVB, which is not included. Therefore, it is not necessary to state bone marrow disease exclusion anymore.	Synopsis – Inclusion Criteria Section 9.3.1
Inclusion Criteria 6: Definition of recovery from adverse effects from any previous CTCL therapy added as "to CTCAE Grade <2".	Added clarification	Synopsis – Inclusion Criteria Section 9.3.1
Exclusion Criteria 1: "CTCL disease with CNS involvement" removed.	Redundant with exclusion criteria 8 "active central nervous system disease"	Synopsis – Exclusion Criteria Section 9.3.2
Exclusion Criteria 3: Active malignancy other than CTCL is now excluded within 2 years instead of 5 years.	Updated criteria and language	Synopsis – Exclusion Criteria Section 9.3.2
Exclusion Criteria 9: Significant or uncontrolled infections requiring systemic anti-infective therapy.	Added clarification, updated term "specific" to "systemic"	Synopsis – Exclusion Criteria Section 9.3.2
Biopsy and histologic characterization requirement during screening updated: In the **Main Study**, biopsy and histologic characterization is strongly recommended <u>if</u> an	Advised by Protocol Steering Committee for disease staging of subjects with N_2/ N_3, which are now included in the study.	Section 9.5.2.2

Change	Rationale	Affected Protocol Sections
abnormal peripheral node suspicious for CTCL is detected by CT scans during Screening.		
Schedule of CT Scans modified: Additional CT scans are now required every 3 cycles (±1 week) during treatment for subjects with N_2, N_3, and N_x. ^{18}FDG-PET-CT scans may also be acquired during screening.	Advised by Protocol Steering Committee for monitoring nodal disease and response assessment	Section 9.5.2.2
Secondary Efficacy Variables: Skin response will be calculated with a 2-sided, exact 95% confidence interval (CI), using the Clopper-Pearson method. Skin response, duration of skin response, and time to skin response are added, which will be calculated based on mSWAT score. Definition DOR updated as "time from the date when criteria for response (CR or PR) based on GRS was first met until the date when the response was first lost (date of loss is date when first meets criteria for PD)". Removed "or relapse" from the date of loss.	These efficacy variables for skin disease are also relevant. Advised by Protocol Steering Committee to avoid scenario where a relapse may not reflect disease progression.	Synopsis- Objectives Criteria for Evaluation, Statistical Methods Section 9.7.1.2 Section 9.7.1.7 Section 8.2
Treatment continuation beyond 8 cycles is now allowed for subjects with **skin** tumor response and deriving clinical benefit from E7777 treatment instead of **objective** tumor response.	Advised by Protocol Steering Committee that in this disease, subjects with skin response are considered to have had clinical benefit.	Synopsis – Study Design Section 9.1.1 Section 9.1.4 Section 9.4.1
Removed requirement of visual acuity tests. Section 9.5.4.7 is removed.	Data from lead-in part should be sufficient for analysis. Severe grade loss of visual acuity was not reported during lead-in part.	Synopsis (Safety Analysis) Section 9.5.4 Section 9.5.4.7 Section 9.5.5.1 Section 9.5.5.2
Appendix 5 Charter for Lymph Node Disease Assessment is added.	Added clarification	Appendix 5

Change	Rationale	Affected Protocol Sections
Appendix 4 – Global Response Score Added "Only N_3 is considered as nodal disease (nodal involvement) for Global Response Score assessment."	Advised by Protocol Steering Committee – only N_3 is considered as CTCL nodal involvement. Per ISCL/EORTC Staging, N_0 to N_2 is included from stage IIA to IVA1 and does not change the disease stage, whereas N_3 is stage IVA_2.	Appendix 4, Table 5 Appendix 5

The table below describes revisions in Amendment 05 per the new protocol template (Nov 2016).

Revisions per Amendment 05 (Version 6.0)

Date: 03 May 2018

Change	Rationale	Affected Protocol Sections
Updated Principles of the World Medical Association Declaration of Helsinki from 2008 to 2013.	2013 is the current version.	5.2
Inclusion Criteria 3; Other Screening Assessments; Tumor Assessment Methods and Schedule: Deleted specific references to "skin" (in the context of CD25 detection on lymphoid infiltrate in biopsied lesions by immunohistochemistry), and replaced with general reference to "tumor".	There is no rationale to limit assessment of CD25 expression only in "skin" biopsies. CD25 expression can be detected by the same central laboratory IHC-based assessment in malignant cells within the skin biopsies or in other tumor lesions, e.g. in lymph node biopsies.	Synopsis – Inclusion Criteria Section 9.3.1 Section 9.5.1.2 Section 9.5.5.1, Table 4
Included creatine phosphokinase (CPK) testing as a monitoring procedure.	CPK testing was included as a monitoring procedure as requested by FDA in response to a safety report (fatal AE rhabdomyolysis) under IND 110489 (SD 51/SN 0050).	Section 9.4.1.3 Section 9.5.4.3, Table 3 Section 9.5.5.1, Table 4 (footnote h)
Updated CTCAE from v4.03 to v5.0.	v5.0 CTCAE is the current version.	9.5.4.1, 9.7.1.9, 10, 12 (Appendix 6)
Revised guidelines for ECG monitoring as follows: • Triplicate ECGs are no longer required • QT/QTcF interval will no longer be assessed by a central laboratory • Single 12-Lead ECGs will be performed during Screening,	Rationale: Reduce ECG monitoring based on Lead-in part ECG data analysis, ONTAK safety profile and E7777 clinical experience.	Section 9.5.4.6 Section 9.5.5.1, Table 4 (footnote f)

Change	Rationale	Affected Protocol Sections
Day 1 of each cycle and End of Treatment		

The table below describes revisions in Amendment 06 per the previous protocol template (Nov 2016).

Revisions per Amendment 06 (Version 7.0)

Date: 29 Oct 2019

Change	Rationale	Affected Protocol Sections
Removed 'registration of' from GCP statement	ICH updated its formal title in 2018.	Title page Section 4 Investigator signature page
Updated exploratory objective quality of life (QoL) to include Stage I-III subjects.	QoL will be assessed in Stage I – III Main Study subjects and Stage I – III Lead-In subjects from the 9µg/kg/day dose group combined.	Synopsis Section 8.2 9.5.5.1, Table 4 (footnote p)
Included Stage I – III subjects in evaluation of efficacy and safety for the Main Study and Stage I – III Lead-In subjects from the 9µg/kg/day dose group. Stage I – III subjects will be used for the primary efficacy analysis.	ONTAK study L4389-11 is the reference study from which this current study (E7777-G000-302) derives the statistical basis to calculate the sample size and the lower bound criteria for the 95% confidence interval (25%) for the objective response rate. ONTAK study L4389-11 was conducted in subjects with Stage I-III cutaneous T-cell lymphoma (CTCL). To align with that study population, the primary analysis of the current study will be conducted in Stage I – III Main Study subjects and Stage I – III Lead-In subjects from the 9µg/kg/day dose group combined. Subjects with Stage IVA1 and IVA2 CTCL will no longer be eligible to participate in the study.	Synopsis Section 8.2 Section 9.3Section 9.5.2.1
Updated the target number of Stage I – III study subjects.	A sufficient number of subjects will be treated for a total of approximately 70 Stage I – III subjects from the Lead-In and Main parts of the study combined.	Synopsis Section 9.1.1 Section 9.1.3 Section 9.3 Section 9.7.2
Updated number of study sites.	The number of study sites was updated to provide flexibility in accommodating the updated number of subjects for the study (approximately 115 subjects total).	Synopsis Section 9.3
Corrected the scale and score for assessment of pruritus.	Updated to show the correct scale (100 indicates worst possible itch); updated baseline score to be ≥20.	Synopsis 9.5.2.3

Change	Rationale	Affected Protocol Sections
Updated immunogenicity assessments.	Evaluation of positive anti-IL-2 immunogenicity samples after treatment with E7777 will be carried out for 3 years or until samples are negative.	Synopsis 9.5.3.2 9.5.5.1, Table 4 (footnote i)
Updated definitions of analysis sets.	Stage I – III subjects will be used for the primary efficacy analysis.	Synopsis Section 9.7.1.3
Updated the planned efficacy analyses.	Stage I – III subjects will be used for the primary efficacy analysis.	Synopsis Section 9.7.1.7
Updated the planned safety analyses.	Safety analyses for the main part of the study will be performed in all subjects, and Stage I – III subjects separately.	Synopsis Section 9.7.1.9
Clarified criteria for follow-up of subjects with immunogenicity.	Immunogenicity should be followed up in subjects who develop progressive disease since they are exposed to E7777.	Section 9.5.5.1, Table 4 (footnote q)

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7777-G000-302	
Study Protocol Title:	A Clinical Study to Demonstrate Safety and Efficacy of E7777 in Persistent or Recurrent Cutaneous T-Cell Lymphoma	
Sponsor	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 US	
Investigational Product Name:	E7777	
Indication:	Cutaneous T-Cell Lymphoma	
Phase:	3	
Approval Date:	V1.0	05 Sep 2012 (Original Protocol)
	V2.0	17 Apr 2013 (Protocol Amendment 01)
	V3.0	22 Apr 2014 (Protocol Amendment 02)
	V4.0	20 Apr 2016 (Protocol Amendment 03)
	V5.0	26 Jun 2017 (Protocol Amendment 04)
	V6.0	03 May 2018 (Protocol Amendment 05)
	V7.0	29 Oct 2019 (Protocol Amendment 06)
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local 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: Recombinant fusion protein composed of the amino acid sequences for diphtheria toxin fragments A and B (Met_1-Thr_{387})-His and for human interleukin-2 (Ala_1-Thr_{133})

Study Protocol Title:

A Clinical Study to Demonstrate Safety and Efficacy of E7777 in Persistent or Recurrent Cutaneous T-Cell Lymphoma

Investigator(s)

Multiple Investigators

Site(s)

Approximately 20 centers globally

Study Period and Phase of Development

Approximately 12 months for the Lead-In

Approximately 30 months for the Main Study (from first subject in to data cutoff)

Registrational study

Objectives

Lead-In Objectives

- Primary objectives: Establish the maximum tolerated dose (MTD) of E7777 and to select the dose of E7777 to be used in the Main Study
- Secondary objectives: Assess safety, tumor response, pharmacokinetics (PK) and immunogenicity after treatment with E7777

Main Study Objectives

All Main Study efficacy analyses will be performed primarily in the Stage I – III Main Study subjects plus the Stage I – III Lead-In subjects from the 9µg/kg/day dose group, as well as additionally in all subjects from the Main Study.

Primary Objective:

- To demonstrate efficacy of E7777 in subjects with recurrent or persistent cutaneous T-cell lymphoma (CTCL) in Stage I – III subjects as assessed by objective response rate (ORR) (Objective Response is Complete Response and Partial Response, according to the ISCL/EORTC* Global Response Score [Olsen 2011])

Secondary Objectives:

- To determine Duration of Response (DOR) for E7777
- To determine Time to Response (TTR) after E7777 treatment
- To determine skin response after E7777 treatment
- To determine duration of skin response after E7777 treatment
- To determine time to skin response after E7777 treatment
- To assess ORR for E7777 using the alternate response assessment criteria of Prince (2010)
- To evaluate safety and tolerability of E7777 in all subjects
- To evaluate safety and tolerability of E7777 in the Stage I – III Main Study subjects plus the Stage I – III Lead-In subjects from the 9µg/kg/day dose group combined

- To characterize the pharmacokinetics (PK) of E7777 and immunogenicity after treatment with E7777

Exploratory Objectives:

- To assess the following efficacy endpoints for subjects treated with E7777: progression free survival (PFS), and time to progression (TTP) (using Global Response Score)
- To assess pruritus improvement reported by subjects treated with E7777
- To assess Quality of Life (QoL) for (1) all subjects treated in the Lead-In part, (2) all subjects treated in the Main Study, (3) Stage I – III Main Study subjects plus Stage I – III Lead-In subjects from the 9µg/kg/day dose group combined

* International Society for Cutaneous Lymphomas/European Org of Research and Treatment of Cancer

Study Design

This will be a multicenter open-label single-arm study of E7777 in subjects with recurrent or persistent CTCL.

The study will consist of an initial **Lead-In** part followed by the **Main Study**:

Lead-In: A Continuous Reassessment Method (CRM) will be employed to establish the MTD of E7777 and to select the dose of E7777 to be used in the Main Study. Approximately 20 subjects will be treated.

Main Study: A sufficient number of subjects in the Main Study will be recruited so that approximately 70 Stage I – III subjects from both the Main Study and from the Lead-In subjects in the 9µg/kg/day dose group with recurrent or persistent CTCL will be treated with E7777 to assess efficacy. Safety will be evaluated in all subjects from the Main Study, and in the Stage I – III Lead-In subjects from the 9µg/kg/day dose group. The dose of E7777 in the Main Study will be the dose selected in the Lead-In part of the study. The primary efficacy analysis will be based on Stage I – III subjects from both the Main Study plus from the Lead-In 9µg/kg/day dose group combined.

Lead-In

A Continual Reassessment Method (CRM) will be employed to determine the maximum tolerated dose (MTD) of E7777, targeting a rate of dose-limiting toxicity (DLT) of approximately 20%.

Subjects will be treated with E7777 using the regimen described under "Study Treatment". The doses of E7777 that may be used are 3, 6, 9, 12, 15, or 18 µg/kg/d, with 6 µg/kg/d specified as the starting dose. Each subject will be assigned a dose of E7777 in accordance with the rules of the CRM design. The CRM design is described under "Statistical Methods".

Dose-limiting toxicities (DLTs) are based on known toxicities of ONTAK as described in the US product label. A DLT will be any of the following occurring within the **first cycle** of therapy:

- Serious infusion reaction, defined as CTCAE Grade 4 adverse event of "Infusion related reaction", or recurrent CTCAE Grade 3 despite administration of systemic steroid premedication after initial occurrence. Infusion reactions are defined as symptoms (e.g., fatigue, nausea, vomiting, arthralgia, myalgia, pyrexia, chills, rigors) occurring within 24 hours of E7777 infusion.
- Capillary leak syndrome (CLS) CTCAE Grade 4 or Grade 3 (with exceptions).

  The CTCAE definitions are broad and general, therefore, the following guidance is provided:

  - Grade 4 is severity such as subjects experiencing hypovolemic shock or renal failure, or who need treatment with vasopressors or oxygen.
  - Grade 3 is severe symptoms (less severe than the Grade 4 symptoms above) that may or may not be dose-limiting. For example, severe symptoms requiring hospitalization for acute intervention would be a DLT, whereas less severe symptoms leading to hospitalization for prophylactic treatment with fluids or diuretics would not be a DLT. Hospitalization or medical intervention to prevent hospitalization is not in itself a DLT as the threshold for hospitalization may differ by doctor and region.

  CLS is defined as the noted occurrence of at least 2 of the following: hypotension, edema, or serum albumin < 3.0 g/dL. These are not required to occur simultaneously to be characterized as CLS.
- Loss of visual acuity. This could be with loss of color vision, with or without retinal pigment mottling.
- Any CTCAE ≥ Grade 4 adverse event that may represent an infusion reaction

- Any CTCAE Grade 3 adverse event that may represent an infusion reaction that prevents the entire dose of E7777 from being administered despite appropriate treatment
- Any other Grade 3 or greater toxicity assessed as related to E7777 treatment, and which in the opinion of a safety consultancy investigator panel constitutes a dose-limiting toxicity.

Determination as to whether a subject has experienced a DLT will be made by the treating physician in consultation, as needed, with the medical monitor and investigator(s) on the Protocol Steering Committee (PSC) who are experienced in the use of denileukin diftitox.

Subjects who are not evaluable for DLT in Cycle 1 should be replaced.

If, during the course of the Lead-In, a trend is noted by the PSC where the E7777 toxicities described above are observed beyond the first cycle but not in Cycle 1, the definition of DLT may be amended to reflect that.

Selection of the dose of E7777 that will be used in the Main Study was made in consultation with the PSC, based on review of the full output of the CRM data.

Main Study

Enrollment in the **Main Study** will commence after an acceptably safe dose has been established in the **Lead-In** part (as described above), and there is at least one objective response by investigator assessment recorded in the Lead-In.

The objectives of the **Main Study** are to assess efficacy and safety of E7777 in Stage I - III subjects with recurrent and persistent CTCL. A sufficient number of subjects in the Main Study will be treated for an approximate total of 70 Stage I – III subjects from both the Main Study and from Lead-In subjects from the 9µg/kg/day dose group combined.

Study Phases for Each Subject

All subjects in the study will move through three Phases while on study.

- Pre-Treatment Phase, consists of two Periods:
  - Screening
  - Baseline
- Treatment Phase, consists of the following Periods:
  - **Treatment** with E7777 for up to 8 Cycles; each Cycle of 21 days is one Period. Subjects who have attained skin tumor response and are deriving clinical benefit from E7777 treatment may continue receiving treatment beyond 8 cycles, at the discretion of the treating physicians.
  - **Follow-up**: Tumor assessment until discontinuation of treatment due to PD; immunogenicity, and survival follow-up until relapse or initiation of new systemic anti-cancer therapy. All Follow-up assessments performed for up to 3 years after end of treatment, or until sponsor termination of the study.

After data cutoff for the primary analysis in the Main Study, the study moves to the Extension Phase.

- Extension Phase, consists of the following Periods:
  - **Treatment**, for continued treatment of subjects with ongoing treatment at data cutoff. Subjects will be treated for up to 8 cycles. Subjects who have attained skin tumor response and are deriving clinical benefit from E7777 treatment may continue receiving treatment beyond 8 cycles, at the discretion of the treating physicians.
  - **Follow-up**: Tumor assessment until discontinuation of treatment due to PD; immunogenicity, and survival follow-up until relapse or initiation of new systemic anti-cancer therapy. All Follow-up assessments performed for up to 3 years after end of treatment, or until sponsor termination of the study.

Pharmacokinetic (PK) assessment of E7777 will be performed in all subjects in the Lead-In part and in the first 12 subjects in the Main Study, using serial blood PK sampling on Day 1 in Cycles 1, 3, and 5, with sparse sampling in Cycle 8. In addition, sparse sampling will be performed in the Main Study in the rest of the subjects on Day 1 of Cycle 1.

Immunogenicity (formation of antibodies to E7777 or IL-2) will be assessed in all subjects in both the Lead-In part and the Main Study. A predose blood sample for immunogenicity assessment will be collected prior to Day1 dosing in Cycles 1, 2, 3, 5, and 8; after that, all subjects will be followed up for immunogenicity testing for anti-IL2 on a 6-month schedule for one year and every year thereafter until antibody titers decrease to baseline level or upon study termination.

The primary analysis will be performed after data cut-off which will be either of the following two events, whichever occurs later: (1) when all subjects in the Main Study have either completed Cycle 8 or are off treatment, or (2) when all subjects with at least one documented timepoint response of PR or better have undergone the subsequent tumor assessments necessary for confirmation of response (unless subject had disease progression or discontinued from study before that).

Number of Subjects

Approximately 20 subjects will be treated in the Lead-In part. A sufficient number of subjects in the Main Study will be treated for an approximate total of 70 Stage I – III subjects from both the Main Study and from Lead-In subjects from the 9μg/kg/day dose group combined. The study total will be approximately 115 subjects with recurrent or persistent CTCL.

Inclusion Criteria

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

1. Age ≥18 years.
2. Histopathologic diagnosis of CTCL (mycosis fungoides or Sezary Syndrome), confirmed by skin biopsy, or lymph node, or blood assessment, of current disease.
3. CD25 assay-positive tumor, defined as detectable CD25 on ≥ 20% of total lymphoid infiltrate in biopsied lesions by immunohistochemistry, assessed by central pathology laboratory. Results obtained at Screening or from an archival tumor biopsy (≤ 6 months) can be used as long as the test was performed by the study-designated central laboratory. Re-biopsy is required if the subject had disease progression or relapse since the last biopsy, or had received anti-cancer therapy since the last biopsy.
4. CTCL disease at study entry according to ISCL/EORTC (Olsen 2011).
   - Lead-in part: Stage IA – IV, except subjects with CNS involvement
   - Main Study: Stage I – III
5. History of prior therapies for CTCL as follows: must have had prior therapy; any number of prior therapies allowed.

   Topical treatments (except topical chemotherapy) and steroids are not considered as prior therapies.

   Prior therapies include: cytotoxic chemotherapy, combination cytotoxic chemotherapy, electron beam radiotherapy (EBRT), phototherapy (e.g., PUVA or UVB), photophoresis, interferon, topical chemotherapy (e.g., carmustine, nitrogen mustard), systemic retinoids, cyclosporin A (≥4 mg/kg/d for ≥1 month), or histone deacetylase inhibitors.

