STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E7777-J081-205
Study Protocol Title:	A Phase 2 study of E7777 in patients with relapsed or refractory peripheral T-cell lymphoma and cutaneous T-cell lymphoma
Date:	29 Jul 2019
Version:	Version 2.0

SIGNATURE PAGE

Authors:

PPD

Eisai Co., Ltd.

PPD

Date 2019/07/29

Approval:

Functional Management (Biostatistics):

PPD

Eisai Co., Ltd.

PPD

Date 2019/7/29

Study Director:

PPD

Oncology Business Group
Eisai Co., Ltd.

PPD

Date 2019/7/29

Pharmacokinetic Analyst:

PPD

Eisai Co., Ltd.

PPD

Date 2019/7/29

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
$AUC_{(0\text{-}inf)}$	area under the concentration-time curve from zero time extrapolated to infinite time
$AUC_{(0\text{-}t)}$	area under the concentration-time curve from zero time to time of last quantifiable concentration
BLQ	below the limit of quantification
CCR4	CC chemokine receptor 4
CI	confidence interval
CL	total clearance
CR	complete response
CRF	case report form
CTCAE	common terminology criteria for adverse events
CTCL	cutaneous T-cell lymphoma
CV	coefficient of variation
C_{max}	maximum observed concentration
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	full analysis set
IC	informed consent
IL-2	interleukin-2
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
MedDRA	medical dictionary for regulatory activities
ORR	objective response rate
OS	overall survival
PD	Pharmacodynamics
PD	progression disease

PFS	progression-free survival
PK	Pharmacokinetic
PS	performance status
PT	preferred term
PTCL	peripheral T-cell lymphoma
QT	ECG interval from the beginning of the Q wave to the end of the Twave
QTc	QT interval corrected for heart rate
R_{2adj}	adjusted regression coefficient
R_{ac}	accumulation index
SD	Standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TTR	time to response
V_{ss}	volume of distribution at steady state
V_z	volume of distribution at terminal phase
WHO DD	World Health Organization Drug Dictionary
sIL-2R	soluble interleukin-2 receptor
$t_{1/2}$	terminal elimination phase half-life
t_{max}	time at which the highest drug concentration occurs
λ_z	terminal phase rate constant

3 INTRODUCTION

The purpose of this statistical analysis plan is to describe the procedures and the statistical methods and pharmacokinetics (PK) analysis methods that will be used to analyze and report results for Eisai Protocol E7777-J081-205.

3.1 Study Objectives

3.1.1 Primary Objective

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

3.1.2 Secondary Objectives

(1)To evaluate the efficacy of E7777 below.
- ·Progression-free survival (PFS)
- ·Duration of response (DOR)
- ·Time to response (TTR)
- ·Complete response (CR) rate
- ·Overall survival (OS)

(2)To evaluate the safety of E7777.
(3)To evaluate the PK and immunogenicity (anti-E7777 antibody, anti- interleukin-2 (IL-2) antibody and neutralizing activity of anti-E7777 antibody) of E7777.

3.1.3 Exploratory Objectives

To preliminarily explore the biomarkers of tumor and the blood below.
(1)To measure the rate of CD25+ cells in tumor by immunohistochemistry.
(2)To measure the amount of serum soluble IL-2 receptor (sIL-2R) and lactate dehydrogenase (LDH).
(3)To measure the T-cell subsets in the peripheral blood.

3.2 Overall Study Design and Plan

This is a multicenter, single-arm, open label, Phase 2 to evaluate efficacy, safety, PK and immunogenicity of E7777 in patients with relapsed or refractory PTCL and CTCL. This study composed of the following 3 periods: preparation, treatment and follow-up periods. The preparation period consists of the following four procedures: informed consent (IC), screening, enrollment, and baseline assessment. Informed consent (IC) is able to obtain 28 days before the treatment. Enroll the patient who meet the inclusion criteria and does not meet the exclusion criteria. Conduct the baseline assessment within 7 days before the treatment. Confirm that the patient continue to meet the inclusion criteria and does not meet the exclusion criteria before moving to the treatment period. The

treatment period consists of 1 cycle of 3 weeks and lasts until meet the “discontinuation criteria” or Day 21 of Cycle 8. The evaluation at discontinuation will be performed within 7 days after termination of study treatment.