   Repeated use of the same agent counts as one therapy, unless part of a different combination regimen.
6. A minimum wash-out period of 4 weeks after previous CTCL therapy is recommended before the first dose of E7777. Subjects must have recovered from any adverse effects from any previous CTCL therapy to CTCAE Grade <2 before starting study drug. A shorter washout may be allowed if subject is experiencing progressive disease despite ongoing treatment.
7. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2 in the Lead-in part, and performance status 0 or 1 in the Main Study.
8. Life expectancy ≥3 months in the Lead-in part, and ≥12 months in the Main Study.
9. Adequate bone marrow reserve as evidenced by:
   - platelets ≥ 100,000/mm^3 ($100x10^9$/L)
   - clinically stable hemoglobin ≥ 9 g/dL (90 g/L) and hematocrit ≥27% without transfusion support.
10. Normal hepatic function as evidenced by:
    - bilirubin ≤ 1.5 × ULN and alkaline phosphatase ≤3.0 × ULN

- aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 × ULN
- albumin ≥ 3.0 g/dL (30 g/L)

If AST or ALT values are elevated, a second determination may be done ≥ 4 days later; if the values obtained upon the retest meet the above criteria, then the subject is considered to have met this criteria for entry

11. Adequate renal function as evidenced by serum creatinine ≤ 1.8 mg/dL (158 µmol/L) OR calculated creatinine clearance ≥ 50 mL/min (per the Cockcroft-Gault formula) with < 2+ protein OR 24-hour urine creatinine clearance ≥ 50 mL/minute with 24-hour urine protein < 1g.
12. Willing and able to comply with all aspects of the protocol.
13. Provide written informed consent prior to any study-specific screening procedures.
14. Females may not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
15. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (i.e., bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).
16. Females of childbearing potential must agree to use a highly effective method of contraception (e.g., total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. If currently abstinent, the subject must agree to use a double-barrier method as described above if she becomes sexually active during the study period or for 30 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation.
17. Male subjects must have had a successful vasectomy (confirmed azoospermia) or they and their female partner must meet the criteria above (i.e., not of childbearing potential or practicing highly effective contraception throughout the study period and for 30 days after study drug discontinuation).

Exclusion Criteria

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

1. Prior denileukin diftitox therapy.
2. Use of topical steroids within 14 days of Day 1 of initial therapy is not allowed, with the following exception:

   Topical steroids or systemic low dose steroids (≤10 mg/day prednisone) are allowed in subjects with erythroderma who have been on corticosteroids for a prolonged period of time and where discontinuation may lead to rebound flare in disease. The concomitant steroid medication is allowed as long as the type of steroid, route of administration, and steroid dose remain the same as the subject had been receiving for a prolonged period of time
3. Active malignancy (except for CTCL, definitively treated basal or squamous cell carcinoma of the skin, and carcinoma in-situ of the cervix) within the past 24 months.
4. Serious intercurrent illness.
5. Significant cardiac disease requiring ongoing treatment, including congestive heart failure (CHF), severe coronary artery disease (CAD), cardiomyopathy, uncontrolled cardiac arrhythmia, unstable angina pectoris, or myocardial infarction (MI) (within 6 months of study enrollment).
6. Significant pulmonary symptoms or disease.
7. History of uncontrolled seizure disorder or active central nervous system disease.
8. Major surgery within 2 weeks of study enrollment.

9. Significant or uncontrolled infections requiring systemic anti-infective therapy.
10. Known human immunodeficiency virus (HIV) infection; known active hepatitis B or hepatitis C infection.
11. Females who are pregnant (positive urine test) or breastfeeding.
12. Any history of a medical condition or a concomitant medical condition that, in the opinion of the investigator, would compromise the subject's ability to safely complete the study.

Study Treatment(s)

E7777 administered by intravenous (i.v.) infusion over 60 minutes on 5 consecutive days every cycle of 21 days.

- Premedication regimen for all subjects:

  Premedication for E7777 is required in Cycles 1 to 3, and is optional from Cycle 4 onward. The following should be administered approximately 30 minutes prior to each E7777 drug infusion:
  - Acetaminophen 650 mg by mouth (or per local institutional guideline [eg, paracetamol 500 mg by mouth]) to prevent fever and chills
  - Diphenhydramine 25 mg intravenous push or other antihistamine per local institutional guideline, to prevent hives, itching, rash, shortness of breath, and chills
  - Antiemetic agents per institutional standard
  - Hydration with 250 to 500 mL normal saline i.v. (or other amount of fluid considered to be most appropriate for the subject's condition, according to the judgment of the treating physician) before and after each E7777 infusion
- Premedication with systemic steroids:
  - **Lead-In part**. Subjects <u>should not</u> receive premedication with systemic steroids with the following <u>exception</u>:
    - In the event that a subject experiences an **<u>infusion reaction</u>** (i.e. within 24 hours of infusion) CTCAE (grade 2 or 3) after the first administration of E7777 on Cycle 1 Day 1, the premedication regimen for that subject <u>must</u> be supplemented during the rest of Cycle 1 (Days 2-5) with systemic corticosteroids (see below). Steroid premedication may be administered during subsequent treatment cycles at the discretion of the treating physician
    - In the event that a subject experiences an **<u>infusion related reaction</u>** at any time during any treatment cycle, the premedication regimen for that subject <u>may</u> be supplemented with systemic corticosteroids during the remainder of treatment days for that cycle (if event occurred before completion of cycle treatment) and/or in subsequent treatment cycles, at the discretion of the treating physician
    - Systemic corticosteroid premedication should be dexamethasone 4 mg, slow intravenous push OR equivalent corticosteroid dose according to institutional guidance.
  - **Main Study**. Same guidance as for the Lead-In.

Duration of Treatment

Study duration for each subject is as follows:

- Pre-treatment (screening and baseline): 4 weeks
- Treatment: up to 24 weeks (8 cycles)
- Extension: follow-up only, for up to 3 years after the end of study treatment

Treatment will stop upon completion of 8 cycles or disease progression* or unacceptable toxicity. The investigator or subject may also stop study treatment at any time for safety or personal reasons; however subject should remain on study, if possible, for follow-up.

* Treatment may continue after first notation of disease progression (PD) if the investigator is of the opinion that PD needs to be confirmed, e.g. in cases where (a) the apparent increased tumor burden in the skin or lymph nodes may reflect immune reaction/flare, or (b) the subject shows improvement or stable disease in the skin but increase in lymph node size.

Concomitant Drug/Therapy

- Topical steroids or systemic low dose steroids (equivalent to ≤ 10 mg/day prednisone) may be considered in subjects with erythroderma who have been on corticosteroids for a prolonged period of time and where

discontinuation may lead to rebound flare in disease, adrenal insufficiency, and/or unnecessary suffering. The concomitant steroid medication is allowed as long as the type of steroid, route of administration, and steroid dose remain the same as what the subject had been receiving for the prolonged period.

Medications allowed for relief of CTCL signs and symptoms are: hydroxyzine (25 mg), or ointments/lotions as specified in the protocol.

Assessments

Analysis Sets:

All Enrolled Subjects: All subjects who signed informed consent, and at Screening were assessed as meeting all inclusion criteria and not meeting any exclusion criteria. This will be the analysis set for demographics and baseline characteristics analyses.

Dose-Finding Analysis Set: All subjects in the Lead-In Part who completed Cycle 1 treatment and were evaluated for DLT, and those who discontinued during Cycle 1 due to DLT. This will be the analysis set for MTD determination in the Lead-In.

Full Analysis Set: All subjects who received study drug in the Main Study.

Primary Efficacy Analysis Set: All Stage I – III Main Study subjects who received study drug plus the Stage I – III Lead-In subjects from the 9µg/kg/day dose group.

Safety Analysis Set: All subjects who received study drug. This will be the analysis set for all safety analyses.

Stage I-III Safety Analysis Set: All Stage I – III Main Study subjects who received study drug plus the Stage I – III Lead-In subjects from the 9µg/kg/day dose group treated with E7777.

Per Protocol Set: All subjects in the Primary Efficacy Analysis and Full Analysis Sets who received study drug, and had a baseline and at least one post-dose tumor assessment and had no major protocol deviations. The per protocol analysis set will be identified prior to database lock. Full criteria for exclusion from the analysis set will be detailed in the statistical Analysis Plan. This will be the secondary analysis set for the efficacy analyses.

PK Analysis Set: All subjects from whom at least one valid E7777 pharmacokinetic parameter is obtained will comprise the analysis set for the PK and immunogenicity.

Population PK Analysis Set: All subjects from whom at least one quantifiable concentration of E7777 is available with a documented dosing history.

Population PK/PD Analysis Set: All subjects in the Population PK Analysis Set in whom efficacy and safety variables are also available.

Efficacy Assessments:

The ISCL/EORTC response criteria for mycosis fungoides and Sezary syndrome (Olsen 2011) will be used for efficacy analysis in the Lead-In as well as for primary efficacy analysis in the Main Study.

Tumor responses will be assessed by an independent central Response Review Committee (IRC) (Imaging Core Laboratory) for primary efficacy analysis in the Main Study. Tumor responses will also be assessed by the site investigator, and these site assessments will be used to make subject treatment decisions.

The response criteria described in Prince (2010) will be used as a supplemental alternate method (SAM) for the secondary objective of ORR. This supplemental assessment will be conducted by the IRC only.

For both the Lead-In and Main Study, photographs and CT scans will be sent by the investigator site to an Independent Imaging Core Laboratory designated by the sponsor for analysis. Laboratory results, including blood, as well as investigator skin assessments as entered in the CRF, will be sent to the Core Laboratory by the sponsor. At the time of data cutoff for primary analysis of the Main Study, the sponsor may choose to discontinue sending data (including photographs and scans) to the Imaging Core Laboratory.

Tumor assessment schedule (see protocol body for details):

- At screening, skin, lymph node assessment by palpation, blood assessment, and CT scan for assessment of nodal and visceral disease.
- During treatment: (1) skin and blood disease assessment, on Day 1 of every cycle, (2) lymph node assessment by palpation and CT scans of nodal disease (as needed) and visceral disease (as needed), and (3) lymph node biopsy is only recommended in situations where the histology would affect the Global

Response score. End-of-treatment tumor assessments should be performed if required for Global Response Score determination.

Follow-up: (1) skin and blood disease assessment to be performed every 4 weeks for 1 year after end of study treatment, then every 12 weeks thereafter for up to 3 years, or sooner if clinically indicated, (2) other assessments e.g. lymph node palpation, CT scans of nodal and visceral disease, or lymph node biopsy only if appropriate, as described in Section 9.5.2.2 of the protocol.

Measurement of Tumor Burden (see protocol body for details)

Tumor assessment and response criteria will be according ISCL/EORTC response criteria described in Olsen (2011). This is a composite measure of Tumor Burden in skin, lymph node, blood, and viscera. Briefly:

- Skin disease will be assessed by quantifying total body surface area (BSA) involvement using a modified Severity Weighted Assessment Tool (mSWAT). Since the IRC will perform a supplemental analysis using alternate method described in Prince (2010), the investigator will identify, photograph, and measure up to five representative skin lesions for subjects with skin lesions comprising <10% of BSA at all mSWAT assessment timepoints.
- Lymph node disease will be monitored by palpation and assessed by CT scan and/or biopsy, as necessary for determination of GRS.
- Blood tumor burden will be assessed by quantifying CD4+CD26- cells by flow cytometry; CD4+CD7- cells may be used in CD26+ subjects
- Visceral disease will be assessed by CT scan as appropriate.

Definitions of responses in skin, lymph node, blood, and viscera are provided in Appendix 4 of the protocol.

Secondary Tumor Assessment Method (Independent Review only)

The response criteria described in Prince (2010) will be used as a supplemental alternate method, for the secondary objective of ORR (IRC review only).

Patient's Pruritus Assessment

Subjects will rate the severity of pruritus using a 100-mm visual analog scale (VAS), on which zero indicates no itch and 100 indicates worst possible itch. A clinically significant improvement is defined as an absolute decrease of 20 mm from baseline maintained for ≥ 4 weeks; baseline score must be ≥ 20.

Subjects will be asked to refrain from the use of topical medication for the relief of pruritus symptoms for at least 12 hours prior to evaluation. Assessments should be performed during treatment and follow-up at the same time as skin disease SWAT assessments are performed.

Quality of Life assessments

Quality of Life assessments will be performed using Skindex-29 and FACT-G tools.

Efficacy Variables in the Main Study

All efficacy variables will be analyzed primarily in the Stage I – III Main Study subjects and the Stage I – III Lead-In subjects from the 9µg/kg/day dose group combined, and additionally in all subjects from the Main Study.

Primary Efficacy Variable:

Objective response (OR); OR is defined as the proportion of subjects with best response of CR or PR, using the Global Response Score of Olsen (2011).

Secondary Efficacy Variables:

- Duration of response (DOR) is defined as time from the date when criteria for response (CR or PR) based on GRS was first met until the date when the response was first lost (date of loss is date when first meets criteria for PD).
- Time to response (TTR) is defined as time from the date of first dosing to the date when criteria for response (CR or PR) based on GRS are first met.

- Skin response based on the mSWAT score is defined as the proportion of subjects with best response of CR or PR in skin.
- Duration of skin response based on the mSWAT Score is defined as time from the date when criteria for response in skin (CR or PR) was first met until the date when the response was first lost (date of loss is date when first meets criteria for global response PD).
- Time to skin response based on the mSWAT Score is defined as time from the date of first dosing to the date when criteria for response in skin (CR or PR) are first met.
- Objective response as determined by the alternate criteria of Prince (2010)

Exploratory Variables:

- Progression free survival (PFS) is defined as the date of first dosing to the first date that meets the criteria for PD or death as a result of any cause
- Time to Progression (TTP) is defined as time from the date of first dosing to the first date that meets the criteria for PD or death as a result of CTCL.
- Subject's Pruritus improvement rate is defined as the proportion of subjects with a clinically significant improvement in pruritus

Note: The same efficacy variables apply to the Lead-In.

Pharmacokinetics:

Non-Compartmental PK:

The following PK parameters will be determined from subjects with full PK profiles using noncompartmental methods:

- C_{max}, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$, T_{max}, $t½$, CL, Vd_{ss}

Population PK:

A population PK model for E7777 will be developed using non-linear mixed effect modeling. The model will be parameterized in terms of clearance and volume of distribution.

Population PK/PD:

PK/PD relationships between exposure to E7777 and some efficacy and safety variables will be explored graphically and may be followed by model-based analysis.

Further details of the population PK and PK/PD analyses will be documented separately in a stand-alone data analysis plan.

Immunogenicity:

Immune response to E7777 during the study treatment will be assessed by determining the anti-E7777 and anti-IL2 antibodies in serum during the study treatment. Additionally, neutralizing antibody assessment will also be performed in subjects who tested positive for anti-E7777 or anti-IL2 antibodies.

Safety:

Safety will be assessed by the regular monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs), hematology, blood chemistry, and urine values, vital signs, electrocardiograms (ECGs) and the performance of physical examinations including body weight and height.

Bioanalytical Methods

Quantitation of E7777 and Immunogenicity Assessments (Anti- E7777, Anti-IL2, and Neutralizing antibody)

E7777 will be measured in serum samples using validated bioanalytical methods.

Immunogenicity assessment in serum will be performed using validated bioanalytical methods to screen, confirm, and characterize the presence of anti-E7777 and anti-IL2 antibodies and, as necessary, neutralizing antibodies.

Statistical Methods

Statistical Design of Dose Escalation during the Lead-In Part:

The Lead-In part will be a dose-finding study including approximately 20 subjects. A CRM design will be used to determine the MTD of E7777. The MTD is defined in this study as the highest dose that has a ≤ 20% rate of DLT.

Six experimental doses are proposed and can be investigated: 3, 6, 9, 12, 15, and 18 µg/kg/d. The starting dose will be 6 µg/kg/d.

Starting with the 6 µg/kg/d dose, the prior distribution of the logistic parameters for P_T will be updated by the accruing data on DLTs each time a subject completes evaluation for toxicity in Cycle 1. Additional subjects will be allocated to the highest dose that has at least a 50% posterior probability of being tolerable (i.e., having a ≤ 20% DLT rate); the next dose allocated may be modified upon consultation with the safety consultancy investigator panel that is reviewing DLTs, based on overall cumulative safety results from the current study and/or on any emerging data from other studies with E7777. The first four subjects will be treated in series, i.e. each subject will be required to complete Cycle 1 before the next subject can be treated; open enrollment will start with the fifth subject. Dose levels cannot be skipped when escalating. The MTD will be determined when approximately 20 subjects have been tested, or when futility is declared. Futility is defined as having a <25% probability that any of the doses is safe (i.e., the probability that none of the six doses have a ≤ 20% DLT rate is <25%).

For additional details regarding the CRM, please refer to Sections 9.1.2 and 9.7.1 of the protocol.

Lead in:

The preliminary safety and efficacy endpoints will be summarized and listed for all subjects in the Safety Analysis Set.

Main Study:

All of the efficacy analyses for tumor assessment related endpoints will be performed using independent central review data as primary analyses. In addition, similar analyses will be performed using investigator assessment data as the secondary analyses.
All efficacy and Quality of Life (QoL) analyses will be performed primarily in Stage I – III Main Study subjects plus the Stage I – III Lead-In subjects from the 9µg/kg/day dose group combined, and additionally in all subjects from the Main Study.

Primary Efficacy Analysis:

ORR will be calculated in Stage I – III CTCL in subjects from the Main Study plus the Lead-In subjects from the 9µg/kg/day dose group combined, using a 2-sided, exact 95% confidence interval (CI), using the Clopper-Pearson method. The treatment will be considered efficacious and demonstrating clinical benefit of E7777 if the lower limit of the 2-sided 95% exact CI of the observed ORR exceeds 25%.

Secondary Efficacy Analyses:

- Skin response will be calculated with a 2-sided, exact 95% confidence interval (CI), using the Clopper-Pearson method.
- Duration of response (DOR), Time to Response (TTR), duration of skin response and time to skin response for E7777 will be calculated using Kaplan-Meier product-limit estimates and plotted over time. The medians for these endpoints and their corresponding 2-sided 95% CIs will be provided.
- ORR (by Prince [2010] criteria) will be calculated with a 2-sided, exact 95% confidence interval (CI), using the Clopper-Pearson method.

Exploratory Efficacy Analyses:

- Progression Free Survival (PFS) and Time to Progression (TTP) for E7777 will be calculated using Kaplan-Meier product-limit estimates and plotted over time. The medians for these endpoints and their corresponding 2-sided 95% CIs will be provided.
- Subject's Pruritus Improvement Rate will be calculated with a 2-sided exact 95% CI using the Clopper-Pearson method. In addition, the percentages of subjects who have ≥ 20% and ≥ 50% improvements relative to baseline in each of the VAS-based assessment scores will be tabulated. The frequency of use of rescue

medications will determined by comparing the number of packages dispensed and the number of packages returned.

- Sensitivity analyses for ORR in subjects receiving vs not receiving steroid premedication.
- QoL analyses will be performed.

Pharmacokinetic and Immunogenicity Analyses

Pharmacokinetics

PK parameters will be summarized descriptively based on the PK analysis set, and will be compared between E7777-treated subjects. Potential relationships between the E7777 serum concentration data and tumor response as well as adverse events will be explored.

Immunogenicity

The percentage of subjects testing positive for anti-E7777 and anti-IL-2 antibodies at baseline and during study treatment will be assessed. Potential relationships between presence of anti-E7777 antibodies and tumor response as well as adverse events will be explored.

Safety Analyses

Evaluation of safety will be performed on the Safety Analysis Set. Safety analyses for the Lead-In part will be done using all the Safety Analysis Set subjects. The safety analyses for the Main Study will be performed in all Safety Analysis Set subjects and all Safety Analysis Set Stage I – III subjects, separately. Safety data to be evaluated include AEs, clinical laboratory results (including thyroid function assessments), vital signs, electrocardiograms (ECGs), and the results of physical examinations.

Safety parameters will be summarized using descriptive statistics (mean, standard deviation, median, Q1, Q3, and range for continuous variables; numbers and percentages for categorical measures).

Dose-limiting toxicities will be listed for each Lead-In dose cohort. DLT rates will be calculated.

Sample Size Rationale

Sample size for Lead-In Part

The number of subjects in the Lead-in will be approximately 20, based on the CRM design requirements.

Sample size for Main Study

The sample size of approximately 70 Stage I – III subjects (including Stage I – III subjects from both the Main Study plus from the Lead-In part 9 μg/kg/day dose group combined) was estimated assuming that the lower limit of the 2-sided 95% CI of ORR exceeding 25% indicates clinical benefit in persistent and recurrent CTCL; and that in this population we can reasonably expect to observe an ORR ≥ 36%, i.e., at least 25 subjects with CR+PR among 70 subjects.

With a sample size of approximately 70 Stage I – III subjects (including Stage I – III subjects from both the Main Study and from the Lead-In part 9 μg/kg/day dose group), the 2-sided 95% exact Clopper-Pearson confidence interval of an observed 36% ORR would range from 25% to 48%. Thus, an observed ORR that is ≥ 36% would be significantly higher than 25%, thereby demonstrating the presence of clinical benefit.

Sample size estimates were calculated using PASS 2008.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
$AUC_{(0-t)}$	area under the curve from time 0 to time t
$AUC_{(0-inf)}$	area under the curve from time 0 to infinity
β-hCG	beta-human chorionic gonadatropin
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
CA	Competent Authority
CAD	severe coronary artery disease
CBC	complete blood count
CD4	cluster of differentiation 4, a marker antigen for helper T-cells
CD7	cluster of differentiation 7
CD25	cluster of differentiation 25, α-chain subunit of the IL-2R
CFR	Code of Federal Regulations
CDF	cumulative distribution function
CI	confidence interval
CL	total body clearance
CLS	capillary leak syndrome
C_{max}	maximum drug concentration
CPK	creatine phosphokinase
CPMP	Committee for Proprietary Medicinal Products
CR	complete response
CRA	clinical research associate
CRF	case report form
CRM	continual reassessment method
CS	color distortion
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	cutaneous T-cell lymphoma

CV	curriculum vitae
DAB_{389}IL-2	denileukin diftitox, ONTAK®
DLT	dose-limiting toxicity
DOR	duration of response
EBRT	electron beam radiotherapy
ECG	electrocardiagram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
EORTC	European Organization for Research and Treatment of Cancer
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
^{18}FDG-PET	^{18}fluorodeoxyglucose positron emission tomography
FFPE	formalin fixed paraffin embedded
GCP	Good Clinical Practice
GRS	Global Response Scoring
HDI	histone deacetylase inhibitor
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IHC	immunohistochemistry
IL-2	interleukin-2
IRB	Institutional Review Board
IRC	Independent Review Committee
ISCL	International Society for Cutaneous Lymphomas
IUD	intrauterine device
i.v.	intravenous
IxRS	interactive voice and web response system
LDi	longest diameter
LNH	low/normal/high
MedDRA	Medical Dictionary for Regulatory Activities
MF	mycosis fungoides

MHRA	Medicines and Healthcare Products Regulatory Agency
MI	myocardial infarction
mmHg	millimeters of mercury
mSWAT	modified Severity Weighted Assessment Tool
MTD	maximum tolerated dose
N/A	not applicable
NI	not involved
ONTAK®	DAB_{389}IL-2, denileukin diftitox
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic(s)
PR	partial response
PUVA	psoralen ultraviolet light A
QoL	Quality of Life
QT	measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's correction
RBC	red blood cells
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SD	standard deviation
SDi	short axis
SOC	system organ class
SPD	sum of the products of the perpendicular diameters
SS	Sézary syndrome
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
T_3	triiodothyronine
T_4	thyroxine

TEAE	treatment-emergent adverse event
Treg	regulatory T-lymphocyte
t_{max}	time to reach maximum (peak) concentration following drug administration
TSH	thyroid stimulating hormone
TTP	time to progression
TTR	time to response
US	United States
USP	United States Pharmacopoeia
ULN	upper limit of normal
UVB	ultraviolet light B
VA	visual acuity
VAS	visual analog scale
Vd_{ss}	volume of distribution at steady state
WBC	white blood cell
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent, and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the informed consent form (ICF) will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (e.g., change in clinical research associate(s) [CRA(s), change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (PI) (or if regionally required, 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 (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to the IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The end of the study will be the date of the last study visit for the last subject in the study. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

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, 2013

- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312

- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.

- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP

- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject (or guardian/legally authorized representative) 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. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations and provided to the sponsor. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 15 global investigational sites.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor are listed in the Regulatory Binder provided to each site.

7 INTRODUCTION

7.1 E7777

Denileukin diftitox is a recombinant cytotoxic fusion protein composed of the amino acid sequences for diphtheria toxin fragments A and B (Met_1-Thr_{387})-His and for human interleukin-2 (Ala_1-Thr_{133}). Denileukin diftitox has been marketed in the US as ONTAK® (Eisai code name E7272) since 1999 and is indicated for the treatment of patients with persistent or recurrent cutaneous T-cell lymphoma (CTCL) whose malignant cells express the CD25 component of the IL-2 receptor.

ONTAK may exhibit antineoplastic action through a direct cytocidal action on IL-2-expressing tumors, or through its ability to deplete immunosuppressive regulatory T-lymphocytes (Tregs) that are recruited into tumor infiltrates to assist tumors in evading host immune surveillance.

E7777 is the same recombinant protein as denileukin diftitox but has improved purity compared with ONTAK. E7777 was developed as a result of a refined manufacturing process and has an increased percentage of protein monomer species, with a concomitant decrease in levels of misfolded protein and protein aggregates compared with ONTAK. The increase in bioactivity per milligram of protein in the E7777 finished drug product has been confirmed in nonclinical studies.

7.2 Mechanism of Action of E7777 / Denileukin Diftitox

Denileukin diftitox is a cytotoxic protein designed to direct the cytocidal action of diphtheria toxin to cells that express the IL-2 receptor. The mechanism of action for E7777 is the same as for ONTAK, as both proteins comprise the same amino acid sequence and active domains. Upon binding to the IL-2 receptor on the cell surface, denileukin diftitox is internalized by receptor-mediated endocytosis. The fusion protein is subsequently cleaved, releasing diphtheria toxin enzymatic and translocation domains from the IL-2 fragment, resulting in the inhibition of protein synthesis and, ultimately, cell death. As a result, clinical antitumor activity against a range of tumor types expressing the IL-2 receptor (e.g., CTCL) has been observed with ONTAK.[1] In addition, ONTAK has been reported to have antineoplastic effects against tumors in which IL-2R-expressing Tregs play a role in helping tumors escape host immunesurveillance.[2] E7777 likely retains the activity of ONTAK against IL-2R-expressing Tregs.

7.3 Clinical Experience With ONTAK and E7777

7.3.1 Clinical Experience with ONTAK (Denileukin Diftitox)

Since E7777 and ONTAK have a common active moiety, clinical experience with ONTAK in T-cell lymphoma provides relevant background information. The most extensive clinical experience for denileukin diftitox is in CTCL. More than 300 subjects have been treated in Phase 3 and Phase 4 studies, including one randomized placebo-controlled trial. Data on efficacy, safety, pharmacokinetics (PK), and immunogenicity are summarized below:

- Efficacy: ONTAK has shown clinical efficacy at doses of 9 or 18 µg/kg/day administered intravenously for 5 consecutive days every 3 weeks, with an objective response rate (ORR) of 38% in 263 subjects.
- Safety: ONTAK is generally well tolerated, with the most notable AEs being infusion reaction and capillary leak syndrome (CLS). Please refer to the Investigator's Brochure (IB) for details on the safety profile.[3]
- PK: After the first dose, ONTAK is rapidly distributed and has a terminal elimination half-life ($t_{½}$) of 70 to 80 minutes. No accumulation was apparent between Day 1 and Day 5 of dosing, and the clearance increased from Cycle 1 to Cycle 3 corresponding to a 75% decrease in exposure.
- Immunogenicity: Immune response to ONTAK was tested in the Phase 3 studies. At baseline, 66% of subjects (N=95) tested positive for antibodies to denileukin diftitox; after 1, 2, or 3 cycles of treatment, 94%, 99%, and 100% of subjects tested positive, respectively. Antibody titers increased after 2 cycles, with PK parameters indicating decreased systemic exposure to drug.

Please refer to the Investigator's Brochure for more detailed information on clinical experience with ONTAK.

7.3.2 Clinical Experience With E7777

E7777 has been tested on one other study in addition to this protocol. A Phase 1/1b first-in-human trial was conducted in Japan, with the objective to establish the maximum tolerated dose (MTD) and to assess tolerability of E7777 administered as a continuous 5-day schedule every 21 days. As of Feb 2016, accrual was completed at 13 subjects and the MTD was determined to be 9 µg/kg/day.

Please refer to the Investigator's Brochure for more detailed information on clinical experience with E7777.

7.4 CTCL and Current Therapeutic Options

Cutaneous T-cell lymphomas account for about 10 to 15 percent of all cases of non-Hodgkins lymphoma. The most common variant of CTCL (about 50% of cases) is mycosis fungoides (MF). Less common is Sézary syndrome (SS), a leukemic variant that affects about 5% of patients with CTCL.

Typically, the natural history of MF is indolent, with cutaneous symptoms waxing and waning over a period of years. Cutaneous disease progresses from an eczematous patch/plaque stage (T1) to plaque stage covering (T2), and finally to tumors (T3) that frequently undergo necrotic

ulceration. SS is thought to be an advanced form of MF with generalized erythroderma (T4) and peripheral blood involvement at presentation. The prognosis of patients with MF/SS is based on the extent of disease at presentation; patients with stage IA disease have a median survival of 20 or more years while patients with stage III through stage IV disease have a median survival of less than 5 years.

A number of therapeutic options are available to treat CTCL; these include skin-directed therapies, phototherapies, radiation, and systemic therapies. Often a combination of either sequential or concomitant therapies gives a higher rate of response, but patients with advanced disease often relapse and no therapy has been proven to be curative. Extensive skin or blood involvement, tumors, or nodal disease require systemic therapy with biologic response modifiers, bexarotene, ONTAK (denileukin diftitox), skin radiation, and single- or multi-agent chemotherapy. Over the past few years, the FDA has approved two histone deacetylase inhibitors (HDIs), vorinostat and romidepsin, for treatment of CTCL.

7.5 Study Rationale

This study is intended to demonstrate the efficacy and safety of E7777 to support a marketing application.

The rationale for developing E7777 for the indication of CTCL is based on the structure and preclinical activity of E7777. E7777 is composed of the same amino acid sequences as ONTAK (i.e., has the same active moiety). In addition, in preclinical studies ONTAK and E7777 have been shown to have cytocidal activity in a cell-based viability inhibition assay using the HH cell line, which was derived from a CTCL patient and expresses the intermediate affinity form of the IL-2 receptor, supporting the concept that E7777 will have a cytocidal activity against IL-2R-expressing CTCL tumor cells.

E7777 is increased-purity ONTAK, with a higher proportion of active monomer species and a lower proportion of protein aggregates and misfolded proteins compared to ONTAK. An increase in specific bioactivity (on a weight basis) of the E7777 finished drug product has been confirmed in nonclinical studies. Due to the altered proportion of different protein species and the 1.5- to 2-fold increased potency of E7777 compared to commercial ONTAK, this clinical study is being conducted to establish the appropriate clinical dose of E7777 to administer and to confirm the safety and efficacy of E7777 in CTCL.

8 STUDY OBJECTIVES

8.1 Lead-In Part

Primary Objectives:

- To establish the maximum tolerated dose (MTD) of E7777 and to select the dose of E7777 to be used in the Main Study.

Secondary Objectives:

- To assess safety, tumor response, pharmacokinetics (PK), and immunogenicity after treatment with E7777.

8.2 Main Study

All Main Study efficacy analyses will be performed primarily in the Stage I – III Main Study subjects plus the Stage I – III Lead-In subjects from the 9µg/kg/day dose group, as well as additionally in all subjects from the Main Study.

Primary Objective:

- To demonstrate efficacy of E7777 in subjects with recurrent or persistent CTCL in Stage I – III subjects as assessed by ORR; Objective Response is Complete Response (CR) plus Partial Response (PR), according to ISCL/EORTC Global Response Score (Olsen 2011)[6]

Secondary Objectives:

- To determine Duration of Response (DOR) for E7777
- To determine time to response after E7777 treatment
- To determine skin response after E7777 treatment
- To determine duration of skin Response after E7777 treatment
- To determine time to skin response after E7777 treatment
- To assess ORR for E7777 using the alternate response assessment criteria of Prince (2010)[5]
- To evaluate safety and tolerability of E7777 in all subjects and in subjects
- To evaluate safety and tolerability of E7777 in the Stage I – III Main Study subjects plus the Stage I – III Lead-In subjects from the 9µg/kg/day dose group combined

- To characterize the pharmacokinetics (PK) of E7777 and immunogenicity after treatment with E7777

Exploratory Objectives:

- To assess two efficacy endpoints for subjects treated with E7777: progression-free survival (PFS) and time to progression (TTP) (using Global Response Score)
- To assess pruritus improvement reported by subjects treated with E7777
- To assess Quality of Life (QoL) for (1) all subjects treated in the Lead-In part, (2) all subjects treated in the Main Study part, and (3) Stage I – III Main Study subjectsplus Stage I – III Lead-In subjects from the 9µg/kg/day dose group combined.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

9.1.1 Overall Design

This is a multicenter open-label, single-arm study of E7777 in subjects with recurrent or persistent CTCL.

The study will consist of an initial Lead-In part followed by the Main Study:

- **Lead-In**: A Continual Reassessment Method (CRM) will be employed to establish the MTD of E7777 and to select the dose of E7777 to be used in the Main Study. Approximately 20 subjects will be treated.
- **Main Study**: A sufficient number of subjects in the Main Study will be recruited so that approximately 70 Stage I – III subjects from both the Main Study and from the Lead-In subjects in the 9µg/kg/day dose group with recurrent or persistent CTCL will be treated with E7777 to assess efficacy. Safety will be evaluated in all subjects from the Main Study, and in the Stage I – III Lead-In subjects from the 9µg/kg/day dose group. The dose of E7777 in the Main Study will be the dose selected in the Lead-In part of the study. The primary efficacy analysis will be based on Stage I – III subjects from both the Main Study plus from the Lead-In 9µg/kg/day dose group combined.

The Lead-In and Main Study designs are described in detail in Sections 9.1.2 and 9.1.3.

Study Phases for Each Subject

Subjects in the study will move through three phases while on study.

- **Pretreatment Phase**, consisting of two Periods:
  - Screening

- Baseline

- **Treatment Phase**, consisting of the following periods:
  - **Treatment Period.** Treatment with E7777 for up to 8 cycles; each cycle of 21 days is one Period. Subjects who have attained skin tumor response and are deriving clinical benefit from E7777 treatment may continue receiving treatment beyond 8 cycles, at the discretion of the treating physician.
  - **Follow-Up Period**, for follow-up of tumor assessment, with immunogenicity and survival follow-up as appropriate.

After data cutoff for the primary analysis in the Main Study, the study moves to the Extension Phase.

- **Extension Phase**, consisting of the following periods:
  - **Treatment Period**, for continued treatment of subjects with ongoing treatment at data cutoff.
  - **Follow-Up Period**, for follow-up of tumor assessment, with immunogenicity and survival follow-up as appropriate.

The Study Phases are described in more detail in Section 9.1.4.

Pharmacokinetics and Immunogenicity

Serial PK assessment of E7777 will be performed on all subjects in the Lead-In part and on the first 12 subjects in the Main Study, using serial blood PK sampling on Day 1 in Cycles 1, 3, and 5, with sparse sampling in Cycle 8. In addition, sparse sampling will be performed in the Main Study on the rest of the subjects on Day 1 of Cycle 1.

Immunogenicity (formation of antibodies to E7777 or IL-2, and of neutralizing antibodies) will be assessed in all subjects in both the Lead-In part and the Main Study. A predose blood sample for immunogenicity assessment will be collected before Day 1 dosing in Cycles 1, 2, 3, 5, and 8; after that, subjects who tested positive at any time for anti-IL2 will be followed up for immunogenicity testing for anti-IL2 on a 6-month schedule for one year and every year thereafter until antibody titers decrease to baseline level or upon study termination.

Primary Analysis

The primary analysis will be performed after data cutoff, which will be either of the following two events, whichever occurs later: (1) when all subjects in the Main Study have either completed Cycle 8 or are off treatment, or (2) when all subjects with at least one documented time point response of PR or better have undergone the subsequent tumor assessments necessary for confirmation of response (unless the subject had disease progression or discontinued from study before then).

9.1.2 Lead-In Part

A Continual Reassessment Method (CRM) will be employed to determine the MTD of E7777,

targeting a rate of dose-limiting toxicity (DLT) of approximately 20%.

Subjects will be treated with E7777 for 5 consecutive days during every cycle of 21 days. The doses of E7777 that may be used are 3, 6, 9, 12, 15, or 18 µg/kg/d, with 6 µg/kg/d specified as the starting dose. Each subject will be assigned a dose of E7777 in accordance with the rules of the CRM design. The CRM design is described under Section 9.7 "Statistical Methods."

Dose-limiting toxicities are based on known toxicities of ONTAK, as described in the US product label. A DLT will be any of the following occurring within the **first cycle** of therapy:

- Serious infusion reaction, defined as CTCAE Grade 4 adverse event of "Infusion related reaction", or recurrent CTCAE Grade 3 despite administration of systemic steroid premedication after initial occurrence. Infusion reactions are defined as symptoms (e.g., fatigue, nausea, vomiting, arthralgia, myalgia, pyrexia, chills, rigors) occurring within 24 hours of E7777 infusion.

- Capillary leak syndrome (CLS) CTCAE Grade 4 or Grade 3 (with exceptions).

  The CTCAE definitions are broad and general, therefore the following guidance is provided:

  - Grade 4 is life-threatening severity such as subjects experiencing hypovolemic shock or renal failure, or who need treatment with vasopressors or oxygen
  - Grade 3 is severe symptoms (less severe than the Grade 4 symptoms above) that may or may not be dose-limiting. For example, severe symptoms requiring hospitalization for acute intervention would be a DLT, whereas less severe symptoms leading to hospitalization for prophylactic treatment with fluids or diuretics would not be a DLT. Hospitalization or medical intervention to prevent hospitalization is not in itself a DLT as the threshold for hospitalization may differ by doctor and region.

  CLS is defined as the noted occurrence of at least 2 of the following: hypotension, edema, or serum albumin < 3.0 g/dL. These are not required to occur simultaneously to be characterized as CLS.

- Clinical visual impairment. This could be loss of visual acuity and/or color vision.

- Any CTCAE ≥ Grade 4 adverse event that may represent an infusion reaction.

- Any CTCAE Grade 3 adverse event that may represent an infusion reaction that prevents the entire dose of E7777 from being administered despite appropriate treatment.

- Any other Grade 3 or greater toxicity assessed as related to E7777 treatment, and which in the opinion of a safety consultancy investigator panel constitutes a dose-limiting toxicity.

Determination as to whether a subject has experienced a DLT will be made by the treating physician in consultation, as needed, with the medical monitor and investigator(s) on the Protocol Steering Committee (PSC) who are experienced in the use of denileukin diftitox.

Subjects who are not evaluable for DLT in Cycle 1 should be replaced.

If, during the course of the Lead-In part, a trend is noted by the PSC (see DLT assessment above) where the E7777 toxicities described above are observed beyond the first cycle but not in Cycle 1, the definition of DLT may be amended to reflect that observation.

Selection of the dose of E7777 that will be used in the Main Study will be made in consultation with the PSC based on review of the full output of the CRM data.

The dose-finding steps of the CRM design are shown in Figure 1.

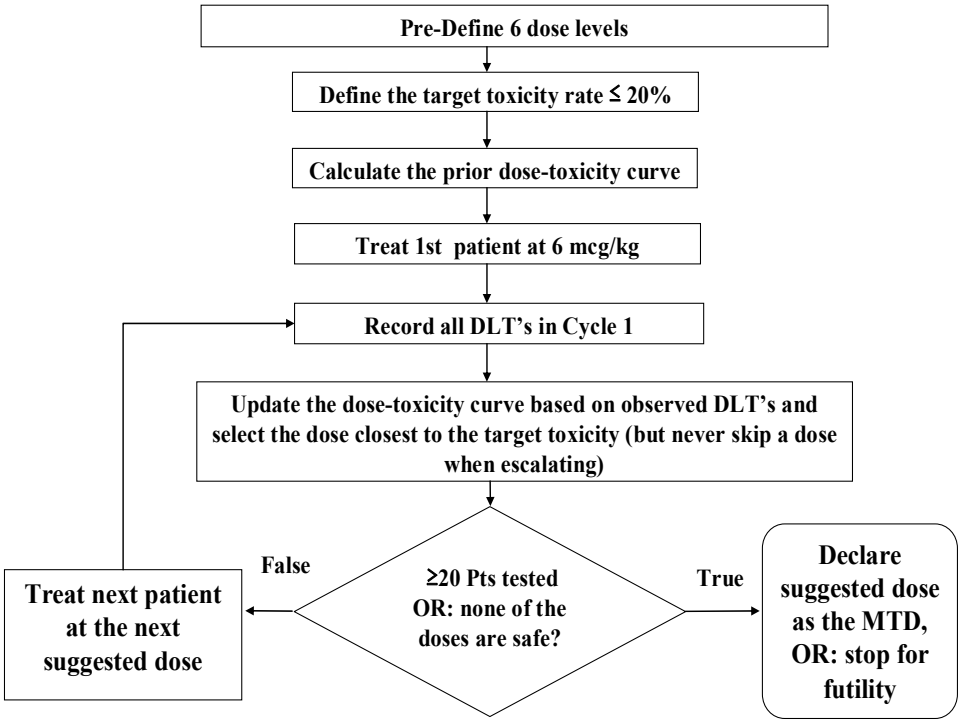

Figure 1 Continual Reassessment Method

9.1.3 Main Study

Enrollment in the Main Study will commence after an acceptably safe dose has been established in the Lead-In part, as described in Section 9.1.2, and there is at least one objective response by investigator assessment recorded in the Lead-In.

The objectives of the Main Study are to assess the efficacy and safety of E7777 in Stage I - III subjects with recurrent and persistent CTCL. A sufficient number of subjects in the Main

Study will be treated for an approximate total of 70 Stage I – III subjects combined from both the Main Study plus from the Lead-In subjects from the 9µg/kg/day dose group .

9.1.4 Study Phases

Subjects in the study will move through study phases as described below.

Pretreatment Phase

The Pretreatment Phase includes a Screening Period and a Baseline Period.

- The Screening Period is from Day -28 to the start of treatment (Cycle 1 Day 1) except for signing of the informed consent form (ICF) which may be up to 8 weeks before the first dose of study drug. The purpose of the Screening Period is to obtain informed consent and to ensure that each subject will meet all the specified eligibility criteria.