4 DETERMINATION OF SAMPLE SIZE

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

5 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

5.1 Study Endpoints

5.1.1 Primary Endpoint

Objective response rate (ORR) of best overall response

5.1.2 Secondary Endpoints

- Progression-free survival (PFS)
- Duration of response (DOR)
- Time to response (TTR)
- Complete response (CR) rate
- Overall survival (OS)
- Safety endpoints (adverse events [AEs], clinical laboratory parameters, vital signs, weight, Eastern Cooperative Oncology Group [ECOG] performance status [PS], 12-lead electrocardiograms [ECGs] results, and ophthalmologic test results)
- Pharmacokinetic (PK) parameters
- Immunogenicity (anti-E7777 antibody, anti-IL-2 antibody and neutralizing activity of anti-E7777 antibody)

5.1.3 Exploratory Endpoints

Biomarkers of tumor (CD25+, CC chemokine receptor 4 [CCR4] expression) and following Pharmacodynamics (PD) biomarkers from the blood.

- sIL-2R, LDH

・T-cell subsets (CD4+, CD4+/CD25+, CD4+/CD25+/Foxp3+, *CD4+/CD7－, *CD4+/CD26－)(*Only for mycosis fungoides and Sézary syndrome)

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

Full Analysis Set (FAS):
Defined as a group of subjects who have received at least one dose of the study drug. This group will be the population for the evaluation of efficacy.

Safety Analysis Set:
Defined as a group of subjects who have received at least one dose of the study drug with at least one evaluable post- baseline safety data. This group will be the population for the evaluation of safety.

Pharmacokinetics Analysis Set:
Defined as a group of subjects in who have received at least one dose of the study drug with at least one serum concentration data.

Pharmacodynamics Analysis Set:
Defined as a group of subjects in who have received at least one dose of the study drug with at least one evaluable pre and post-baseline PD data.

On eligibility-confirmed subjects, the number (percentage) of subjects included in each analysis set will be summarized.

5.2.2 Subject Disposition

The number (and percentage as needed) of subjects signed IC, continued in the study after screening and screen failures will be provided and primary reasons for screening failure will be summarized for all subjects. The number and percentage of subjects treated, untreated, completed the study, discontinued the study and the primary reasons for study discontinuation will be summarized for each disease (PTCL, CTCL, Other, as appropriate, determined by central review) and overall.

5.2.3 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics for FAS and the safety analysis set (and the PK analysis set if any discrepancy) will be summarized for each disease and overall using descriptive statistics. Continuous demographic and baseline variables include Age, Height, and Weight. Categorical variables include Sex, Age group (<65, 65<=), Race, Ethnicity, ECOG PS, CCR4 Expression category, CD25+ Cell Rate category and Relapsed/Refractory status (Relapsed: BOR of CR or PR in last previous systemic chemotherapy, Refractory: BOR of SD or PD in last previous systemic chemotherapy, and Unknown). In addition, number and percentage of subjects with each disease histology and each stage will be summarized for each disease and overall.

5.2.4 Prior and Concomitant Therapy

For the FAS, the number and percentage of subjects with each prior treatment (systemic chemotherapy, systemic anti-neoplastic [except systemic chemotherapy], topical therapy, autologous stem-cell transplantation, extracorporeal therapy [except radiotherapy], radiotherapy, surgery[except biopsy]) will be provided. The number of previous systemic chemotherapy regimen will be summarized as categorical variable and continuous variable for each disease and overall. The number and percentage of subject with each previous systemic chemotherapy will be also provided for each disease and overall.

All investigator terms for medications recorded in the case report form (CRF) will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). Prior medications are defined as medications that stopped before the first dose of study drug. Concomitant medications are defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug. Any subthequent anti-cancer therapies are not regared as concomitant but listed separately. All medications will be presented in subject data listings.

5.2.5 Treatment Compliance

For the Safety Analysis set, the number and percentage of subjects who experienced at least one dose skipping / delay of the start of the cycle / dose reduction will be provided for each cycle/all period for each disease and overall. Reasons of delay and reduction will also be summarized for each disease and overall.

5.3 Data Analysis General Considerations

All efficacy analyses will be conducted based on FAS.

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

No adjustment for covariates will be performed.

5.3.3 Multiple Comparisons/Multiplicity

No statistical comparison is planned in this study.