- The Baseline Period is from Day -7 to the start of treatment. Subjects who complete Baseline assessments and meet the eligibility criteria will begin treatment in the Treatment Phase.

Treatment Phase

The Treatment Phase will consist of the following Periods:

- **Treatment Period**. Treatment with E7777 for up to 8 cycles. Each cycle of 21 days is one Period. Subjects who have attained skin tumor response and are deriving clinical benefit from E7777 treatment may continue receiving treatment beyond eight cycles, at the discretion of the treating physician.

- **Follow-up Period.** Tumor assessment until discontinuation of treatment due to progressive disease [PD]); immunogenicity, and survival follow-up until relapse or initiation of new systemic anti-cancer therapy. All Follow-up assessments performed for up to 3 years after end of treatment, or until sponsor termination of the study.

After data cutoff for the primary analysis in the Main Study, the study moves to the Extension Phase.

Extension Phase

The Extension Phase consists of the following Periods:

- **Treatment Period**, for continued treatment of subjects with ongoing treatment at data cutoff. Subjects will be treated for up to 8 cycles. Subjects who have attained skin tumor response and are deriving clinical benefit from E7777 treatment may continue receiving treatment beyond 8 cycles, at the discretion of the treating physicians.

- **Follow-up Period**. Tumor assessment until discontinuation of treatment due to PD;

immunogenicity, and survival follow-up until relapse, or initiation of new systemic anticancer therapy. All Follow-up assessments will be performed for up to 3 years after the end of treatment, or until sponsor termination of the study.

9.2 Discussion of Study Design, Including Choice of Control Groups

The primary objective of the study is to confirm efficacy and safety of E7777. This will be done using a single-arm design in the Main Study. A single-arm design is considered appropriate since E7777 has the same active ingredient as ONTAK, and efficacy of ONTAK has already been demonstrated in multiple Phase 3 studies, including a randomized placebo-controlled study.

The Main Study is preceded by a Lead-In part to establish the maximum tolerated dose of E7777. The MTD or a lower acceptably safe dose established in the Lead-In part will be used in the Main Study to assess the efficacy and safety of E7777. Selection of the dose of E7777 that will be used in the Main Study will be made in consultation with the safety consultancy investigator panel (comprised of selected investigators from this study), based on review of the full output of the CRM data. Establishment of the dose of E7777 is necessary because E7777 has increased potency compared with ONTAK, due to an increased proportion of active monomer species and a decrease in levels of misfolded protein and protein aggregates compared with ONTAK. Safety, PK, and immunogenicity for E7777 will be established as well because of this increased potency.

A CRM will be employed to determine the maximum tolerated dose for E7777. This is an accepted adaptive design that is statistically more robust than the conventional 3+3 dose-escalation method used in most Phase 1 studies. Dose-limiting toxicities are defined based on known serious ONTAK toxicities, but also include any unexpected toxicities. The selection of the < 20% DLT rate for MTD definition is based on the observed DLT level for ONTAK in previous Phase 3 studies.

9.3 Selection of Study Population

Approximately 20 subjects will be treated in the Lead-In part. A sufficient number of subjects in the Main Study will be treated for an approximate total of 70 Stage I – III subjects from both the Main Study and from Lead-In subjects from the 9µg/kg/day dose group. The study total will be approximately 115 subjects treated at approximately 20 global investigational sites. 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.

In the Main Study, the study population is defined so that it will match as closely as possible the study population of the pivotal ONTAK study L4389-11. This is because the primary efficacy of objective response rate in this study is being compared to the historical response rates observed with treatment and placebo groups in the ONTAK study L4389-11. The definition of CTCL disease stage and status at study entry in this study takes into account the new CTCL staging criteria that was published in 2007 (Olsen 2007).

9.3.1 Inclusion Criteria

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

1. Age ≥ 18 years.

2. Histopathologic diagnosis of CTCL (mycosis fungoides [MF] or Sézary Syndrome [SS]), confirmed by skin biopsy, or lymph node, or blood assessment, of current disease.

3. CD25 assay-positive tumor, defined as detectable CD25 on ≥ 20% of total lymphoid infiltrate in biopsied lesions by immunohistochemistry, assessed by a central pathology laboratory. Results obtained at Screening or from an archival tumor biopsy (≤ 6 months) can be used as long as the test was performed by the study-designated central laboratory. Re-biopsy is required if the subject had disease progression or relapse since the last biopsy or had received anticancer therapy since the last biopsy.

4. CTCL disease at study entry according to ISCL/EORTC[4,6] (see Appendix 1).
   - Lead-In part: Stage IA – IV, except subjects with CNS involvement
   - Main Study: Stage I – III

5. History of prior therapies for CTCL as follows: must have had prior therapy, any number of prior therapies allowed.

   Topical treatments (except topical chemotherapy) and steroids are not considered as prior therapies.

   Prior therapies allowed include:

   - Cytotoxic chemotherapy
   - Combination cytotoxic chemotherapy
   - Electron beam radiotherapy (EBRT)
   - Phototherapy (e.g., psoralen ultraviolet light A [PUVA] or ultraviolet light B [UVB])
   - Photophoresis
   - Interferon
   - Topical chemotherapy (e.g., carmustine, nitrogen mustard)
   - Systemic retinoids
   - Cyclosporin A (≥ 4 mg/kg/d for ≥ 1 month)
   - Histone deacetylase inhibitors

   Repeated use of the same agent counts as one therapy, unless it is part of a different combination regimen.

6. A minimum washout period of 4 weeks after previous CTCL therapy is recommended before the first dose of E7777. Subjects must have recovered from any adverse effects from any previous CTCL therapy to CTCAE Grade <2 before starting study drug. A shorter washout may be allowed if a subject is experiencing progressive disease despite

ongoing treatment.

7. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2 in the Lead-In part, and performance status 0 or 1 in the Main Study (Appendix 2).

8. Life expectancy ≥ 3 months in the Lead-In part and ≥ 12 months in the Main Study.

9. Adequate bone marrow reserves as evidenced by:
    a. platelets ≥ 100,000/mm^3 (100 × 10^9/L)
    b. clinically stable hemoglobin ≥ 9 g/dL (90 g/L) and hematocrit ≥27% without transfusion support

10. Normal hepatic function as evidenced by:
    a. bilirubin ≤ 1.5 × the upper limit of normal (ULN) and alkaline phosphatase ≤3.0 × ULN
    b. aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 × ULN
    c. albumin ≥ 3.0 g/dL (30 g/L)

    If AST or ALT values are elevated, a second determination may be made ≥ 4 days later; if the values obtained upon the retest meet the above criteria, then the subject is considered to have met this criterion for entry.

11. Adequate renal function as evidenced by serum creatinine ≤ 1.8 mg/dL (158 µmol/L) OR calculated creatinine clearance ≥ 50 mL/min (per the Cockcroft–Gault formula [Appendix 3]) with < 2+ protein OR 24-hour urine creatinine clearance ≥ 50 mL/minute with 24-hour urine protein < 1 g.

12. Willing and able to comply with all aspects of the protocol.

13. Provide written informed consent prior to any study-specific screening procedures.

14. Females may not be lactating or pregnant at Screening or Baseline (as documented by a negative beta-human chorionic gonadotropin [ß-hCG] test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

15. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (i.e., bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).

16. Females of childbearing potential must agree to use a highly effective method of contraception (e.g., total abstinence, an intrauterine device [IUD], a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 30 days after study drug discontinuation. If currently abstinent, the subject must agree to use a double-barrier method as described above if she becomes sexually active during the study period or for 30 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks prior to dosing and must continue to use the same contraceptive during the study and for 30 days after study drug discontinuation.

17. Male subjects must have had a successful vasectomy (confirmed azoospermia) or they and their female partner must meet the criteria above (i.e., not of childbearing potential or practicing highly effective contraception throughout the study period and for 30 days after study drug discontinuation).

9.3.2 Exclusion Criteria

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

1. Prior denileukin diftitox therapy.

2. Use of topical steroids within 14 days of Day 1 of initial therapy is not allowed, with the following exception:

   Topical steroids or systemic low dose steroids (≤ 10 mg/day prednisone) are allowed in subjects with erythroderma who have been on corticosteroids for a prolonged period of time and where discontinuation may lead to rebound flare in disease. The concomitant steroid medication is allowed as long as the type of steroid, route of administration, and steroid dose remain the same as what the subject had been receiving for a prolonged period of time.

3. Active malignancy (except for CTCL, definitively treated basal or squamous cell carcinoma of the skin, and carcinoma in-situ of the cervix) within the past 24 months .

4. Serious intercurrent illness.

5. Significant cardiac disease requiring ongoing treatment, including congestive heart failure (CHF), severe coronary artery disease (CAD), cardiomyopathy, uncontrolled cardiac arrhythmia, unstable angina pectoris, or myocardial infarction (MI) (within 6 months of study enrollment).

6. Significant pulmonary symptoms or disease.

7. History of uncontrolled seizure disorder or active central nervous system disease.

8. Major surgery within 2 weeks of study enrollment.

9. Significant or uncontrolled infections requiring systemic anti-infective therapy.

10. Known human immunodeficiency virus (HIV) infection; known active hepatitis B or hepatitis C infection.

11. Females who are pregnant (positive urine test) or breastfeeding.

12. Any history of a medical condition or a concomitant medical condition that, in the opinion of the investigator, would compromise the subject's ability to safely complete the study.

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator 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; however, the subject should remain on study, if possible, for follow-up.

If a subject discontinues early from study treatment, the subject will enter the Follow-Up Period and complete protocol-specified off-treatment visits, procedures, and survival follow-up unless the subject withdraws consent.

During the Lead-In part, subjects who are not evaluable for DLT in Cycle 1 should be replaced. In the Main Study, subjects who withdraw from treatment or study participation will not be replaced. Treatment will stop upon disease progression, unacceptable toxicity, or death.

During the Follow-Up Period, subjects who have discontinued study treatment without progression should have disease assessments as specified in Section 9.5.2.2 until disease progression is documented or another new systemic anti-cancer therapy is initiated.

9.4 Treatments

9.4.1 Treatments Administered

E7777 will be administered by intravenous (i.v.) infusion over 60 minutes (± 10 minutes) on 5 consecutive days in every 21-day cycle.

The E7777 dose in the Lead-In will be as assigned by CRM.

The E7777 dose in the Main Study will be 9 µg/kg.

Treatment will stop upon completion of 8 cycles or disease progression* or unacceptable toxicity. Subjects who have attained skin tumor response and are deriving clinical benefit from E7777 treatment may continue receiving treatment beyond 8 cycles, at the discretion of the treating physician.

The investigator or subject may also stop study treatment at any time for safety or personal reasons; however subject should remain on study, if possible, for follow-up.

*Treatment may continue after first notation of disease progression (PD) if the investigator

is of the opinion that PD needs to be confirmed, eg, in cases where (a) the apparent increased tumor burden in the skin or lymph nodes may reflect immune reaction/flare, or (b) the subject shows improvement or stable disease in the skin but increase in lymph node size. In this case, treatment will stop after 2 successive notations of PD.

9.4.1.1 Premedication

Premedication for All Subjects

Premedication for E7777 is required in Cycles 1 to 3 and is optional from Cycle 4 onward. The following should be administered approximately 30 minutes before each E7777 drug infusion:

- Acetaminophen 650 mg by mouth (or per local institutional guideline [e.g., paracetamol 500 mg by mouth]) to prevent fever and chills
- Diphenhydramine 25 mg i.v. push or other antihistamine per local institutional guideline to prevent hives, itching, rash, shortness of breath, and chills
- Antiemetic agents per institutional standard
- Hydration with 250 to 500 mL normal saline i.v. (or other amount of fluid considered to be most appropriate for the subject's condition, according to the judgment of the treating investigator) before and after each E7777 infusion

Premedication with Systemic Steroids

- **Lead-In part**. Subjects should not receive premedication with systemic steroids, with the following exceptions:
    - In the event that a subject experiences an **infusion reaction** (i.e. within 24 hours of infusion) CTCAE grade 2 or 3 after the first administration of E7777 on Cycle 1 Day 1, the premedication regimen for that subject must be supplemented during the rest of Cycle 1 (Days 2-5) with systemic corticosteroids (see below). Steroid premedication may be administered during subsequent treatment cycles at the discretion of the treating physician
    - In the event that a subject experiences an infusion related reaction at any time during any treatment cycle, the premedication regimen for that subject may be supplemented with systemic corticosteroids during the remainder of treatment days for that cycle (if event occurred before completion of cycle treatment) and/or in subsequent treatment cycles, at the discretion of the treating physician
    - Systemic corticosteroid premedication should be dexamethasone 4 mg, slow intravenous push OR equivalent corticosteroid dose according institutional guidance.
- **Main Study**. Same guidance as for the Lead-In part.

9.4.1.2 Drug Preparation and Administration

Frozen Drug Formulation (Lead-In only)

The instructions below should be followed for preparation and administration of the frozen formulation of E7777 which is used in the Lead-In part:

- Thaw vials in the refrigerator at 2 to 8 °C (36 to 46 °F) for not more than 24 hours or at room temperature for 1 to 2 hours.
- Bring E7777 to room temperature, before dose preparation.
- Mix the solution in the vial by gentle swirling; do not shake.
- Visually inspect for particulate matter and discoloration prior to administration, whenever solution and container permit. Use only if the solution is clear, colorless, and without visible particulate matter. After thawing, a haze may be visible which should clear when the solution is at room temperature.
- Do **not** refreeze E7777 after thawing.
- Prepare and hold diluted E7777 in plastic syringes or soft plastic i.v. bags. Do **not** use glass containers.
- Maintain concentration of E7777 at 15 μg/mL or higher during all steps in the preparation of the solution for i.v. infusion.
- Withdraw the calculated dose from the vial(s) and inject it into an empty i.v. infusion bag. Do not add more than 9 mL of sterile saline without preservative to the i.v. bag for each 1 mL of E7777.
- Do **not** administer as bolus injection.
- Do **not** mix E7777 with other drugs.
- Do **not** administer E7777 through an in-line filter.

- Administer prepared solutions of E7777 within 6 hours, using a syringe pump or i.v. infusion bag.

- Discard unused portions of E7777 immediately.

Lyophilized Drug Formulation (Main Study only)

The instructions below should be followed for preparation and administration of the lyophilized formulation of E7777 which is used in the Main Study only:

- E7777 is reconstituted with 2.1 mL of sterile Water for Injection prior to administration.

- Mix the solution in the vial by gentle swirling; do not shake.

- Visually inspect all the vials reconstituted for particulate matter and discoloration prior to administration. Use only if the solution is clear, colorless, and without visible particulate matter. After reconstitution, a haze may be visible which should clear when the solution is allowed to stand for a while at room temperature.

- Prepare and hold diluted E7777 in plastic syringes or soft plastic (except for polystyrene) i.v. bags. Do **not** use glass containers.

- Maintain concentration of E7777 at 15 μg/mL or higher during all steps in the preparation of the solution for i.v. infusion.

- Withdraw the calculated dose from the vial(s) and inject it into an empty i.v. infusion bag. Do not add more than 9 mL of sterile saline without preservative to the i.v. bag for each 1 mL of E7777.

- Do **not** administer as bolus injection.

- Do **not** mix E7777 with other drugs.

- Do **not** administer E7777 through an in-line filter.

- Administer prepared solutions of E7777 within 6 hours, using a syringe pump or i.v. infusion bag.

- Discard unused portions of E7777 immediately.

9.4.1.3 Monitoring Procedures During Administration

Prior to administering E7777:

- Ensure the facility is equipped and staffed for cardiopulmonary resuscitation.

- Monitor vital signs.

- Monitor the following protocol-specified tests to ensure criteria for treatment are met: liver function tests, complete blood count (CBC), albumin, creatine phosphokinase (CPK), and renal function (Day 1 only).
- Assess neurological status prior to each infusion including memory, orientation, gait, and numbness in extremities.
- Monitor body weight prior to each infusion.
- Monitor blood pressure.
- Perform medical exploration specifically addressed to detect early signs of peripheral edema.

During administration of E7777, monitor as follows:

- Ensure epinephrine (0.1 to 0.5 mL of 1:1000 solution subcutaneous), diphenhydramine (50-mg i.v. push), and methylprednisolone sodium succinate (250-mg/mL i.v. push) or other medical preparation per local institutional guidelines for the treatment of infusion reactions are at the bedside.
- Monitor for allergic reaction.
- Perform frequent respiratory assessments.
- Monitor vital signs before and at the end of the infusion and at 30 minutes postinfusion.

General recommendations for administration of E7777 are: to minimize the risk or to reduce the intensity of acute infusion-related reactions (e.g., fever, chills, tachycardia, etc.) that may occur, the infusion may be slowed or stopped temporarily until symptoms resolve. Withhold E7777 treatment if serum albumin levels are < 3.0 g/dL (CTCAE Grade ≥ 2) or if clear signs of CLS occur e.g. peripheral edema, with or without functional impairment, cardiopulmonary impairment, or hypotension. CPK testing is required if CLS is suspected and it should be monitored frequently as clinically indicated until resolution of CLS.

9.4.1.4 Management of Acute Infusion Reaction and Hypersensitivity During Administration

The administration of E7777 should be withheld if the subject develops any of the following:

- Diastolic pressure below 60 mmHg or above 100 mmHg
- Pulse rate faster than 130 beats per minute (bpm)
- Shaking chills, rigors
- Oral temperature higher than 39.4 °C

- Respiratory distress

Administration of E7777 can be resumed if the subject's signs and symptoms return to baseline; E7777 administration will be withheld for that day if the condition does not resolve.

In the event a hypersensitivity reaction occurs, the following medications should be readily available during each administration:

- Diphenhydramine (50-mg i.v. push) or other antihistamine per local institutional guideline for hives, itching, rash, shortness of breath, and/or chills
- Methylprednisolone sodium succinate (250-mg/mL i.v. push) or per local institutional guideline for decrease in blood pressure (BP) and/or respiratory distress
- Epinephrine 0.1 to 0.5 mL of a 1:1000 solution subcutaneous for anaphylaxis
- Prochlorperazine (10-mg i.v. push) or institutional antiemetic agent of choice. Subjects may receive antiemetics, as needed, for the control of nausea and/or vomiting

9.4.1.5 Dose Interruption or Modification

Dose Delays

- Dose delays will be allowed for toxicities. Resumption of dosing will be according to the guidelines provided in Table 1.
- The maximum delay is 21 days before the day the next course is scheduled to start.
    - A full dose will be given if toxicities are resolved within this 21-day period.
    - A dose delay lasting > 21 days will lead to permanent discontinuation of treatment.
    - If a cycle is not delivered in full, regardless of the reason, the missing doses will not be replaced and the cycle will be considered as complete. The missing doses will be captured per dose intensity calculations.
- Two consecutive dose delays due to toxicity will lead to a permanent dose reduction by 50% without possible reescalation.
    - Only one dose reduction to 50% will be allowed, regardless of the reason. The requirement for additional dose reductions, as defined previously, will lead to permanent discontinuation of treatment.
- The starting date of a new cycle will coincide with the date of treatment resumption following a dose delay or dose reduction.
- Dose delays are also allowed for scheduling purposes and if in the subject's best interest in the opinion of the investigator. The maximum delay for this is 42 days.

Study drug interruption and dose reduction instructions for subjects who experience an E7777-related toxicity are presented in Table 1.

Table 1 Dose Interruption and Modification During Treatment Period

Toxicity	Dose Interruption	Dose Modification
Capillary leak syndrome[a] Grade 4	Discontinue study treatment permanently	N/A
Capillary leak syndrome Grade 3, 2. assessed as dose-limiting, e.g. severe symptoms requiring hospitalization for acute intervention	Interrupt dosing until resolved to ≤ Grade 1	Resume at 50% dose
Capillary leak syndrome Grade 3, - assessed as not dose-limiting, e.g. less severe symptoms leading to hospitalization for prophylactic treatment with fluids or diuretics	Interrupt dosing until resolved to ≤ Grade 1	Resume at full dose
Infusion reaction[b] Grade 4 or Recurrent infusion reaction Grade 3 that recurs despite premedication with systemic steroids	Discontinue study treatment permanently	N/A
Infusion reaction Grade 2 or 3, first occurrence	None	Continue at full dose, but add systemic steroid premedication
Recurrent infusion reaction Grade 2 that recurs despite premedication with systemic steroids	Interrupt dosing until resolved to ≤ Grade 1	Resume at full dose, but may add systemic steroid premedication[f]
Infusion related reaction[c] Grade 2 or 3	Interrupt dosing until resolved to ≤ Grade 1	Resume at full dose, but may add systemic steroid premedication[f]
Visual loss[d]	Discontinue study treatment permanently	N/A
Grade ≥ 3 hematological ≥ 7 days, or febrile neutropenia, or bleeding. Exception: Grade 3 lymphopenia[e]	Interrupt dosing until toxicity ≤ Grade 1, or until clinical symptoms are resolved	No change; Resume at full dose
Grade 3 nonhematologic toxicity except nausea, vomiting, or elevation of liver enzymes.	Interrupt dosing until toxicity ≤ Grade 1 or baseline	No change; Resume at full dose
Grade 4 nonhematologic toxicity other than, nausea, and vomiting.	Discontinue study treatment permanently	N/A

Table 1 Dose Interruption and Modification During Treatment Period

Toxicity	Dose Interruption	Dose Modification
CLS = capillary leak syndrome, CTCAE = Common Terminology Criteria for Adverse Events, IRR = infusion-related reaction, N/A = not applicable. [a] Refer to Section 9.1.2 for definition of capillary leak syndrome (CSL) and of DLT for CLS [b] Infusion reactions are infusion related reactions that occur within 24 hr of E7777 administration; see Section 9.1.2 definitions [c] Infusion related reactions can occur at any time during the treatment cycle [d] Visual loss is defined as visual acuity impairment, color or shape distortion, or blurred vision [e] These toxicities were observed for E7777 in a Phase 1 study and are expected toxicities. [f] See Section 9.4.1.1 for detailed instructions on systemic steroid premedication		

9.4.2 Identity of Investigational Products

E7777 is a recombinant fusion protein composed of the amino acid sequences for diphtheria toxin fragments A and B (Met_1-Thr_{387})-His and for human IL-2 (Ala_1-Thr_{133}). E7777 is improved purity ONTAK resulting from an improved manufacturing process for ONTAK.

9.4.2.1 Frozen Formulation (Lead-In only)

E7777 is supplied in single-use vials as a sterile, frozen solution intended for i.v. administration. Each 2-mL vial of E7777 contains approximately 300 µg (150 µg/mL) of recombinant E7777 in a sterile solution of citric acid (20 mM), ethylenediamine tetraacetic acid ([EDTA], 0.05 mM), and polysorbate 20 (< 1%) in Water for Injection, United States Pharmacopoeia (USP). Please refer to the label for the exact drug concentration in each vial.

9.4.2.2 Lyophilized Formulation (Main Study only)

E7777 is supplied in single-use vials as a sterile, white lyophilized cake intended for i.v. administration. E7777 white lyophilized cake is reconstituted with 2.1 mL of sterile Water for Injection prior to administration. After that, each 5-mL vial contains approximately 300 µg (150 µg/mL) of recombinant E7777, 5% (w/v) trehalose, 10 mM citric acid, 10 mM methionine, 0.05 mM EDTA, and 0.06% polysorbate 20, at a pH of approximately 7 in Water for Injection, United States Pharmacopoeia (USP).

9.4.2.3 Chemical Name, Structural Formula of E7777

- Test drug code: E7777
- Generic name: Not Applicable
- Chemical name: diphtheria fragment A and B (Met_1-Thr_{387})-His-Interleukin-2 (Ala_1-Thr_{133})
- Molecular weight: ~58 kD

9.4.2.4 Comparator Drug

Not applicable.

9.4.2.5 Labeling for Study Drug

E7777 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries.

9.4.2.6 Storage Conditions

Frozen Formulation (Lead-In only)

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature be monitored throughout the total duration of the trial and that records be maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

Lyophilized Formulation (Main Study only)

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature be monitored throughout the total duration of the trial and that records be maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects in the Lead-In part will be assigned a dose of E7777 in accordance with the rules of the CRM.

Main Study: Not applicable, as there is only one treatment group.

9.4.4 Selection of Doses in the Study

Lead-In part

The doses of E7777 planned for testing in the CRM design are 3, 6, 9, 12, 15, and 18 µg/kg/day. E7777 has a higher proportion of active monomer species compared to current commercial

ONTAK. Consistent with this, the bioactivity of E7777 on a weight basis is approximately 1.5- to 2-fold higher than ONTAK. The range of E7777 doses that are selected for the Lead-In part takes into account this increased potency so that E7777 will be tested at approximate dose equivalents of FDA-approved ONTAK doses, as well as at surrounding lower and higher dose levels. The starting dose of 6 µg/kg/day corresponds approximately to a 9 to 12 µg/kg/day dose of ONTAK in terms of bioactivity; this represents a reasonable starting dose as the approved ONTAK doses are 9 and 18 µg/kg/day administered at the same schedule.

Main Study

The E7777 dose for the Main Study will be 9 µg/kg/day.

9.4.5 Selection and Timing of Dose for Each Subject

Treatment with E7777 will be by i.v. infusion over 60 minutes, on 5 consecutive days during every 21-day cycle, for up to eight cycles. This is the schedule approved for ONTAK in the US.

9.4.6 Blinding

Not applicable.

9.4.7 Prior and Concomitant Therapy

The following are allowed:

- Required premedications as described in Section 9.4.1.1.
- Except as otherwise stated in this section of the protocol, only those concomitant medications intended to alleviate the signs and symptoms of CTCL will be allowed. Examples of such medications are: antihistamine agents such as hydroxyzine, cyclizine, meclizine, or cetirizine; topical anesthetics such as lidocaine or benzocaine; ointments and lotions such as menthol, camphor, or calamine.
- Topical steroids or systemic low dose steroids (≤ 10 mg/day prednisone) may be considered in subjects with erythroderma who have been receiving corticosteroids for a prolonged period of time and where discontinuation may lead to rebound flare in disease, adrenal insufficiency, and/or unnecessary suffering. The concomitant steroid medication is allowed as long as the type of steroid, route of administration, and steroid dose remain the same as what the subject had been receiving for the prolonged period.

The following are not allowed:

- Use of topical steroids within 14 days of Cycle 1 Day 1; exception is noted in the section above (bullet #3 of allowed Concomitant Therapy).
- While the subject is receiving study drug: other anticancer treatment for CTCL, including chemotherapy, radiation therapy, immunotherapy, phototherapy, hormonal

therapy (with the exception of contraceptives or hormonal replacement), or experimental/investigational.

The investigator will record on the AE case report form (CRF) any AE for which the concomitant medication/therapy was administered.

9.4.8 Treatment Compliance

Records of treatment compliance will be kept for each subject during the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes, or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the PI and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the PI and a copy of the PI's current medical license (required in the US), or medical registration number on the CV
- A signed and dated clinical trials agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required) and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping), following the sponsor's instructions as provided in the Pharmacy Manual, and adherence to GCP guidelines as well as to local or regional 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 site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) a study drugs dispensing/return reconciliation log, (c) a study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by 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 (e.g., FDA, Medicines and Healthcare products Regulatory Authority [MHRA]). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject. Empty containers from the subjects, along with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will occur only under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed and sealed and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand-delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures, and certificates of destruction will be provided to the sponsor.

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

9.5 Study Assessments

9.5.1 Screening and Baseline Assessments

9.5.1.1 Demography

Subject demography will be collected at the Screening Visit. Demographic information includes date of birth (or age), sex, and race/ethnicity (record in accordance with local regulations).

Medical History and Physical Examination

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All pertinent medical and surgical history must be noted in the Medical History and Current Medical Conditions CRF.

Standard comprehensive physical examinations will be performed as designated on the Schedule of Procedures/Assessments (Table 4). Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs CRF.

A serum β-hCG pregnancy test will be performed.

9.5.1.2 Other Screening Assessments

Tumor Assessments

- A biopsy sample will be sent to a central laboratory for testing of CD25 expression by IHC; the sample may be sent in formalin, or may be a formalin fixed paraffin embedded (FFPE) sample, or may be sent as slides (minimum of 5 slides). Results must be obtained before enrollment of the subject in the study. Results obtained at Screening or from an archival tumor biopsy (≤ 6 months) can be used as long as the test was performed by the study-designated central laboratory. Multiple lesions may be tested. Re-biopsy with selection of the most representative lesion is required if the subject had disease progression or relapse since the last biopsy.
- A whole blood sample should be collected for flow cytometry analysis by a central laboratory.
- A lymph node biopsy should be obtained only if required for CTCL diagnosis and/or staging (see Section 9.5.2.2); lymph node analysis is to be performed by a local laboratory.

NOTE: Subjects may be enrolled in the study only after they have been confirmed to have a CD25 assay-positive tumor biopsy based on results from the central laboratory.

9.5.2 Efficacy Assessments

9.5.2.1 Overview

Primary Method for Tumor Assessment (Site review plus Independent Central review)

The ISCL/EORTC response criteria[6] (Olsen 2011) will be used as the primary method for efficacy analysis. This method will be used by both the Site investigator and the Independent Review Committee (IRC).

The dataset from the Stage I – III Main Study subjects plus the Stage I – III Lead-In subjects from the 9µg/kg/day dose group combined as generated by the IRC will be the primary efficacy analysis dataset. All subjects from the Main Study will be assessed for efficacy by the IRC.

For both the Lead-In and the Main Study, the site will report on the CRF their local/investigator tumor response assessment; site assessments will be used to make subject treatment decisions.

Tumor assessment methods and schedules are provided in Section 9.5.2.3.

Tumor burden scoring and the ISCL/EORTC response criteria are described in Appendix 1.

Supplemental Alternate Method (SAM) for Tumor Assessment (IRC only)

The response criteria described in Prince (2010)[5] will be used as a supplemental alternate method, for the secondary objective of ORR and will be conducted by the IRC only.

Imaging Core Laboratory

For both the Lead-In and the Main Study, photographs and CT scans will be sent by the investigator site to an independent imaging core laboratory designated by the sponsor for analysis. Laboratory results, including blood, as well as investigator skin assessments as entered in the eCRF, will be sent to the core laboratory by the sponsor. At the time of data cutoff for primary analysis of the Main Study, the sponsor may choose to discontinue sending data (including photographs and scans) to the imaging core laboratory.

9.5.2.2 Tumor Assessment Methods and Schedule

In the ISCL/EORTC criteria, a composite measure of disease in skin, lymph node, blood, and viscera will be used to assess tumor burden. A Global Response Score will indicate the overall response assessment based on the composite measure.

1. Skin Disease Assessment

Skin tumor burden will be quantified using a modified Severity Weighted Assessment Tool (mSWAT) that provides an mSWAT score. The mSWAT score measures the body surface area (BSA) involved in skin disease with a weighting factor applied according to the severity of the type of skin lesion, which can be patch, plaque, or tumor. The mSWAT

can be utilized to track erythroderma by the summation of BSA involved with patch disease (macular erythema) and plaque disease (erythema with induration/edema). In addition, subject(s) should be evaluated for the appearance of new skin tumor lesion(s) at each time point after the initiation of treatment. A sample of the worksheet for calculating the mSWAT score is provided in Appendix 4. Note: The worksheet for use at the site will be provided separately to each site.

Supplemental Assessment Method (SAM) using Prince (2010) Criteria (only for subjects with skin lesions comprising < 10% of BSA)

Since the IRC will perform a secondary analysis based upon the method of Prince (2010), a supplemental measurement will be made by the site investigator at the time of mSWAT assessment, for subjects with skin lesions comprising < 10% of BSA. The investigator will identify, photograph, and measure up to five representative skin lesions (generally the largest and most representative of different locations, such as chest, abdomen, leg, arm, head, neck, if applicable; measurements will be of two-dimensional perpendicular diameters). These measurements will be collected on the eCRF and will be used only by the IRC. These lesions (even if they have disappeared) should be evaluated and photographed at all mSWAT assessment time points. A sample of the worksheet for collecting skin lesion data per supplemental assessment method (by Prince 2010) is shown in Appendix 4. Note: The worksheet for use at the site will be provided separately to each site.

The assessment schedule is as follows:

a. At Screening, assessment to determine study eligibility
b. During treatment
    - Day 1 (-3 days) of every treatment cycle (minus 3-day window allowed)
c. At EOT, if required for Global Response Score determination
d. During Follow-up: every 4 weeks (± 1 week) for 1 year after end of study treatment, then every 12 weeks (± 3 weeks) thereafter for up to 3 years, or sooner if clinically indicated

The mSWAT scoring and supplemental assessment method (SAM) scoring should be performed by the same investigator at all time points. If the same investigator cannot perform all the assessments, then all personnel grading the same subject must have completed prior training, ideally before study initiation.

Standardized photographs of the skin are required to document the presence of skin lesions at all assessment times. If the Screening assessment is within 1 week prior to Cycle 1 Day 1, photographs are not required on Cycle 1 Day 1 as long as, in the investigators judgment, there is not a significant enough change in the subject's skin disease involvement to warrant repeat photographs on Cycle 1 Day 1.

The required views are:

- Head and neck anterior view

- Head and neck posterior view
- Head and neck left profile
- Head and neck right profile
- Head top of scalp
- Upper body anterior (includes arms and hands)
- Upper body posterior (includes arms and hands)
- Upper body left flank with arm raised
- Upper body right flank with arm raised
- Lower body anterior (includes feet)
- Lower body posterior (includes feet)
- Lower body left side (includes foot)
- Lower body right side (includes foot)

When scoring by supplemental assessment method is being made, close-up and localization photographs including a millimeter ruler of target lesions are also required.

2. Lymph Node Disease Assessment

Assessment Methods and Schedules

Lymph node involvement (see Appendix 5) will be assessed at Screening (and serve as baseline) by CT scan. Biopsy will be performed if necessary, as described below (Part a, iii).

N_x status may be assigned if there is no histologic information available:

- N_x may be considered non-involved if the node >1.5 cm diameter is clinically not suspicious for lymphoma (Reactive/Inflammatory OR Dermatopathic) according to judgement of the investigator.
- N_x should be considered involved if clinically suspicious for lymphoma (High SUV/ increasing size on scan).

Lymph node status will be monitored on study during scheduled physical examination by palpation of peripheral nodes. CT assessment or biopsy will be performed if necessary, as described below.

a. At Screening, to record lymph node involvement at study entry, for use as baseline reference values
   i. Physical examination by palpation
   ii. CT scan and/or ^{18}FDG-PET-CT scan
      - To identify any abnormal nodes (i.e., >1.5 cm diameter) at study entry.
      - To document normal nodes that may be used as reference for any subsequent PD in these nodes

- Scans performed prior to Screening that are within 6 weeks prior to C1D1 are acceptable as Screening/baseline scans as long as they meet the requirements of the Imaging Acquisition Guideline from the Imaging Core Laboratory.

iii. Biopsy and histologic characterization (per guidelines in Olsen 2007)

In the **Main Study**, biopsy and histologic characterization is strongly recommended if an abnormal peripheral node suspicious for CTCL is detected by CT scans during Screening. The most recent biopsy of a representative abnormal peripheral lymph node may be used as long as there has been stable lymph node size since that biopsy. No biopsy of abnormal central nodes is required even if detected as abnormal upon CT scan at Screening (Olsen 2007).

b. Treatment Phase:

i. Physical examination by palpation

Lead-In Part (scheduled examination)

- During treatment: Day 1 (-3 days) of every cycle (minus 3-day window allowed)
- At the end of treatment
- During Follow-up: every 4 weeks (± 1 week) for 1 year after end of study treatment, then every 12 weeks (± 3 weeks) thereafter for up to 3 years, or sooner if clinically indicated.

Main Study

To be performed as necessary for monitoring of lymph node disease, with frequency according to the judgment of the investigator.

ii. CT Scan

CT assessment if any of the following conditions are met, during Treatment or Follow-up **in Lead-in part**

- In subjects with more advanced disease (maximum/current TNMB greater than $T_{1-2}N_0M_0B_{0-1}$) at study entry, the CT assessment is to be performed at the time of CR or PR in skin disease
- In subjects with early disease (maximum/current $T_{1-2}N_0M_0B_{0-1}$) at study entry, the CT is to be performed at time of CR or PR in skin disease, only if this affects the GRS
- In all subjects, the CT is to be performed any time there is suggestion of new or progressive disease/relapse in lymph nodes or viscera (by

palpation of lymph nodes, liver, and/or spleen) and only in the absence of PD by skin or blood

- Exceptions: the CT need not be performed under the above circumstances if the lymph node response is not needed for GRS, e.g., if CR or PR is in skin but PD is in blood.

CT assessment **in Main Study** is as described in Appendix 5 Figure 1.

- In subjects with N0 and N1 at study entry:
  - CT is to be performed at time of CR or PR in skin disease, only if this affects the GRS
  - CT is to be performed any time there is suggestion of new or progressive disease/relapse in lymph nodes or viscera (by palpation of lymph nodes, liver, and/or spleen) and only in the absence of PD by skin or blood
- In subjects with N_2, N_3 and N_x at study entry:
  - CT scans of the affected/suspected area are required every 3 cycles beginning at Cycle 3 (±1 week)
- Exceptions: the CT need not be performed under the above circumstances if the lymph node response is not needed for GRS, e.g., if there is already a PD assessment in another disease site.

iii. Lymph node biopsy: A repeat peripheral lymph node biopsy during the study is recommended only in situations where the histology would affect the Global Response score. A fine needle aspirate or core biopsy with supportive ancillary studies may be acceptable.

3. Blood Disease Assessment

Blood tumor burden will be assessed by quantifying CD4+CD26− cells by flow cytometry; CD4+CD7− cells may be used in CD26+ subjects.

Assessment frequency

a. At Screening
b. During treatment
   i. Day 1 (-3 days) of every treatment cycle
c. At EOT, if required for Global Response Score determination
d. During Follow-up: Every 4 weeks (± 1 week) for 1 year after end of study treatment, then every 12 weeks (± 3 weeks) thereafter for up to 3 years, or sooner if clinically indicated.

4. Visceral Disease Assessment

Subjects with visceral involvement at study entry are only allowed in the Lead-In part.

Subjects will be assessed at Screening by CT scan (if applicable). Viscera status will be monitored on study during scheduled physical examination by palpation (if applicable). CT assessment will be performed if necessary for GRS, as described below.

a. At Screening, to exclude viscera involvement at study entry (Lead-In only), or for use as baseline reference values

   i. Physical examination by palpation

   ii. CT scan

   - to identify any measurable nodules or other visceral disease of any organ at study entry. Measurable lesions are a minimum size of 1.0 × 1.0 cm; lesions smaller than this will be considered non-measurable. Measurable visceral disease will be used to calculate SPD for visceral response assessment
   - to document any enlargement of liver and/or spleen that may be used as reference for any subsequent confirmation of tumor response or PD/relapse
   - Scans performed prior to Screening that are within 6 weeks prior to C1D1 are acceptable as Screening/baseline scans as long as they meet the requirements of the Imaging Acquisition Guideline from the Imaging Core Laboratory.

b. Physical examination by palpation

   During the study, physical examination (by palpation of liver and spleen) will be used to monitor for potential visceral disease.

   Lead-In Part (scheduled examination)

   i. During treatment: Day 1 of every cycle

   ii. At the end of treatment

   iii. During Follow-up: every 4 weeks for 1 year after end of study treatment, then every 12 weeks thereafter for up to 3 years, or sooner if clinically indicated

   Main Study

   To be performed as necessary for monitoring of viscera status, with frequency according to the judgment of the investigator.

c. CT assessments for subjects with no visceral disease at study entry

   During the study, physical examination (by palpation of liver and spleen) will be used to monitor for potential visceral disease.

   If there is suspicion of new visceral disease, a CT scan should be performed to confirm PD/relapse. The confirmatory CT is not necessary for the purposes of the study if PD in other disease sites has already been noted, as the latter is sufficient

for assessing the Global Response score.

The minimum size of a new visceral lesion by CT must be >1.0 × 1.0 cm.

d. Lead-In Part only: CT assessments for subjects with visceral disease at study entry (Stage IVB)

CT assessment if any of the following conditions are met, during Treatment or Follow-up

i. In subjects with visceral disease at study entry, the CT assessment is to be performed every 12 weeks and at the time of CR or PR in skin disease

ii. In all subjects, the CT is to be performed any time there is suggestion of new or progressive disease/relapse in lymph nodes or viscera (by palpation of lymph nodes, liver, and/or spleen) and only in the absence of PD by skin or blood

iii. Exceptions: The CT need not be performed under the above circumstances if the visceral response is not needed for GRS, e.g., if CR or PR is in skin but PD is in blood

The minimum size of a new visceral lesion by CT must be >1.0 × 1.0 cm.

9.5.2.3 Subject Assessment of Pruritus

Subjects will rate the severity of pruritus using a 100-mm visual analog scale (VAS), on which zero indicates no itch and 100 indicates worst possible itch. A clinically significant improvement is defined as an absolute decrease of 20 mm from baseline maintained for ≥ 4 weeks; baseline score must be ≥ 20.

9.5.2.4 Quality of Life Assessments

Two instruments will be used for QoL assessments:

- Skindex-29
- FACT-G

QoL assessments will be performed at Baseline, Day 1 of each cycle during treatment, at end of treatment (EOT), and during every tumor assessment visit during the Extension Phase.

For illiterate subjects, local practices or standards will be utilized to obtain QoL assessments.

9.5.3 PK and Immunogenicity Assessments

9.5.3.1 PK Assessments

PK assessment of E7777 will be performed in all subjects in the Lead-In part and in the first 12 subjects in the Main Study using serial blood PK sampling on Day 1 in Cycles 1, 3, and 5, with sparse sampling in Cycle 8. In addition, sparse sampling will be performed in the Main Study in the remaining subjects on Day 1 of Cycle 1. PK blood samples will be collected as

shown in Table 2. E7777 will be measured in serum samples using validated bioanalytical methods.

Table 2 PK Sampling Time Points

Type of Sampling	Cycle/Day	Time Points
Serial Blood PK Sampling	Cycles 1, 3, 5, Day 1[a]	predose, 30 minutes after the start of the infusion, end-of-infusion, and 30, 60, 90, 120, 180, 240, and 300 minutes postinfusion stop
Sparse PK Sampling	Cycle 8, Day 1[a]	predose, end-of infusion, and between 60 and 180 minutes postinfusion
	Cycle 1, Day 1[b]	

1 PK = pharmacokinetic.

2 a: All subjects in the Lead-In part and the first 12 subjects in the Main Study.