5.3.4 Examination of Subgroups

All efficacy analyses will be conducted for each disease and overall.
Primary efficacy analysis based on the independent assessment results will be performed by the following subgroups: sex (Male/ Female) and age group (<65, >=65), ECOG PS (0/ 1), Baseline CCR4 Status (Postive/ Negative), CD25+ Cell Rate (category1: <1%, 1-<10%, 10-<20%, 20-<50%, >=50, category2: <20%, >=20%), Relapsed/ Refractory status, previous systemic chemotherapy regimen (<=2, >2) and prior use of newly approved agent (Yes/ No).

Analysis of TEAEs by SOC and PT will be performed by the following subgroups: sex, age group and ECOG PS.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

No imputation will be performed for missing data.
Data exceptions will be identified before data base lock based on discussion with medical experts if necessary.

5.4 Efficacy Analyses

FAS will be the primary analysis population. All efficacy result will be summarized for each disease and overall. Results from central assessment by efficacy and safety evaluation committee and investigator assessment will be used, as applicable. If needed, efficacy analysis results per investigator assessment will also be summarized. Unless otherwise noted, overall response considering both “Revised Response Criteria for Malignant Lymphoma (Cheson, J Clin Oncol; 2007)” and “Clinical Endpoints and Response Criteria in Mycosis Fungoides and Sézary Syndrome (Olsen, J Clin Oncol; 2011)” will be used.

For summarization of tumor assessment relevant analysis except PFS and DOR, assessment results until discontinuation from study treatment will be used.

5.4.1 Primary Efficacy Analyses

The rate of subjects whose best overall response is CR or PR is calculated as ORR, and the Exact 95% CI is also calculated. Analysis based on central assessment by Efficacy and safety evaluation committee will be regarded as primary result.
Additionally, For PTCL, best overall response and ORR using overall response evaluated according to “Revised response criteria for malignant lymphoma” will be summarized. And for CTCL, best overall response and ORR based on global response score of “Clinical end points and response criteria in mycosis fungoides and Sézary syndrome” will be summarized.

5.4.2 Secondary Efficacy Analyses

- Analysis of PFS

PFS will be summarized by Kaplan-Meier method using median with 95% CI. Kaplan-Meier curve will be provided. The number of event/censor (percentage) will be also summarized.

・ Analysis of DOR

DOR will be summarized by Kaplan-Meier method using median with 95% CI in responders. The number of event/censor (percentage) will be also summarized.

・ Analysis of TTR

TTR will be summarized using descriptive statistics in responders.

・ Analysis of CR rate

Best overall response will be summarized. For CR rate (the rate of subjects whose best overall response is CR) Exact 95% CI will also be provided.

・ Analysis of OS

OS will be summarized by Kaplan-Meier method using median with 95% CI. Kaplan-Meier curve will be provided. The number of event/censor (percentage) will be also summarized. In addition, summarization for follow-up time will be provided using Kaplan-Meier method.

PFS will be calculated as:
End date for PFS – Date of administration of the first dose of study drug + 1 (day)
DOR will be calculated as:
End date for DOR – Date of the first response + 1 (day)

End date of PFS and DOR is defined as the table below:

Situation	End Date for PFS and DOR	Censored
Documented progression disease (PD) during the study	Date of the first assessment of the series of the tests that determined PD	No
Death during the study before PD	Date of death	No
No baseline assessments	Date of administration of the first dose of study drug	Yes
Treatment discontinuation without post-baseline tumor assessments	Date of administration of the first dose of study drug	Yes
New anticancer treatment started prior to disease progression	Date of last tumor assessment before start of new treatment	Yes
Death or PD after more than one missed tumor assessments	Date of the last tumor assessment before missed assessments	Yes
Subjects still on treatment without PD as of data cut-off	Date of last tumor assessment	Yes

TTR will be calculated as:
Date of first response – Date of administration of the first dose of study drug + 1 (day)

OS will be calculated as:
End date for OS – Date of administration of the first dose of study drug + 1 (day)

End date for OS is defined as the table below:

Situation	End Date for OS	Censored
Death during the study	Date of death	No
Alive at cut-off	Date of cut-off	Yes
Other than the above	Last known alive date	Yes

5.4.3 Other Efficacy Analyses

Best overall response will be summarized and ORR will be provided for each disease histology.
Best response (including CR+PR) will be summarized for each lesion (target lesion, skin lesion, and peripheral blood lesion).
Waterfall plot of target lesions and mSWAT score for maximum tumor shrinkage as a percent change of target lesions will be provided. Also, percent change from baseline over time will be presented using spider plot.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual E7777 serum concentrations listings. The PK Analysis Set will be used for the summaries of E7777 serum concentrations and PK parameters.

5.5.1.1 Serum Concentration and its PK Parameter Analysis

<Serum Concentration>

E7777 serum concentrations for non-compartmental analysis will be summarized using summary statistics (n, mean, standard deviation [SD], median, minimum [min] and maximum [max]) by nominal time point.

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

<PK Parameter>

PK parameters will be derived by non-compartmental analysis using WinNonlin software (version 6.2.1 or later) according to 302-104.01-MNL.

The following pharmacokinetic parameters for E7777 will be calculated: maximum observed concentration (C_{max}), time at which the highest drug concentration occurs (t_{max}), area under the concentration-time curve from zero time to time of last quantifiable concentration ($AUC_{(0-t)}$), area under the concentration-time curve from zero time extrapolated to infinite time ($AUC_{(0-inf)}$), terminal elimination phase half-life ($t_{½}$), total clearance (CL), volume of distribution at terminal phase (V_z), volume of distribution at steady state (V_{ss}), accumulation index (R_{ac}) of C_{max} ($R_{ac}(C_{max})$), R_{ac}(AUC).

Other PK parameters may be calculated as appropriate.

Summary statistics will be tabulated for the PK parameters of E7777. Summary statistics (n, mean, SD, median, min, and max) will be presented for all parameters (apart from t_{max} where mean and SD are not required). In addition, geometric mean and coefficient of variation (CV) will also be presented for all parameters apart from t_{max}.

PK parameters of E7777 for each subject will be listed.

5.5.1.2 Pharmacokinetic Data Figures

The linear and semi-log plots of E7777 serum concentration versus actual time will be displayed by individual subjects. The actual time will be plotted on the X axis and the concentrations of E7777 will be plotted on the Y axis.

The linear and semi-log mean (+SD) plots of E7777 serum concentration versus nominal time will be displayed. The nominal time will be plotted on the X axis and the mean (+SD) will be plotted on the Y axis on the same graph by visit (Day 1 of Cycle 1, 3 and 5).

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Immunogenicity:
The measurement value will be listed for anti-E7777 antibody, anti-IL-2 antibody and neutralizing activity of anti-E7777 antibody in safety analysis set.

If antibody production is observed, the frequency and percentage of all antibody and neutralization activity will be calculated by visit. Titers of antibody will be summarized using summary statistics (n, mean, SD, median, min and max) by visit.

The semi-log mean plots of titer of antibody (anti-E7777 antibody and anti-IL-2 antibody) versus nominal time will be displayed. The nominal time will be plotted on the X axis and the mean will be plotted on the Y axis on the same graph.

Pharmacodynamics:
PD analysis will be performed on the PD analysis set. The measurement value (and the change from baseline, if necessary) of sIL-2R, LDH and T-cell subsets (CD4+, CD4+/CD25+, CD4+/CD25+/Foxp3+, *CD4+/CD7－, *CD4+/CD26－) (*Only for mycosis fungoides and Sézary syndrome) for each evaluation period will be summarized using the number of subjects, mean, SD,

median, minimum and maximum for each disease and overall. In addition, mean plot of recorded values over time will be created.

5.6 Safety Analyses

All safety analyses will be performed on the safety analysis set. All safety result will be summarized for each disease and overall. Safety variables include AEs, clinical laboratory parameters, vital signs, weight, ECOG PS, 12-lead ECGs results, and ophthalmologic test results.

5.6.1 Extent of Exposure

Number of cycles received, duration of treatment, total number of doses, total doses (overall/ by cycle) and relative dose intensity will be summarized. Number and percentage of subject with each starting dose will be provided by cycle.

5.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.1 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerged on or after the date of first dose of study drug, having been absent at pretreatment (Baseline) or
• Reemerged during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
• Worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

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

Over view of TEAEs and treatment-related TEAEs include the number and percentage of subjects with any TEAEs, treatment-related TEAE, TEAEs with grade 3 or higher, serious TEAEs (death, other SAEs) and TEAEs leading to study drug dose adjusment (study drug withdrawal, dose reduction, interruption).