3 b: In the remaining subjects in the Main Study.

Instructions for the processing, storage, and shipping of PK samples will be provided in the Laboratory Manual.

The following PK parameters will be determined after serial blood PK sampling using noncompartmental methods:

- Maximum drug concentration (C_{max})
- Area under the curve from time 0 to time t ($AUC_{(0-t)}$)
- Area under the curve from time 0 to infinity ($AUC_{(0-inf)}$)
- Time to reach maximum (peak) concentration after drug administration (t_{max})
- Terminal elimination half-life ($t_{½}$)
- Total body clearance (CL)
- Volume of distribution at steady state (Vd_{ss})

Data will also be evaluated for correlation between selected PK parameters with AEs and with objective responses.

Population PK:

A population PK model for E7777 will be developed using nonlinear mixed effect modeling. The model will be parameterized in terms of clearance and volume of distribution.

Population PK/PD

Pharmacokinetic/PD relationships between exposure to E7777 and some efficacy and safety variables will be explored graphically and may be followed by model-based analysis.

All the PK samples noted in Table 2 will be utilized for the population PK analysis.

9.5.3.2 Immunogenicity Assessments

Immunogenicity (formation of antibodies to E7777) will be assessed in all subjects in both the Lead-In part and the Main Study. Immunogenicity assessment in serum will be performed using validated bioanalytical methods to screen, confirm, and characterize the presence of anti-E7777, anti-IL-2, and neutralizing antibodies. Only samples with confirmed positive antibodies to E7777 and/or IL-2 will be tested by a neutralizing antibody assay. A predose blood sample for immunogenicity assessment will be collected prior to dosing on Day 1 in Cycles 1, 2, 3, 5, and 8. After that, all subjects will be followed up for immunogenicity for anti-IL2 on a 6-month schedule for 1 year and every year thereafter until antibody titers decrease to baseline level or until study conclusion/termination. Blood samples will be collected prior to study drug administration.

9.5.4 Safety Assessments

Safety will be assessed by the regular monitoring and recording of all AEs and serious adverse events (SAEs), hematology, blood chemistry, and urine values, vital signs, electrocardiograms (ECGs), and the performance of physical examinations including body weight and height as detailed in Section 9.5.5.

9.5.4.1 AEs and Other Events of Interest

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. 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 are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

- 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 (e.g., ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation from study drug.

- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.

- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not.

A laboratory result should be considered by the investigator to be an AE if it:

- Results in the withdrawal of study drug
- Results in withholding of study drug pending some investigational outcome
- Results in an intervention, based on medical evaluation (e.g., potassium supplement for hypokalemia)
- Results in any out-of-range laboratory value that in the investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile
- Worsens (increases) to Grade 2 or higher based on the Sponsor's Grading for Laboratory Values
- Increases in severity compared to Baseline by ≥ 2 CTCAE grades (see Appendix 6 for CTCAE v5.0), with the exception of lymphocytes, albumin, cholesterol, glucose, and phosphate. For these tests, any change of ≥ 2 grades will be evaluated by the investigator to determine if it is of clinical significance and, if so, will be considered an AE.

All AEs observed during the study will be reported 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 last visit and for 30 days after the subject's last dose. Serious AEs (SAEs) will be collected for 30 days after the last dose. Any SAE that the investigator considers related to a protocol-required procedure must also be reported, regardless of the length of time since study-drug discontinuation.

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. Any laboratory abnormality considered to constitute an AE should be reported on the AE CRF.

It is the responsibility of the investigator to review all laboratory findings in all subjects and to determine whether 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 (QT interval corrected for heart rate [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 > 450 ms or there is an increase of > 60 ms from baseline. Any ECG abnormality that the investigator considers an AE should be reported as such.

Progression of malignant disease will not be recorded as an AE. If the progression leads to an untoward medical occurrence (increased pain, pleural effusion, etc.), then this medical occurrence will be recorded as an AE.

All AEs must be followed for 30 days after the subject's last dose, or until resolution, whichever comes first.

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

AEs will be graded on a 5-point scale according to CTCAE v5.0. Investigators will report all CTCAE grades for AEs (see Appendix 6).

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

Not Related — A causal relationship between the study treatment and the AE is not a reasonable possibility.

Related — A causal relationship between the study treatment and the AE is a reasonable possibility. The investigator must further qualify the degree of certainty as "possible" or "probable."

9.5.4.2 Serious Adverse Events and Other Events of Interest

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (i.e., the subject was at immediate risk of death from the AE 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, other events of interest include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error; any treatment-emergent significant laboratory abnormality; and vision loss. These events of interest 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 events of interest are to be reported on the CRF whether or not they meet the criteria for SAEs.

The following hospitalizations are not considered to be SAEs because there is no "AE" (i.e., 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 post-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 (e.g., battery replacement) that was in place prior to study entry

If possible, a blood sample for PK analysis should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.4.3 Laboratory Measurements

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 3. Subjects should be in a seated or supine position during blood collection. The Schedule of Assessments (Table 4) shows the visits and time points at which blood for clinical laboratory tests and urine for analysis will be collected in the study.

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), and ANC
Chemistry	
Screening/Baseline/ End-of-Treatment Panel	Pregnancy test (serum β-hCG), LDH, chloride, potassium, sodium, BUN, serum creatinine, phosphorus, calcium, albumin, total protein, alkaline phosphatase, ALT, AST, total bilirubin, CPK, TSH, and free T_4 in the case of abnormal TSH
Treatment Panel	Chloride, potassium, sodium, BUN, serum creatinine, phosphorus, calcium, albumin, total protein, alkaline phosphatase, ALT, AST, total bilirubin, CPK Serum TSH, free T_3, and free T_4, and in the case of abnormal TSH: anti-thyroglobulin antibodies and anti-thyroid peroxidase antibodies
Urinalysis[a]	Glucose, protein, leukocytes, nitrites, ketones, bilirubin, blood, urobilinogen, pH, and specific gravity. Microscopic examination of sediment to include: bacteria, casts, crystals, epithelial cells, RBCs, and WBCs Urine pregnancy test (Cycle 1 Day 1 only)

ALT = alanine aminotransferase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, ß-hCG = beta human chorionic gonadotropin, BUN = blood urea nitrogen, LDH = lactate dehydrogenase, RBC = red blood cell, T_3 = triiodothyronine, T_4 = thyroxine, TSH = thyroid-stimulating hormone, WBC = white blood cell, CPK = creatine phosphokinase.

a: When a local laboratory is required for a urinalysis, a Urinalysis Reagent Test Strip (URS-10) may be used.

Clinical laboratory tests will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split, or two samples drawn, to allow a local laboratory analysis in addition to the central laboratory.

All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained before study drug administration and results reviewed before administration/dispensing of study drug at the beginning of each treatment cycle. Refer to Table 1 for dose interruption and reduction instructions in the event of clinically significant laboratory abnormalities.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see AEs and Other Events of Interest [Section 9.5.4.1]). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the AE CRF. Assessment of what constitutes a laboratory abnormality will take the underlying disease into consideration.

For laboratory abnormalities meeting the criteria of SAEs (see SAEs and Other Events of Interest [Section 9.5.4.2]), the site must fax or email the SAE report including the laboratory report (as regionally required) to the sponsor using the SAE form (see Reporting of SAEs [Section 9.5.7.1]).

9.5.4.4 Vital Signs

Vital sign measurements (i.e., systolic and diastolic BP [mmHg], pulse [bpm], respiratory rate [per minute], body temperature [in degrees centigrade]), will be measured as signals for potential vascular leak syndrome. Measurements will be obtained before and at the end of the infusion and 30 minutes post-infusion on treatment days at the visits designated in the Schedule of Assessments (Table 4).

9.5.4.5 Physical Examinations and Weight

A complete physical examination including weight will be performed at baseline, Day 1 of each cycle and at study termination as designated on the Schedule of Assessments (Table 4). Height should be collected as part of the physical exam at the baseline visit. A symptom-directed examination will be performed on all other visit days. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings the meet the definition of an AE will be recorded on the AE CRF.

9.5.4.6 Electrocardiograms

12-lead ECGs will be taken as designated on the Schedule of Assessments (Table 4).

Complete, standardized, single 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of three full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Adverse Events and Other Events of Interest [Section 9.5.4.1]) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF. For ECG abnormalities meeting criteria of an SAE (see Serious Adverse Events and Other Events of Interest [Section 9.5.4.2]), the site must fax or email the SAE report including the ECG report to the sponsor using the SAE form (see Reporting of Serious Adverse Events [Section 9.5.7.1]).

9.5.5 Schedule of Procedures/Assessments

9.5.5.1 Schedule of Assessments

Table 4 Schedule of Assessments

PHASE[a]	PRETREATMENT		TREATMENT							
Period[a]	Screening	Baseline	Cycles 1 to 8 (Cycle 9 and beyond, if applicable)[a]							Follow-Up
Cycle Day	Up to -28	Up to -7	1	2	3	4	5	8	EOT [a]	
Procedures/Assessments										
Informed consent	X									
Medical history	X									
Inclusion/exclusion	X									
Tumor biopsy for CTCL diagnosis [b]	X									
Blood sampling or lymph node biopsy for CTCL diagnosis [c]	X									
Prior/concomitant medications [d]	X	X	X						[X]	
Vital signs [e]		X	X	X	X	X	X	[X]	[X]	
Physical examination and ECOG [e]		X	X						[X]	
ECG [f]	X		X						[X]	
Urine pregnancy test[g]			X							
Urinalysis [g]		X	X					[X]		
Serum β-hCG pregnancy test [h]	X	X							X	
Hematology laboratory tests [h]	X	X	X					[X]	[X]	
Chemistry laboratory tests [h]	X	X	X					[X]	[X]	
PK and Immunogenicity blood samples [i]			[X]							[X]
Drug administration: E7777 [j]			X	X	X	X	X			
Tumor assessment: skin mSWAT with photography[k]	X		X						[X]	[X]
Tumor assessment: lymph node PE[k]	X		X						[X]	[X]
Tumor assessment: blood disease[k]	X		X						[X]	[X]
Patient-reported pruritus assessment[l]	X		X						[X]	[X]

Table 4 Schedule of Assessments

PHASE[a]	PRETREATMENT		TREATMENT							
Period[a]	Screening	Baseline	Cycles 1 to 8 (Cycle 9 and beyond, if applicable)[a]							Follow-Up
Cycle Day	Up to -28	Up to -7	1	2	3	4	5	8	EOT [a]	
Procedures/Assessments										
CT scans[m]	X		[X]						[X]	
Adverse event[n]		X	X						X	
Survival[o]										X
QoL[p]		X	X						X	X

Table 4 Schedule of Assessments (cont'd)

PHASE[a]	EXTENSION							
Period[a]	Treatment (Continued treatment after data cut-off)[a]							Follow-Up [q]
Cycle Day	1	2	3	4	5	8	EOT [a]	
Procedures/Assessments								
Prior/concomitant medications [d]	X						[X]	
Vital signs [e]	X	X	X	X	X	[X]	[X]	
Physical examination and ECOG [e]	X						[X]	
ECG [f]	X						[X]	
Urine pregnancy test[g]	X							
Urinalysis [g]	X					[X]		
Serum β-hCG pregnancy test [h]							X	
Hematology laboratory tests [h]	X					[X]	[X]	
Chemistry laboratory tests [h]	X					[X]	[X]	
PK and Immunogenicity blood samples[i]	[X]							[X]

Table 4 Schedule of Assessments (cont'd)

PHASE[a]	EXTENSION							
Period[a]	Treatment (Continued treatment after data cut-off)[a]							Follow-Up [q]
Cycle Day	1	2	3	4	5	8	EOT [a]	
Procedures/Assessments								
Drug administration: E7777[j]	X	X	X	X	X			
Tumor assessment: skin mSWAT with photography[k]	X						[X]	[X]
Tumor assessment: lymph node PE[k]	X						[X]	[X]
Tumor assessment: blood disease[k]	X						[X]	[X]
Patient-reported pruritus assessment[l]	X						[X]	[X]
CT scans[m]	[X]						[X]	[X]
Adverse event[n]	X						X	X
Survival[o]								X
QoL[p]	[X]						X	X

ALT = alanine aminotransferase, ANC = absolute neutrophil count, AST = aspartate aminotransferase, β-hCG = beta-human chorionic gonadotropin, BUN = blood urea nitrogen, CR = complete response, CRM = Continual Reassessment Method, CS = Color Distortion test, CT = computed tomography, CTCL = cutaneous T-cell lymphoma, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EOT = End of Treatment, FFPE = formalin-fixed paraffin embedded, IHC = immunohistochemistry, i.v. = intravenous, LDH = lactate dehydrogenase, min = minutes, mSWAT = modified Severity Weighted Assessment Tool, N/A = Not applicable, PD = progressive disease, PE = physical examination, PR = partial response, QoL = quality of life, RBC = red blood cell, TSH = thyroid-stimulating hormone, WBC = white blood cell
Note: [X] = Either: not required in all cycles, or not required in all subjects. See footnotes.

a: Pretreatment: Screening up to 28 days before start of treatment except for signing of the ICF which may be up to 8 weeks before the first dose of study drug; Baseline up to 7 days before start of treatment. If Screening laboratory tests (Hematology, Chemistry, and serum pregnancy) are performed within 7 days prior to Cycle 1 Day 1, these tests may count as Baseline tests and need not be repeated at Baseline. If Baseline central laboratory test results are not available in time to confirm eligibility, the local site laboratory results (including from Cycle 1 Day 1) may be used for this purpose.

Treatment: cycles of 21 days, up to 8 cycles; applicable to the Lead-in only, if subject is treated beyond Cycle 8 per protocol, the same assessments should be performed as for Cycles 1 to 8; however, no PK samples will be collected after Cycle 8.

Extension: Up to 3 years.

Day 8 Assessments: Day 8 assessments are required in cycles 1-3, and are optional on cycle 4 and beyond.

EOT: Tumor assessments are only required at EOT if they affect GRS. Other EOT tests (with the exception of serum pregnancy test, and QoL) need only be performed if the EOT visit is > 7 days from the most recent Cycle Day 1 visit.

b: A biopsy sample will be sent to a central laboratory for testing of CD25 expression by IHC. The sample may be sent in formalin, or may be a formalin fixed paraffin embedded (FFPE) sample block, or may be sent as slides (minimum of five slides). Results must be obtained before enrollment of subject in the study. Results obtained at Screening or from an archival tumor biopsy (≤ 6 months) can be used as long as the test was performed by the study-designated central laboratory. Multiple lesions may be tested. Re-biopsy with selection of the most representative lesion is required if the subject had disease progression or relapse since the last biopsy, or had received anticancer therapy since the last biopsy.

c: Blood sampling, if blood assessment required for CTCL diagnosis; whole blood to be collected for flow cytometry analysis by central laboratory. Lymph node biopsy (if required per Olsen 2011): allow either fine needle aspirate or core biopsy; if additional lymph node analysis is required, surgical biopsy may follow, if required for CTCL diagnosis and/or staging; lymph node analysis to be performed by local site laboratory.

d: Concomitant medications to be reviewed at every visit, until 30 days after the last treatment dose. Use of topical or systemic steroids within 14 days of Cycle 1 Day 1 is not allowed, with the exception noted under "Concomitant Medications" (see Section 9.4.7).

e: Vital signs measured at baseline and EOT (if necessary), and on drug treatment days and on Cycle Day 8 (± 1 day), before and at the end of the infusion and 30 minutes after infusion. A complete physical examination will be performed at Baseline, Day 1 of each cycle, and at Study Termination (discontinuation from study). A symptom-directed examination will be performed on all other visit days. All physical examinations are to include monitoring of weight and blood pressure as signals for potential vascular leak syndrome.

f: Single 12-lead ECGs will be performed during Screening, on Day 1 of each cycle and at End of Treatment.

g: On Cycle Day 1 (i.e. treatment day), urinalysis will be performed prior to study drug administration. Urinalysis includes glucose, protein, leukocytes, nitrites, ketones, bilirubin, blood, urobilinogen, pH, and specific gravity. Microscopic examination of sediment includes bacteria, casts, crystals, epithelial cells, RBCs, and WBCs. When a local laboratory is required for a urinalysis, a Urinalysis Reagent Test Strip (URS-10) may be used. On Cycle 1 Day 1 only: a urine pregnancy test will be performed prior to study drug administration.

h: Chemistry laboratory tests should include the following thyroid function tests: serum TSH, free T_3, free T4, and if these are abnormal, then include anti-thyroglobulin antibodies and anti-thyroid peroxidase antibodies (reflex testing at central laboratory only). Laboratory tests should also include serum ß-hCG and LDH (screening only), chloride, potassium, sodium, BUN, serum creatinine, phosphorus, calcium, albumin, total protein, alkaline phosphatase, ALT, AST, total bilirubin, and CPK. Hematology laboratory tests include hematocrit, hemoglobin, platelets, RBC count, WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils), and ANC. If Screening laboratory tests (Hematology, Chemistry, and serum pregnancy) are performed within 7 days prior to Cycle 1 Day 1, these tests may count as Baseline tests and need not be repeated at Baseline. On Day 1 of each cycle, laboratory assessments (local site laboratory) must be reviewed prior to drug administration, in addition to submitting to the central lab. For Cycle Day 8, a window of ±1 day is allowed.

i: Blood sampling for pharmacokinetic (PK) and immunogenicity (anti-E7777, anti-IL-2, and neutralizing antibodies) testing. Sample volumes are 3 mL for PK assessments and 3 mL for immunogenicity testing. Pharmacokinetic assessment of E7777 will be performed in all subjects in the Lead-In part and in the first 12 subjects in Main Study. Serial blood samples will be taken on Day 1 of Cycles 1, 3, and 5, with sparse sampling in Cycle 8. Serial blood samples will be collected at predose, 30 min after the start of the infusion, end-of-infusion, and 30, 60, 90, 120, 180, 240, and 300 minutes after the end of the infusion. Sparse samples will be collected at predose, end-of infusion and between 60 and 180 min after the infusion ends. For the remaining subjects in the Main Study, sparse blood samples will be taken on Day 1 of Cycle 1. They will be collected at predose, end-of infusion and between 60 and 180 min after the end of the infusion. Immunogenicity will be assessed in all subjects in both the Lead-In part and the Main Study. A predose blood sample for immunogenicity assessment will be collected prior to dosing on Day 1 in Cycles 1, 2, 3, 5, and 8; after that, all subjects will be followed up for immunogenicity testing for anti-IL2 at 6 months, one year and every year thereafter until antibody titers decrease to baseline level. These blood samples will be collected before study drug administration.

j: E7777 by i.v. infusion over 60 minutes (±10 minutes). Premedication required in Cycles 1 to 3 (see protocol). Lead-In: E7777 at a dose assigned according to the CRM; Main Study: E7777 at a dose determined in the Lead-In. A window of ±1 day is allowed for start of treatment cycle from Cycle 3 onward, inclusive.

k: Assessment of skin disease by mSWAT score, lymph node disease by physical examination, and blood disease by flow cytometry (central laboratory). During the Extension phase, assessment is to be performed every 4 weeks (± 1 week) for 1 year after end of study treatment, then every 12 weeks (± 3 weeks) thereafter for up to 3 years, or sooner if clinically indicated. In addition, skin assessments as needed for the supplemental alternate method for independent review using the method of Prince (2010) are to be performed

as indicated in Section 9.5.2.2 and Appendix 4 of the protocol. The Day 1 assessments can be performed within a -3 day window, i.e., Day 1 (-3 days). Standardized photographs of the skin are to be taken at all assessment time points. The required views are listed in the protocol Section 9.5.2.2. If the Screening assessment is within 1 week prior to Cycle 1 Day 1, photographs are not required on Cycle 1 Day 1 as long as, in the investigators judgment, there is not a significant enough change in the subject's skin disease involvement to warrant repeat photographs on Cycle 1 Day 1.

l: Patient-reported assessments of pruritus will be performed at the same visits as the mSWAT assessments.

m: CT scanning of neck, chest, abdomen, and pelvis is required at Screening (unless scans were performed within 6 weeks prior to C1D1) to assess nodal and visceral disease (scans within 6 weeks prior to C1D1 are acceptable as baseline scans as long as they meet the requirements of the Imaging Acquisition Guideline from the Imaging Core Laboratory). For subjects who failed screening because of lab results, and at re-screening the investigator believes that there is no new disease progression, new scans are not required and previous screening scans are acceptable as baseline if performed within 6 weeks prior to C1D1.

^{18}FDG-PET-CT scans may be performed during screening for lymph node disease assessment.

For subjects with nodal disease N_2, N_3 and N_x at screening, CT scans of the affected/suspected area are required every 3 cycles beginning at Cycle 3 (±1 week) during treatment phase. For all other subjects during treatment phase, CT scans are required at the time of a documented CR or PR or as clinically indicated (eg, suspicion of PD) and at final treatment for responding subjects (PR or CR) during follow-up for responding subjects (PR or CR) who have had documented nodal involvement at baseline and currently there is no suspicion of nodal involvement after the final treatment, at 6 months, 12 months, and yearly for up to 3 years. For subjects in the Lead-In with visceral involvement at screening, CT scans of the chest, abdomen, and pelvis are required every four cycles (±1 week) during treatment; and at the time of a documented CR or PR, and as clinically indicated (e.g., suspicion of PD or relapse) within 1 week after suspicion of response or progression/relapse.