The number and percentage of subjects with TEAEs will be calculated from the following viewpoints.

- All/Treatment-related TEAEs by PT
- All/Treatment-related TEAEs by SOC/PT
- All/Treatment-related TEAEs with Grade 3 or Higher by PT
- All/Treatment-related TEAEs with Grade 3 or Higher by SOC/PT
- All/Treatment-related TEAEs by SOC/PT and Grade
- All/Treatment-related TEAEs with Grade 3 or Higher by SOC/PT and Grade
- All/Treatment-related Serious TEAEs by PT
- All/Treatment-related Serious TEAEs by SOC/PT
- All/Treatment-related Serious TEAEs by SOC/PT and Grade

- All/Treatment-related TEAEs leading to withdrawal by SOC/PT
- All/Treatment-related TEAEs leading to dose reduction by SOC/PT
- All/Treatment-related TEAEs leading to dose interruption by SOC/PT
- All/Treatment-related TEAEs leading to delay by SOC/PT
- Specially grouped TEAE by SOC and PT
- Specially grouped TEAE by SOC and PT and Cycle
- Specially grouped TEAE with Grade 3 or Higher by SOC and PT
- Specially grouped TEAE with Grade 3 or Higher by SOC and PT and Cycle

Where Specially grouped TEAE includes Infusion reactuion, Capillary leak syndrome and related events, Vision disorders, Hepatobiliary disorders, Hematotoxicity, Infection, Skin disorders, Rhabdomyolysis and related events.
In addition, the number and percentage of subjects with TEAEs of infision reaction will be summarized as follows.

- TEAEs of Infusion reaction by SOC/PT and visit
- Time to onset for initial TEAEs of infusion reaction
- Time to onset for initial TEAEs of infusion reaction and visit
- Time to recovery for TEAEs of infusion reaction
- Time to recovery for TEAEs of infusion reaction and visit

In counting numbers of subjects by severity, each subject will be counted only once for that categories. If a subject experienced relevant TEAEs more than once, the subject will be categorized according to the prioritizations of (“Grade 5” > “Grade 4” > “Grade 3” > “Grade 2” > “Grade 1”).

Number of TEAEs and TEAE with grade 3 or higher devided by number of patients treated will be calculated per cycle and presented in figures.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate.
For all quantitative parameters listed in protocol Section 9.5.1.5.4 Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to each post baseline visit and final observation will be summarized by visit using descriptive statistics. Qualitative parameters listed in protocol Section 9.5.1.5.4 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each post baseline visit and final observation will be reported using shift tables. Percentages will be based on the number of subjects with both non-missing baseline and relevant post baseline results.

CTCAE ver.4.03 will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). TEMAV is defined as a post baseline value with an increase from baseline to a grade of 2 or higher. When displaying the incidence of TEMAVs, each subject will be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.
The measured values for quantitative data will be displayed over time using Box plot.

5.6.4 Vital Signs

Descriptive statistics for vital signs parameters (diastolic and systolic blood pressure, pulse rate, body temperature and weight) and changes from baseline will be presented by visit.
The measured values will be displayed over time using Box plot.

5.6.5 12-lead ECGs

ECG assessments were performed at each visit. Descriptive statistics for ECG parameters and changes from baseline will be presented by visit. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) by visit. In addition, the number (percentage) of subjects with at least 1 post baseline abnormal ECG result QTc Fridericia during the treatment period will be summarized. Clinically abnormal ECG results in QTc Fridericia will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 ms
- QTc interval >480 ms
- QTc interval >500 ms

Change from baseline in QTc interval:

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

5.6.6 Other Safety Analyses

ECOG PS :
The number and percentage of subjects included in each category will be cross tabulated based on baseline and each scheduled visit.

Ophthalmologic test :
The eye test result will be cross tabulated based on baseline and worst post-baseline.

5.7 Exploratory Analyses

Exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriate titled and labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the Clinical Study Report.

6 INTERIM ANALYSES

No interim analyses are planned for this study.

7 CHANGES IN THE PLANNED ANALYSES

The list below includes both change from protocol and SAP version 1.0.

- Summarization of "Analysis Sets" has been added (section 5.2.1).
- Summarization of "Completion and discontinuation for treatment" has been deleted because the data is not collected (section 5.2.2).
- Summarization of "CCR4 category", "each disease histology and each stage" and "Relapsed/Refractory status" has been added (section 5.2.3).
- Summarization of "Number of previous systemic chemotherapy regimen" and "each previous systemic chemotherapy" has been added (section 5.2.4).
- Summarization of "prior medication" and "concomitant medication" has been deleted (section 5.2.4).
- Definition of concomitant medication has been changed (section 5.2.4).
- Summarization of "Treatment Compliance" has been added (section 5.2.5).
- Subgroup analyses for efficacy and safety have been added (section 5.3.4).
- Summarization of efficacy endpoints by investigator has been added (section 5.4).
- Handling rule of tumor assessment data has been clarified (section 5.4).
- Summarization of "BOR and ORR focused on PTCL/CTCL evaluation criteris" has been added (section 5.4.1).
- Summarization of "Event/censor" for PFS, DOR and OS has been added (section 5.4.2).
- Kaplan-Meier curve for PFS, OS and OS has been added (section 5.4.2).
- Censoring rule for PFS and DOR has been changed (section 5.4.2).
- Summarization of TTR has been changed to not use Kaplan-Meier method because there is no need to use Kaplan-Meier method if the target is responder. (section 5.4.2).
- Summarization of "Best overall response" has been added (section 5.4.2).

- Summarization of "Best overall response and ORR for each disease histology" has been added (section 5.4.3).
- Summarization of "Best response for each lesion" has been added (section 5.4.3).
- Waterfall plot of "target lesions and mSWAT score" has been added (section 5.4.3).
- Spider plot of "target lesions and mSWAT score" has been added (section 5.4.3).
- Plotting individual values of immunogenity titer and PD markers on mean plot has been deleted (section 5.5.2).
- Summarization of "dose ratio" has been changed to "relative dose intensity" (section 5.6.1).
- Definition of TEAEs has been changed to be conservative (section 5.6.1).
- Detailed listing of AE tables has been added (section 5.6.2).
- Some patterns of summazation on TEAEs has been added (section 5.6.2).
- Summarization of "Specially grouped TEAE" has been defined and added (section 5.6.2).
- Summarizations of "time to onset/recovery of infusion reaction" has been added (section 5.6.2).
- Summarization of "number of adverse events per subject" has been added (section 5.6.2).
- Boxplot of measured laboratory parameter values over time has been added (section 5.6.3).
- Boxplot of measured vital sign parameter values over time has been added (section 5.6.4).
- Summarization of "Ophthalmologic test" has been added (section 5.6.6).
- PK parameters have been added(section 8.2.5)
- CTCAE grading rules have been updated (section 13.1)

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The data will be handled as follows. The sponsor will determine how to handle all data prior to data base lock.

8.1 PHARMACOKINETIC DATA HANDLING

8.1.1 Lower Limit of Quantification (LLOQ) of E7777 Serum Concentration

The LLOQ of E7777 serum concentrations is 5.00 ng/mL

8.1.2 Below the Limit of Quantification (BLQ) Handling for Calculation of PK Parameters

While calculating PK parameters in WinNonlin, BLQ values will be handled according to 302-104.01-MNL, for non-compartmental pharmacokinetic analysis.

8.1.3 BLQ Handling for Developing Concentration-Time Profiles

When developing individual concentration-time profiles, BLQ values will be handled according to 302-104.01-MNL for non-compartmental pharmacokinetic analysis.

8.1.4 Handling of Anomalous Concentration Values

The handling of anomalous concentration values will follow the guidance in the SWP for non-compartmental pharmacokinetic analysis (302-104.01-MNL).

8.2.5 General Rules for Presentation of Drug Concentrations and PK Parameters

When presenting individual/raw (raw, hereafter) values and summary statistics, the following rule will be applied: for drug concentrations and concentration-dependent pharmacokinetic parameters, all summary statistics (mean, median, geometric mean, SD and CV) will have 3 significant digits. For t_{max}, raw values and their median are shown in fixed 2 decimal places.