CT/^{18}FDG-PET-CT scans of skin disease may be performed as necessary for response assessment if the CT acquisition is of diagnostic quality.

n: Adverse events will be assessed at every visit, until 30 days after the last treatment dose.

o: Survival follow-up performed every 3 months after discontinuation from study treatment, up to 3 years from end of study treatment.

p: QoL is to be performed at Baseline, on Day 1 of every cycle during Treatment, at EOT, and during every Tumor Assessment visit during Extension. The QoL will be assessed in Stage I – III Main Study subjects plus the Stage I – III Lead-In subjects from the 9µg/kg/day dose group combined.

q: Follow-up tumor assessments (except in subjects who discontinued treatment due to PD), immunogenicity and survival follow-up until relapse, or initiation of new systemic anti-cancer therapy, for up to 3 years after EOT.

9.5.5.2 Description of Procedures/Assessments Schedule – Lead-In and Main Study

PRETREATMENT PHASE ASSESSMENT SCHEDULE

SCREENING PERIOD ASSESSMENTS

Visit 1 (up to 28 days before start of study treatment)

Prior to performing any procedures or assessments, the nature of the study and the potential risks associated with the study will be explained to all candidates and their respective partners, where applicable, and written informed consent obtained from both, if required. Once informed consent has been obtained, the Screening Period procedures and evaluations will be performed.

Refer to the Schedule of Assessments, Table 4, for a description and the schedule for all other screening assessments.

BASELINE PERIOD ASSESSMENTS

Visit 2 (up to 7 days before the start of study treatment)

The results of all baseline assessments and evaluations must be completed and reviewed by the PI prior to the subject's arrival for the visit. Only those subjects who continue to meet all of the inclusion and none of the exclusion criteria are eligible to continue in the study.

If Screening laboratory tests (Hematology, Chemistry, and serum pregnancy) are performed within 7 days prior to Cycle 1 Day 1, these tests may count as Baseline tests and need not be repeated at Baseline. If Baseline central laboratory test results are not available in time to confirm eligibility, the local site laboratory results (including from Cycle 1 Day 1) may be used for this purpose.

Reasonable efforts should be made to conduct all baseline assessments and subsequent evaluations in the same test order at each subject visit. This is intended to minimize variability in subject response. It is further recommended (whenever possible) that subjects be evaluated at approximately the same time period of the day (e.g., morning or afternoon) at each subsequent visit.

During the Lead-In Period only, IxRS should be called for dose assignment according to CRM design method. Refer to the Schedule of Assessments, Table 4, for a description and the schedule for all other Baseline Visit assessments.

TREATMENT PHASE AND EXTENSION PHASE ASSESSMENT SCHEDULES

Treatment Period:

Refer to the Schedule of Assessments, Table 4, for a description and the schedule for all cycle day and EOT assessments.

Day 8 assessments are required during Cycles 1-3 and are optional on Cycle 4 and beyond.

EOT: Tumor assessments are only required at EOT if they affect GRS. Other EOT tests (with the exception of serum pregnancy test, and QoL) need only be performed if the EOT visit is > 7 days from the most recent Cycle Day 1 visit.

Follow-up Period:

Tumor assessments should be performed until PD. Immunogenicity and survival assessments should be performed until discontinuation from study. All assessments for up to 3 years from EOT. Refer to the Schedule of Assessments, Table 4, for a description and the schedule for all other Follow-Up assessments.

9.5.6 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of treatment of CTCL.

9.5.7 Reporting of SAEs, Pregnancy, and Other Events of Interest

9.5.7.1 Reporting of SAEs

All SAEs, 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.

Deaths and life-threatening events should be reported immediately by telephone. The immediate report should be followed up within 1 business day by emailing or faxing the completed SAE form.

SAEs, regardless of causality assessment, must be collected through the last visit and for 30 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

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.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by the institution. A copy of this communication must be forwarded to the sponsor to be filed in the sponsor's Trial Master File.

9.5.7.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy 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 the 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 SAEs [Section 9.5.7.1]).

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 Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported 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.

9.5.7.3 Reporting of Other Events of Interest

REPORTING OF STUDY DRUG OVERDOSE, MISUSE, ABUSE, OR MEDICATION ERROR

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, 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

Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
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 an overdose should be captured on the Adverse Event CRF. AEs associated with overdose, misuse, abuse, or medication error should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.7.1) 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, abuse, 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.

Any study drug overdose, misuse, abuse, or medication error during the study should be noted on the Study Medication CRF.

REPORTING OF STUDY-SPECIFIC EVENTS

Study-specific events, i.e., vision loss, should be entered on the AE CRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.7.1), even if the study-specific event does not meet serious criteria. If the event 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 AE CRF.

9.5.7.4 Expedited Reporting

The sponsor must inform investigators (or, as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (i.e., within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.7.5 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of 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.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.8 Completion/Discontinuation of Subjects

See Section 9.3.3, Removal of Subjects from Therapy or Assessment, for reasons allowed for discontinuation.

All subjects who discontinue early from the study treatment are expected to complete the EOT procedures indicated on the Schedule of Procedures/Assessments (see Table 4), if possible.

For all subjects who discontinue from the study, study disposition information will be collected on the appropriate eCRF.

A subject who has ceased to return for visits will be followed up by mail, phone, or other means as much as possible to gather protocol-specified follow-up information.

Subjects who are not evaluable for DLT in Cycle 1 should be replaced.

9.5.9 Abuse or Diversion of Study Drug

Not applicable (N/A).

9.5.10 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator 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, 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 and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, 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 or his designee as identified on Form FDA 1572 (where applicable) must sign the CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai 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 (e.g., laboratory data), will be entered into a clinical system as specified in the Data Management Plan.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked. 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 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 Statistical Design in the Lead-In Part: Continual Reassessment Method

The Lead-In part will be a dose-finding study including approximately 12 subjects. A CRM design will be used to determine the MTD of E7777. The MTD is defined in this study as the highest dose that has a ≤ 20% rate of DLT.

Six experimental doses are proposed and can be investigated: 3, 6, 9, 12, 15, and 18 µg/kg. The starting dose will be 6 µg/kg.

The probability of observing (P_T) a DLT at each dose level will be estimated through a two-parameter logistic model:

$$\log\left[\frac{p_T}{1-p_T}\right] = \alpha_1 + \alpha_2 d$$

The independent prior distributions for the two parameters are:

$\alpha_1 \sim N(-2.5, 1)$

$\alpha_2 \sim N(0.05, 0.25^2)$

Starting with the 6 µg/kg dose, the prior distribution of the logistic parameters for P_T will be updated by the accruing data on DLTs each time a subject completes evaluation for toxicity in Cycle 1. Additional subjects will be allocated to the highest dose that has at least a 50% posterior probability of being tolerable (i.e., having a ≤ 20% DLT rate); the next dose allocated may be modified upon consultation with the safety consultancy investigator panel that is reviewing DLTs, based on overall cumulative safety results from the current study and/or on any emerging data from other studies with E7777. The first four subjects will each be required

to complete Cycle 1 before the next subject can be treated, and open enrollment will start with the fifth subject. It is further specified that dose levels cannot be skipped when escalating. The MTD will be determined when approximately 20 subjects have been tested, or when futility is declared. Futility is defined as having a < 25% probability that any of the doses is safe (i.e., the probability that none of the six doses have a ≤ 20% DLT rate is < 25%).

The CRM dose-finding steps are illustrated in Figure 1.

9.7.1.2 Study Endpoints

LEAD-IN PART

The primary endpoints for the Lead-In part are:

- Dose-limiting toxicities (DLTs)
- Maximum tolerated dose (MTD).

The secondary endpoints for the Lead-In part are:

- Safety parameters
- Efficacy parameters (e.g., objective response, duration of response, time to response)
- PK parameters
- Immunogenicity.

MAIN STUDY

The primary efficacy endpoint for the Main Study is objective response (OR) based on GRS.

The secondary endpoints for the Main Study are:

- Duration of response (DOR) based on GRS.
- Time to response (TTR) based on GRS.
- Objective response (OR) using Prince (2010)[5]
- Skin response (according to mSWAT)
- Duration of skin response
- Time to skin response
- Safety parameters
- PK parameters
- Immunogenicity

Exploratory endpoints:

- Progression-free survival (PFS) and time to progression (TTP)

- Pruritus improvement
- QoL using Skindex-29 and the FACT-G Questionnaire

9.7.1.3 Definitions of Analysis Sets

The definitions of the analysis sets are provided below:

All Enrolled Subjects: All subjects who signed informed consent, and at Screening were assessed as meeting all inclusion criteria and not meeting any exclusion criteria. This will be the analysis set for demographics and baseline characteristics analyses.

Dose-Finding Analysis Set: All subjects in the Lead-In part who completed Cycle 1 treatment and were evaluated for DLT, and those who discontinued during Cycle 1 due to DLT. This will be the analysis set for MTD determination in the Lead-In part.

Full Analysis Set: All subjects who received study drug in the Main Study.

Primary Efficacy Analysis Set: All Stage I – III Main Study subjects who received study drug plus the Stage I – III Lead-In subjects from the 9μg/kg/day dose group.

Safety Analysis Set: All subjects who received study drug. This will be the analysis set for all safety analyses.

Stage I-III Safety Analysis Set: All Stage I – III Main Study subjects who received study drug plus the Stage I – III Lead-In subjects from the 9μg/kg/day dose group treated with E7777.
Per Protocol Set: All subjects in the Primary Efficacy Analysis and Full Analysis Sets who received study drug, and had a baseline and at least one postdose tumor assessment and had no major protocol deviations. The per protocol analysis set will be identified prior to database lock. Full criteria for exclusion from the analysis set will be detailed in the SAP. This will be the secondary analysis set for the efficacy analyses.

PK Analysis Set: All subjects from whom at least one valid E7777 PK parameter is obtained will comprise the analysis set for the PK and immunogenicity data.

Population PK Analysis Set: All subjects from whom at least one quantifiable concentration of E7777 is available with a documented dosing history.

Population PK/PD Analysis Set: All subjects in the Population PK analysis set for whom efficacy and safety variables are also available.

9.7.1.4 Subject Disposition

The method for summarizing the number (percentage) of subjects who were screened for the study (enrolled subjects, i.e., those who signed informed consent) and reasons for screen failure is described in the SAP.

9.7.1.5 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized and listed. For continuous demographic/baseline variables including age, weight, and vital signs, results will be summarized and presented as N, mean, standard deviation (SD), median, and minimum and maximum values. For categorical variables such as race/ethnicity, the number and percentage of subjects will be used.

9.7.1.6 Prior and Concomitant Therapy

Concomitant medications will be assigned an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) drug codes. Concomitant medications will be further coded to the appropriate Anatomical-Therapeutic-Chemical (ATC) code indicating therapeutic classification. Prior and concomitant medications will be summarized and listed by drug and drug class in the clinical study report for this protocol.

9.7.1.7 Efficacy Analyses

All efficacy and QoL analyses will be performed primarily in the Stage I – III Main Study subjects plus the Stage I – III Lead-In subjects from the 9μg/kg/day dose group combined, and additionally in all subjects from the Main Study.

The efficacy analyses in the Main Study, including primary efficacy analysis, will be performed by the Independent Review Committee (IRC) as detailed in a Tumor Assessment Charter.

In addition, investigator-assessed response assessments will be recorded for all subjects.

The primary analysis will be performed after data cutoff, which will be either of the following 2 events, whichever occurs later: (1) when all subjects in the Main Study have either completed Cycle 8 or are off treatment, or (2) when all subjects with at least one documented time point response of PR or better have undergone the subsequent tumor assessments necessary for confirmation of response (unless the subject had disease progression or discontinued from study before then).

The efficacy and QoL endpoints in the Lead-In part will be summarized and listed by dose level based on the Safety Analysis Set. No statistical analysis will be performed.

PRIMARY EFFICACY ANALYSIS

The primary endpoint ORR will be analyzed on the full analysis set. ORR will be calculated in Stage I – III CTCL subjects from the Main Study plus the Lead-In subjects from the 9μg/kg/day dose group combined, using a 2-sided, exact 95% confidence interval (CI), using the Clopper-Pearson method. The treatment will be considered efficacious and demonstrating clinical benefit of E7777 if the lower limit of the 2-sided 95% exact CI of the observed ORR exceeds 25%.

SECONDARY EFFICACY ANALYSES

Skin response will be calculated with a 2-sided, exact 95% confidence interval (CI), using the Clopper-Pearson method. DOR, TTR, duration of skin response, and time to skin response for E7777 will be calculated using Kaplan–Meier product-limit estimates and plotted over time. The medians for these endpoints and their corresponding two-sided 95% CIs will be provided.

ORR (by Prince criteria) will be calculated with a 2-sided, exact 95% CI, using the Clopper–Pearson method.[5]

EXPLORATORY EFFICACY ANALYSES

PFS and TTP will be analyzed using Kaplan–Meier product limit estimate. Median PFS and TTP time will be calculated using Kaplan–Meier product limit estimate and presented with corresponding two-sided 95% CIs. The cumulative probabilities will be plotted over time.

Pruritus Improvement Rate will be calculated with a two-sided exact 95% CI using the Clopper–Pearson method. In addition, the percentages of subjects who have ≥ 20% and ≥ 50% improvements relative to baseline in each of the VAS-based assessment scores will be tabulated. The frequency of use of rescue medications will be determined by comparing the number of packages dispensed and the number of packages returned.

Sensitivity analyses for ORR in subjects receiving versus subjects not receiving steroid medication will be performed.

QoL assessment scores, based on Skindex-29 and FACT-G, will be summarized through basic statistics.

9.7.1.8 PK and Immunogenicity Analyses

PK ANALYSES

PK parameters will be summarized based on the PK analysis set. Potential relationships between the E7777/ONTAK serum concentration data and tumor response, as well as AEs, will be explored.

IMMUNOGENICITY ANALYSES

The percentage of subjects testing positive for anti-E7777 and anti-IL-2 antibodies at baseline and during study treatment will be assessed. Potential relationships between presence of anti-E7777 antibodies and tumor response, as well as AEs, will be explored.

9.7.1.9 Safety Analyses

Lead-In Part

DLTs will be summarized and listed by dose for all subjects in the Dose Finding Analysis Set.

The posterior summaries from the CRM will be presented.

Safety analyses for the Lead-In part will be done using all the Safety Analysis Set subjects.

Main Study

Evaluation of safety will be performed on the Safety Analysis Set. The safety analyses for the Main Study will be performed in all Safety Analysis Set subjects and all Safety Analysis Set Stage I – III subjects, separately. Safety data to be evaluated include AEs, clinical laboratory results, vital signs, ECGs, and the results of physical examinations.

Safety parameters will be summarized using descriptive statistics (mean, SD, median, Q1, Q3, and range for continuous variables; numbers and percentages for categorical measures).

EXTENT OF EXPOSURE

The number of subjects in each study arm, the number of days/cycles on treatment, quantity of study drug administered, and the number of subjects requiring dose reductions, treatment interruption, and treatment discontinuation will be summarized by study arm.

ADVERSE EVENTS

AEs will be graded using CTCAE v5.0. Investigators will collect all AE CTCAE grades (for both increasing and decreasing severity). AEs will be classified into standardized medical terminology from the verbatim description (investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be presented by preferred term (PT) nested within system organ class (SOC). Verbatim descriptions and MedDRA SOC PT for all AEs will be contained in the data listings of the clinical study report for this protocol.

An overview table, including the incidence of and the number of subjects with treatment-emergent adverse events (TEAEs), SAEs, deaths, and those TEAEs that led to discontinuation, dose modification, or dose interruption, will be provided.

The incidence of TEAEs will be summarized by SOC, PT, CTCAE grade, and relatedness to study drug. Although a MedDRA term may be reported more than once for a subject, that subject will be counted only one time in the incidence count for that MedDRA term with the highest CTCAE grade (in the summary by CTCAE grade) or with the closest relationship to study treatment (in the summary by relatedness to study treatment).

TEAEs will be analyzed. AEs that are not treatment-emergent will be listed. TEAEs are defined as AEs that emerge during treatment, having been absent at pretreatment (baseline), or those that:

- Reemerge during treatment, having been present at baseline but stopped prior to treatment, or
- Worsen in severity during treatment relative to the pretreatment state, when the AE is continuous.

Separate summary tables will be provided for all TEAEs, treatment-emergent SAEs, TEAEs

reported as treatment-related, treatment-emergent SAEs reported as treatment-related, and TEAEs leading to treatment discontinuation.

LABORATORY VALUES

Clinical laboratory values will be evaluated for each laboratory parameter by subject. Abnormal laboratory values will be identified as those outside (above or below) the normal range. Reference (normal) ranges for laboratory parameters will be included in the clinical study report for this protocol. Descriptive summary statistics for laboratory parameters and their changes from baseline will be calculated.

Laboratory parameters that are graded in CTCAE v5.0 will be summarized by CTCAE grade.

Clinical laboratory results postbaseline will be evaluated for markedly abnormal values. The National Cancer Institute's CTCAE v5.0 will be used to identify subjects with markedly abnormal laboratory values. The incidence of markedly abnormal values will be summarized by cycle. For the incidence of markedly abnormal laboratory values, each subject may be counted once in the laboratory parameter value high category and once in the laboratory parameter low category, as applicable.

VITAL SIGNS

Descriptive statistics for vital signs parameters (i.e., sitting diastolic and systolic BP, sitting pulse rate, respiratory rate, temperature, weight, and changes from baseline) will be presented by visit.

ECGS

Analysis of any drug effect on QT/QTcF will be described in the SAP.

9.7.2 Determination of Sample Size

LEAD-IN PART

The number of subjects in the Lead-In part will be approximately 20, based on the CRM design requirements.

MAIN STUDY

The sample size of approximately 70 Stage I – III subjects (including Stage I – III subjects from both the Main Study plus from the Lead-In part 9 µg/kg/day dose group combined) was estimated assuming that a lower limit of the 2-sided 95% CI of ORR exceeding 25% indicates clinical benefit in persistent and recurrent CTCL. It was also assumed that in this population we can reasonably expect to observe an ORR ≥ 36%, i.e., at least 25 subjects with CR+PR among 70 subjects.

With a sample size of approximately 70 Stage I – III subjects (including Stage I – III subjects from both the Main Study plus from the Lead-In part 9 µg/kg/day dose group combined), the 2-sided 95% exact Clopper–Pearson CI of an observed 36% ORR would range from 25% to

48%. Thus, an observed ORR that is ≥ 36% would be significantly higher than 25%, thereby demonstrating the presence of clinical benefit.

Sample size estimates were calculated using PASS 2008 software.

9.7.3 Interim Analysis

At the end of the Lead-In part of the study, the objective response of all subjects will be evaluated. The study will only continue to the Main Study if there is at least one subject in the Lead-In with a confirmed CR or PR by investigator assessment.

9.7.4 Procedure for Revising the SAP

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

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11. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

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 submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. 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's medical monitor and the IRB/IEC 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 health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or, if regionally required, the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the CA (or, if regionally required, 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 (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's 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 investigator (or, if regionally required, 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 local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts

- Copies or transcribed health care provider notes which have been certified for accuracy after production

- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (e.g., sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, electroencephalograms, polysomnographs, pulmonary function tests), regardless of how these images are stored, including microfiche and photographic negatives

- Pain, QoL, 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 (e.g., urine pregnancy test result documentation and urine dip-sticks)

- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs

- CRF components (e.g., 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 correction 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:

- Study drug compliance (e.g., the reason for the change of dosing)

- Information on the subject's discontinuation (e.g., in the case of lost to follow-up due to the subject choice)

- PK sampling date and time
- Clinical laboratory test sampling date
- Comments and relevant information on the AEs (e.g., severity, relationship to study drug, outcome)

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or, if regionally required, 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 IB, and regulatory agency registration documents (e.g., Form FDA 1572, ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region 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, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's Standard Operating Procedures (SOPs) to evaluate compliance with the principles of ICH, GCP, and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drugs will be supplied to the investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (e.g., locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) 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. 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 site personnel) must not destroy any drug labels or any partly used or unused drug supply prior to approval to do so by the sponsor. At the conclusion of the study and as

appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA or, when approval is given by the sponsor, will destroy supplies and containers at the site.

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 pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either on 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 investigator 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/IEC 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 institution/PI.

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 institution/PI and the sponsor.

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/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/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 institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC 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.