Variable	Unit	N	Digit rule	Raw/ Minimum/ Maximum	Mean Median	SD	Geometric Mean	CV (%)
drug concentration	ng/mL	X	Significant digits	3	3	3	-	-
C_{max}	ng/mL	X	Significant digits	3	3	3	3	3
t_{max}	min	X	Fixed decimal places	2	2	-	-	-
λ_z	1/min	X	Significant digits	3 (Listing only)	-	-	-	-
$t_{1/2}$	min	X	Significant digits	3	3	3	3	3
$AUC_{(0-t)}$, $AUC_{(0-inf)}$	ng•min/mL	X	Significant digits	3	3	3	3	3
$\%AUC_{ex}$	%	X	Significant digits	3 (Listing only)	-	-	-	-
MRT	min	X	Significant digits	3	3	3	3	3
CL	mL/min/kg	X	Significant digits	3	3	3	3	3
V_z, V_{ss}	mL/kg	X	Significant digits	3	3	3	3	3
$R_{ac}(C_{max})$, $R_{ac}(AUC)$		X	Significant digits	3	3	3	3	3

Mean, SD, geometric mean and CV will not be calculated for t_{max}.

CV(%)= sqrt(exp[SD**2 of log transformed data]-1)*100

NOTE

1. The following parameters are reported in the CSR, but appear in Listings only. They are important information to confirm that individual $t_{½}$ and its related parameters such as $AUC_{(0\text{-inf})}$ are appropriately derived and allow those PK parameters to be reproduced when necessary.
   a. Time points used for estimation of terminal phase rate constant (λ_z) (lower and upper)
   b. Number of the time points used for λ_z
   c. Adjusted regression coefficient (R_{2adj})
   d. Percentage of $AUC_{(0\text{-inf})}$ obtained by extrapolation ($\%AUC_{ex}$)

In Listings, a) are shown in same digits as actual sampling time after dosing used for calculation of PK parameters. For b), integer number is used in Listings. For c) and d), significant 3 digits are used in Listing.

8.2 OTHER DATA HANDLING

Baseline

Baseline is defined as the last non-missing value observed prior to the first dose of study drug for a given parameter. For any Baseline value of 0, the subject's corresponding Percent Change from Baseline will not be included in the summary statistics tables.

Handling of Missing data

No imputation will be performed for missing data.

9 PROGRAMMING SPECIFICATIONS

The rules for programing derivations and dataset specification are provided as separate documents.

10 STATISTICAL SOFTWARE

PK Analysis will be performed using SAS for Windows (ver.9.2 or later), WinNonlin (Professional version 6.2.1 or later), Pharsight Knowledgebase Server (version 3.0 or later), Microsoft Excel (97 or later) and S-PLUS (6.1J or later for Windows).
Statistical analyses and summaries will be performed by Takumi Information Technology using SAS for Windows (ver.9.2 or later), and Microsoft Excel (2003 or later). Analyses will be conducted by using validated standard programs or double programming. For analyses needed in data review, single programming will be used.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study table, listing and graph shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

There is no reference.

13 APPENDICES

13.1 Table For Laboratory Result Grading Based on CTCAE version 4.03

This table is based on the CTCAE ver 4.03, but partially modified for the mathematical grading perpose.

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010)					
Adverse event	**Grade**				
	1	**2**	**3**	**4**	**5**
Blood and lymphatic system disorders					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Leukocytosis	-	-	＞100,000 /mm^3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Investigations					
Alanine aminotransferase increased	＞ULN - 3.0 × ULN	＞3.0 - 5.0 × ULN	＞5.0 - 20.0 × ULN	＞20.0 × ULN	-
Alkaline phosphatase increased	＞ULN - 2.5 × ULN	＞2.5 - 5.0 × ULN	＞5.0 - 20.0 × ULN	＞20.0 × ULN	-
Aspartate aminotransferase increased	＞ULN - 3.0 × ULN	＞3.0 - 5.0 × ULN	＞5.0 - 20.0 × ULN	＞20.0 × ULN	-
Blood bilirubin increased	＞ULN - 1.5 × ULN	＞1.5 - 3.0 × ULN	＞3.0 - 10.0 × ULN	＞10.0 × ULN	-
Cholesterol high	＞ULN - 300 mg/dL; ＞ULN - 7.75 mmol/L	＞300 - 400 mg/dL; ＞7.75 - 10.34 mmol/L	＞400 - 500 mg/dL; ＞10.34 - 12.92 mmol/L	＞500 mg/dL; ＞12.92 mmol/L	-
CPK increased	＞ULN-2.5×ULN	＞2.5×ULN-5×ULN	＞5×ULN-10×ULN	＞10×ULN	-
Creatinine increased	＞1 - 1.5 × baseline; ＞ULN - 1.5 × ULN	＞1.5 - 3.0 × baseline; ＞1.5 - 3.0 × ULN	＞3.0 × baseline; ＞3.0 - 6.0 × ULN	＞6.0 × ULN	-
GGT increased	＞ULN - 2.5 × ULN	＞2.5 - 5.0 × ULN	＞5.0 - 20.0 × ULN	＞20.0 × ULN	-
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline	Increase in >2 - 4 gm/dL above ULN or above baseline	Increase in >4 gm/dL above ULN or above baseline	-	-

	if baseline is above ULN	if baseline is above ULN	if baseline is above ULN		
Lipase increased	＞ULN - 1.5 × ULN	＞1.5 - 2.0 × ULN	＞2.0 - 5.0 × ULN	＞5.0 × ULN	-
Lymphocyte count decreased	＜LLN - 800/mm^3; ＜LLN - 0.8 × 10e9 /L	＜800 - 500/mm^3; ＜0.8 - 0.5 × 10e9 /L	＜500 - 200/mm^3; ＜0.5 - 0.2 × 10e9 /L	＜200/mm^3; ＜0.2 × 10e9 /L	-
Lymphocyte count increased	-	＞4,000 - 20,000/mm^3	＞20,000/mm^3	-	-
Neutrophil count decreased	＜LLN - 1,500/mm^3; ＜LLN – 1.5 × 10e9 /L	＜1,500 - 1,000/mm^3; ＜1.5 - 1.0 × 10e9 /L	＜1,000 - 500/mm^3; ＜1.0 - 0.5 × 10e9 /L	＜500/mm^3; ＜0.5 × 10e9 /L	-
Platelet count decreased	＜LLN - 75,000/mm^3; ＜LLN - 75.0 × 10e9 /L	＜75,000 - 50,000/mm^3; ＜75.0 - 50.0 × 10e9 /L	＜50,000 - 25,000/mm^3; ＜50.0 - 25.0 × 10e9 /L	＜25,000/mm^3; ＜25.0 × 10e9 /L	-
Serum amylase increased	＞ULN - 1.5 × ULN	＞1.5 - 2.0 × ULN	＞2.0 - 5.0 × ULN	＞5.0 × ULN	-
White blood cell decreased	＜LLN - 3,000/mm^3; ＜LLN - 3.0 × 10e9 /L	＜3,000 - 2,000/mm^3; ＜3.0 - 2.0 × 10e9 /L	＜2,000 － 1,000/mm^3; ＜2.0 - 1.0 × 10e9 /L	＜1,000/mm^3; ＜1.0 × 10e9 /L	-
Metabolism and nutrition disorders					
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; Lifethreatening consequences	Death
Hyperkalemia	＞ULN - 5.5 mmol/L	＞5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Hypernatremia	＞ULN - 150 mmol/L	＞150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death

Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL – 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
Hyperuricemia	-	>ULN - 10 mg/dL (0.59 mmol/L)	-	>10 mg/dL; >0.59 mmol/L; life-threatening consequences	Death
Hypoalbuminemia	＜LLN - 3 g/dL; ＜LLN - 30 g/L	＜3 - 2 g/dL; ＜30 - 20 g/L	＜2 g/dL; ＜20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; Hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Hypoglycemia	＜LLN - 55 mg/dL; ＜LLN - 3.0 mmol/L	＜55 - 40 mg/dL; ＜3.0 - 2.2 mmol/L	＜40 - 30 mg/dL; ＜2.2 - 1.7 mmol/L	＜30 mg/dL; ＜1.7 mmol/L; lifethreatening consequences; seizures	Death
Hypokalemia	-	＜LLN - 3.0 mmol/L;	＜3.0 - 2.5 mmol/L; hospitalization indicated	＜2.5 mmol/L; life-threatening consequences	Death
Hyponatremia	＜LLN - 130 mmol/L	-	＜130 - 120 mmol/L	＜120 mmol/L; life-threatening consequences	Death
Renal and urinary disorders					
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-

		(Protein/Creatinine) ratio 0.5 - 1.9			