12 APPENDICES

Appendix 1 Classification and Staging of Mycosis Fungoides and Sézary Syndrome

Appendix 1 Table 1 ISCL/EORTC Revisions to the TNMB Classification of MF/SS (from Olsen 2011)

Area	TNMB Stages	Description of TNMB
Skin*	T_1	Limited patches, papules, and/or plaques covering < 10% of the skin surface; may further stratify into T_{1a} (patch only) v T_{1b} (plaque ± patch)
	T_{1a}	Patch only
	T_{1b}	Plaque± patch
	T_2	Patches, papules, and/or plaques covering ≥ 10% of the skin surface; may further stratify into T_{2a} (patch only) v T_{2b} (plaque ± patch)
	T_{2a}	Patch only
	T_{2b}	Plaque ± patch
	T_3	One or more tumors (≥ 1 cm diameter)
	T_4	Confluence of erythema covering ≥ 80% body surface area
Node†	N_o	No clinically abnormal lymph nodes; biopsy not required
	N_1	Clinically abnormal lymph nodes; histopathology Dutch Grade 1 or NCI LN_{0-2}
	N_{1a}	Clone negative
	N_{1b}	Clone positive
	N_2	Clinically abnormal lymph nodes; histopathology Dutch Grade 2 or NCI LN_3
	N_{2a}	Clone negative
	N_{2b}	Clone positive
	N_3	Clinically abnormal lymph nodes; histopathology Dutch Grade 3-4 or NCI LN_4; clone positive or negative
	N_x	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	M_0	No visceral organ involvement
	M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	B_0	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells
	B_{0a}	Clone negative
	B_{0b}	Clone positive
	B_1	Low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2
	B_{1a}	Clone negative
	B_{1b}	Clone positive
	B_2	High blood tumor burden: ≥ 1,000/µL Sézary cells with positive clone[c]; one of the following can be substituted for Sézary cells: CD4/CD8 ≥ 10%, CD4+CD7- cells ≥ 40% or CD4+CD26- cells ≥ 30%

EORTC = European Organization for Research and Treatment of Cancer, ISCL = International Society for Cutaneous Lymphomas, MF = mycosis fungoides, SS = Sézary syndrome, TNMB = tumor-node-metastasis-blood.
*Patch = any size lesion without induration or significant elevation above the surrounding uninvolved skin: poikiloderma may be present.
Plaque = any size lesion that is elevated or indurated: crusting or poikiloderma may be present.
Tumor = any solid or nodular lesion ≥1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

† Lymph node classification has been modified from 2007 ISCL/EORTC consensus revisions1 to include central nodes. Lymph nodes are qualified as abnormal if >1.5 cm in diameter.
‡ The clone in the blood should match that of the skin. The relevance of an isolated clone in the blood or a clone in the blood that does not match the clone in the skin remains to be determined.

Appendix 1 Table 2 Modified ISCL/EORTC Revisions to the Staging of MF/SS (from Olsen 2011)

Stage	T (Skin)	N (Node)	M (Visceral)	B (Blood)
1A	1	0	0	0, 1
1B	2	0	0	0, 1
IIA	1-2	1, 2, X	0	0, 1
IIB	3	0-2, X	0	0, 1
IIIA	4	0-2, X	0	0
IIIB	4	0-2, X	0	1
IVA_1	1-4	0-2, X	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3, X	1	0-2

EORTC = European Organization for Research and Treatment of Cancer, ISCL = International Society for Cutaneous Lymphomas, MF = mycosis fungoides, SS = Sézary syndrome, X = clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize histologic subcategories.

Appendix 2 ECOG Performance Status Scale

Appendix 2 Table 1 ECOG

Grade	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light house work, office work)
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

ECOG = Eastern Cooperative Oncology Group.
Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and Response Criteria of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-56.[9]

Appendix 3 Cockcroft–Gault Calculation of Creatinine Clearance

Subjects must have adequate renal function as evidenced by serum creatinine ≤ 1.8 mg/dL or calculated creatinine clearance ≥ 50 mL/min per the Cockcroft–Gault formula as defined below.

Appendix 3 Table 1 Cockcroft–Gault Calculation for Creatinine Clearance

Male	$\frac{(140 - \text{age}) \times \text{weight (kg)} \times 1.23}{\text{serum creatinine (µmol/L)}} = \text{XX mL/min}$
Female	$\frac{(140 - \text{age}) \times \text{weight (kg)} \times 1.23 \times 0.85}{\text{serum creatinine (µmol/L)}} = \text{XX mL/min}$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.[11]

Appendix 4 CTCL Tumor Response Criteria According to the ISCL/EORTC Consensus (Olsen 2011)

This CTCL tumor response criteria summary guide follows the recommendations in:

> 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(18):2598-607.

A composite measure of disease in skin, lymph node, blood, and viscera will be used to assess Tumor Burden. A Global Response Score will indicate the overall response assessment based on the composite measure.

1. Skin Disease Assessment, Scoring, and Definition of Response

   Skin tumor burden will be quantified using a modified Severity Weighted Assessment Tool (mSWAT) that provides an mSWAT score. The mSWAT score measures the body surface area (BSA) involved in skin disease with a weighting factor applied according to the severity of the type of skin lesion, which can be patch, plaque, or tumor. The mSWAT can be utilized to track erythroderma by the summation of BSA involved with patch disease (macular erythema) and plaque disease (erythema with induration/edema). In addition, subject(s) should be evaluated for the appearance of new skin tumor lesion(s) at each time point. The Day 1 assessments can be performed within a -3-day window, e.g., Day 1 (-3 days).

   A. Assessment Schedule

      See Section 9.5.2.2

   B. Scoring of Skin Tumor Burden

      Tumor burden is quantitated using the mSWAT score. mSWAT measures the body surface area (BSA) involved in skin disease with a weighting factor applied according to the severity of the type of skin lesion.

      mSWAT score = (BSA patch disease × 1) + (BSA plaque × 2) + (BSA tumor × 4)

      The mSWAT score should be computed using the table below. (Note: this table is a sample. The worksheet for use at the site will be provided separately to each site.) In this table, the percent BSA represented by body region is indicated.

Appendix 4 Table 1 Scoring of Skin Tumor Burden and Calculation of mSWAT Score

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch*	Plaque†	Tumor‡
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		×1	×2	×4
Subtotal lesion BSA × weighting factor		A: ___	B: ___	C: ___
mSWAT (A+B+C)				

BSA = body surface area, mSWAT = modified Severity Weighted Assessment Tool

*Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.

†Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.

‡Any solid or nodular lesion ≥ 1 cm in shortest diameter with evidence of deep infiltration in the skin and/or vertical growth.

Supplemental Assessment for Prince (2010) Analysis (only for subjects with skin lesions comprising < 10% of BSA at screening)

Since the IRC will perform a secondary analysis based upon the method of Prince (2010), a supplemental measurement will be made by the site investigator at the time of mSWAT assessment, for subjects with skin lesions comprising < 10% of BSA at screening. The investigator will identify, photograph, and measure up to five representative skin lesions (generally the largest and most representative of different locations, such as chest, abdomen, leg, arm, head, neck, if applicable); measurements will be of two-dimensional perpendicular diameters). These measurements will be collected on the eCRF and will be used only by the IRC. A sample of the worksheet for collecting skin lesion data is shown in the table below. Note: The worksheet for use at the site will be provided separately to each site. These lesions (even if they have disappeared) should be evaluated and photographed at all mSWAT assessment time points.

Lesion number	Cycle (date)	Location	Patch (cm) *		Plaque (cm) †		Tumor (cm) ‡	
			Diameter	Perpendicular Diameter	Diameter	Perpendicular Diameter	Diameter	Perpendicular Diameter
1								
2								
3								
4								
5								

***Any size lesion without induration or significant** elevation above the surrounding uninvolved skin; poikiloderma may be present.

†Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.

‡Any solid or nodular lesion ≥ 1 cm in shortest diameter with evidence of deep infiltration in the skin and/or vertical growth.

C. Definition of Response in Skin

The mSWAT score will be used to quantify tumor burden for determination of skin response. The score of Cycle 1 Day 1 will be used as the baseline reference value. Refer to Appendix 4 Table 2 below.

Appendix 4 Table 2 Definition of Response in Skin

Response	Definition
CR	100% clearance of skin lesions*
PR	50%-99% clearance of skin disease from baseline without new tumors (T3) in patients with T1, T2 or T4 only skin disease
SD	< 25% increase to < 50% clearance in skin disease from baseline without new tumors (T3) in patients with T1, T2, or T4 only skin disease
PD†	≥ 25% increase in skin disease from baseline or New tumors (T3) in patients with T1, T2 or T4 only skin disease or Loss of response: in those with complete or partial response, increase of skin score of greater than the sum of nadir plus 50% baseline score
Relapse	Any disease recurrence in those with complete response

CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease

*A biopsy of normal appearing skin is unnecessary to assign CR. However, a skin biopsy should be performed of a representative area of the skin if there is question of residual disease (persistent erythema or pigmentary change) where otherwise a CR would exit. If histologic features are suspicious or suggestive of MF/SS, the response should be considered a PR only.

†Whichever criterion occurs first

2. Lymph Node Assessment and Definition of Response

A. Assessment Methods and Schedules

See Section 9.5.2.2 and Figure 1 in Appendix 5.

B. Measurements for lymph node disease

a. Palpation. Each palpable node will be assessed as "normal size" or "enlarged/abnormal" and recorded as such.

b. CT.

i. The longest diameter (LDi) and the short axis (SDi) will be recorded for all lymph nodes.

If target lymph node is visible but is too small to measure, a default value of 5 mm should be used for LDi and SDi. If only the SDi is too small to measure, report LDi dimension and report default value of 5 mm for SDi

ii. The SPD will be calculated for target lymph nodes; target nodes are abnormal nodes identified at Screening assessment. Abnormal nodes are > 1.5 cm in the LDi or > 1.0 cm in the SDi.

SPD = Sum of PPDs of all target nodes

PPD (Product of the Perpendicular Diameter) for each target lymph node = LDi × SDi

C. Definition of Response in Lymph Nodes

Appendix 4 Table 3 Definition of Response in Lymph Nodes

Response	Definition
CR	All lymph nodes are now ≤ 1.5 cm in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma; in addition, lymph nodes that were N_3 classification and ≤ 1.5 cm in their long axis and > 1 cm in their short axis at baseline, must now be ≤ 1 cm in their short axis or biopsy negative for lymphoma
PR	Cumulative reduction ≥ 50% of the SPD of target lymph nodes from baseline and no new lymph node > 1.5 cm in the diameter of the long axis or > 1.0 cm in the diameter of the short axis if the long axis is 1-1.5 cm diameter. Non-target lesions not unequivocally increased.
SD	Fails to attain the criteria for CR, PR, and PD
PD	All Target nodes demonstrate a ≥ 50% increase in SPD from SPD nadir and at least one node is >1.5 cm in LDi. Any new node > 1.5 cm in the long axis or. >1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N_3 histologically or Loss of response: > 50% increase from nadir in SPD of lymph nodes in those with PR
Relapse	Any new lymph node > 1.5 cm in the long axis in those with CR proven to be N_3 histologically
NI	Not involved. Lymph nodes are normal at baseline.
UNK	Assessment is not possible due to image quality issues

[4] CR = complete response, LDi = longest diameter, PD = progressive disease, PR = partial response, SD = stable disease, SPD = sum of the products of the perpendicular diameters.

3. Blood Disease Assessment and Definition of Response

   Blood tumor burden will be assessed by quantifying CD4+CD26− cells by flow cytometry; CD4+CD7− cells may be used in CD26+ subjects.

   A. Assessment frequency

      See Section 9.5.2.2.

   B. Quantitation of blood tumor burden

      The absolute number of CD4+CD26− cells will be used to quantify blood tumor burden. This number will be obtained from flow cytometry analysis.

   C. Definition of Response in Blood

      The blood tumor burden of Cycle 1 Day 1 will be used as the baseline reference value.

Appendix 4 Table 4 Definition of Response in Blood

Response	Definition
CR	B_0
PR	> 50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD	B_0 to B_2 or > 50% increase from baseline and at least 5,000 neoplastic cells/µL or Loss of response: in those with PR who were originally B_2 at baseline, > 50% increase from nadir and at least 5,000 neoplastic cells/µL
Relapse	Increase of neoplastic blood lymphocytes to ≥ B_1 in those with CR

CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease.
B_0 is ≤ 250/µL tumor cells.

4. Visceral Disease Assessment and Definition of Response

   A. Assessment method and schedules

      See Section 9.5.2.2.

   B. Measurement for visceral disease

      a. CT Scan

         i. The longest diameter (LDi) and the short axis (SDi) will be recorded for all measurable disease.

         At screening, the minimum size for measurable visceral disease is 1.0 × 1.0 cm; smaller than that will be recorded as non-measurable disease.

If a nodule is visible but is too small to measure, a default value of 5 mm should be used for LDi and SDi. If only the SDi is too small to measure, report LDi dimension and report a default value of 5 mm for SDi.

For follow-up scans, both LDi and SDi will be recorded for all measurable disease identified at screening. If a measurable disease becomes visible but is too small to measure, a default value of 5 mm should be used for LDi and SDi. If only the one diameter is too small to measure, record the default value of 5 mm for that diameter and the measured diameter for the other dimension.

ii. The Sum of the Products of the Perpendicular Diameters (SPD) will be calculated for visceral disease.

SPD = Sum of PPDs of all visceral disease

PPD is the Product of the Perpendicular Diameter; for each lesion PPD = LDi × SDi

b. Physical Examination (by palpation of liver and spleen) will be used to monitor for enlargement and visceral disease.

C. Definition of Response in Viscera

Response in Viscera	
Response	**Definition**
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical examination and should be considered normal by imaging; no nodules or other visceral disease should be present on imaging of liver or spleen or any organ; any posttreatment mass must be determined by biopsy to be negative for lymphoma
PR	≥ 50% regression (SPD) in any splenic or liver nodules, or in measureable disease in any organs abnormal at baseline; no increase in size of liver or spleen and no new sites of involvement; no unequivocal increase in size of non-measurable disease
SD	Fails to attain the criteria for CR, PR, or PD
PD	> 50% increase in size (SPD) from nadir of any visceral disease involved at baseline or unequivocal increase in size of non-measurable disease, or New visceral disease involvement, or Loss of response: > 50% increase from nadir in the size (SPD) of any previous visceral disease involvement in those with PR
Relapse	New visceral disease involvement in those with CR

[5] CR = complete response, PD = progressive disease, PR = partial response, SD = stable disease. SPD = sum of the products of the perpendicular diameters.

The minimum size of a new visceral lesion by CT must be: > 1.0 × 1.0 cm.

5. Global Response Assessment

Each component of the tumor-node-metastasis-blood (TNMB) staging (i.e., skin, nodes, viscera, and blood) has been given its own definition of response (see Tables in the sections above) and these definitions are incorporated in and used to define the Global Response score.

Appendix 4 Table 5 Definition of the Global Response Score

Global Score	Definition	Skin	Nodes/Blood/Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD
		PR	No category has a PD and if any category involved at baseline, at least one has a CR or PR
SD	Failure to attain CR, PR, or PD representative of all disease	PR	No category has a PD and if any category involved at baseline, no CR or PR in any
		SD	CR/NI, PR, SD in any category and no category has a PD
PD	Progressive disease	PD in any category	
Relapse	Recurrence disease in prior CR	Relapse in any category	

CR = complete response, PD = progressive disease, NI = noninvolved, PR = partial response, SD = stable diseas

Notes:

1. No Global Score of CR can be assigned if the subject received concomitant therapy of topical steroids or low dose systemic steroids; in such a case, the maximum response is PR.
2. In cases where the definition of PD or relapse is met but the clinical impression is questionable, the PD should be confirmed after at least 4 weeks in order to avoid premature removal of the subject from the study.
3. Only N_3 is considered as nodal disease (nodal involvement) for Global Response Score assessment.

6. Best Response (Objective Response)

The Best Response or Objective Response for the subject is the best Global Response Score that is at least 3 weeks in duration.

Please note the following:

- Olsen (2011) states 4 weeks duration, but this was based on drugs that had 4-week treatment cycles. The intent is that the response should last at least one treatment cycle (based on consult with study investigators who are also co-authors of Olsen (2011).

- Treatment may continue after first assessment of disease progression (PD) if the investigator is of the opinion that PD needs to be confirmed (see Section 9.4.1). If PD is not confirmed and subject continues treatment, any subsequent time point assessment of CR/PR will be used in assessing Best Response.

Appendix 5 Lymph Node Disease Assessment

Lymph node assessment is according to Olsen 2007, with the following clarifications.

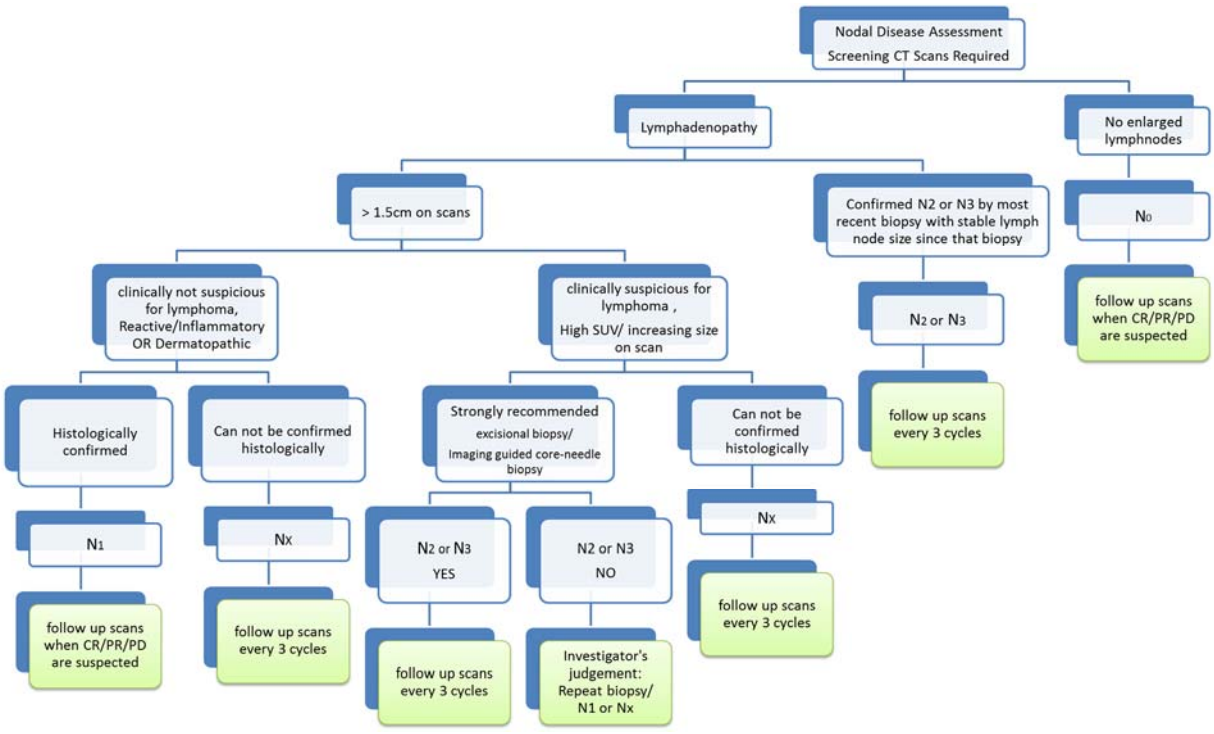
Only N_3 is considered as nodal disease (nodal involvement) for Global Response Score assessment.

N_x status may be assigned if there is no histologic information available:

- N_x may be considered non-involved if the node >1.5 cm diameter is clinically not suspicious for lymphoma (Reactive/Inflammatory OR Dermatopathic) according to judgement of the investigator.
- N_x should be considered involved if clinically suspicious for lymphoma (High SUV/ increasing size on scan).

A flow chart depicting lymph node evaluations/assessments on study according to lymph node status is provided below.

Appendix 5 Figure 1 Nodal Disease Assessment



Appendix 6 CTCAE (v5.0)

The National Cancer Institute's *Common Terminology Criteria for Adverse Events* (CTCAE v5.0 published 27 Nov 2017) provides descriptive terminology to be used for AE reporting in clinical trials. A brief definition is provided to clarify the meaning of each AE term. To increase the accuracy of AE reporting, all AE terms in CTCAE version 5.0 have been correlated with single-concept, Medical Dictionary for Regulatory Activities (MedDRA®) terms.

CTCAE v5.0 grading refers to the severity of the AE. CTCAE Grades 1 through 5, with unique clinical descriptions of severity for each AE, are based on this general guideline:

Appendix 6 Table 1 CTCAE v5.0

Grade	Status
1	Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate: minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).[a]
3	Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL.[b]
4	Life-threatening consequences: urgent intervention indicated.
5	Death related to adverse event.

a: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
Source: Cancer Therapy Evaluation Program, NCI. CTCAE v5.0. Available from https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/CTCAE_v5.0_2017-11-27.xlsx.

For further details regarding MedDRA, refer to the MedDRA website: http://www.meddramsso.com.

CTCAE v5.0 (published 27 Nov 2017) is available online:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/CTCAE_v5.0_2017-11-27.xlsx.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E7777-G000-302

Study Protocol Title: A Clinical Study to Demonstrate Safety and Efficacy of E7777 in Persistent or Recurrent Cutaneous T-Cell Lymphoma

Investigational Product Name: E7777

SIGNATURES

Authors:

PPD

04 Nov. 2019
Date

Oncology Business Group, Eisai Co., Ltd.

PPD

01 Nov 2019
Date

Oncology Business Group, Eisai Inc.

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04 Nov 2019
Date

Oncology Business Group, Eisai Inc.

PPD

01 Nov 2019
Date

Oncology Business Group, Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7777-G000-302
Study Protocol Title:	A Clinical Study to Demonstrate Safety and Efficacy of E7777 in Persistent or Recurrent Cutaneous T-Cell Lymphoma
Investigational Product Name:	E7777

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date