1 TITLE PAGE

STATISTICAL ANALYSIS PLAN

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
Date:	25 February 2022
Version:	Final Version 2.0

REVISION HISTORY

Revisions to Version 1.0
Date: 25 February 2022

Change	Rational	Affected Sections
Objective for Quality of Life (QoL) analysis is updated.	Addition of Lead-in subjects treated at the same dose provides a more complete population to assess QoL at 9 µg/kg/day, therefore QoL is expanded to include Lead-In subjects.	4.1.3 Exploratory Objective(s)
Full Analysis Set (FAS) and Safety Analysis Set are updated.	Addition of Lead-in subjects treated at the same dose provides a more complete population to assess safety at 9 µg/kg/day, therefore Safety Analysis Set is expanded to include Lead-In subjects. For completeness, the same additional subjects are included in FAS as well. The FAS and Safety Analysis Set now include all subjects in the Primary Efficacy Population.	6.2.1 Analysis Sets 8.1 Changes in the Planned Analyses from those in the Protocol
Analysis Set for Immunogenicity is updated.	To include all available data points for Immunogenicity analysis per protocol (Safety Analysis Set).	6.2.1, Table 1
Pharmacokinetic (PK) Analysis Set is updated.	The PK Analysis Set is expanded to include Lead-In subjects as well, so that all subjects treated at the 9 µg/kg/day dose can be pooled for analysis.	6.2.1 Analysis Sets 6.6.1 Pharmacokinetic Analyses
Best Overall Response (BOR) derivation rules for Global Response Score (GRS) per Olsen criteria are updated.	Additional details for derivation of BOR rule are inserted to provide clarification about additional scenarios of timepoint GRS responses. Clarification is also provided for: (1) rules on time interval needed for confirmation of response; (2) definition of date of response; (3) rules for handling missing/UNK GRS timepoint responses; and 4) rules for 2 progressive diseases (PDs) within 7 days being counted as a single PD event (which is based on a reasonable clinical picture of duration of disease flare and of how fast progression may occur).	6.4.1 Best Overall Response (BOR) based on GRS
"How to handle PD" for Prince criteria is added.	Clarification. Same rationale as that for BOR GRS per Olsen criteria	6.4.3 Best Overall Response (BOR)

		using Prince (2010)
Definition of Clinical Benefit Rate is updated.	Clinical Benefit Rate is based on CR, PR, or Durable SD (≥ 23 weeks).	6.5.3.1 Exploratory Efficacy Analyses 8.1 Changes in the Planned Analyses from those in the Protocol
Remove "pre" from wording "premedication in sensitivity analysis.	Typo in protocol, should be "steroid medication" instead of "steroid premedication".	6.5.3.1 Exploratory Efficacy Analyses
Two figures are removed. Figure "Semi-log box plot for Anti-E7777 and Anti-IL-2 titers by cycle" is added.	To clarify ADA data types by assays rather than confirmation rate; Semi-log box plot will be used to present titer data rather than semi-log plot of titers from individual.	6.6.2 Immunogenicity Analysis
Dose intensity is removed. Definition for received dose as percentage of planned starting dose are updated.	Relative dose intensity as a percentage of actual total dose over total planned dose is more meaningful than dose intensity (as average daily dose) since the drug is given 5 days per 21-day cycle.	6.7.1 Extent of Exposure
The version of CTCAE grade is added.	To clarify that CTCAE version was upgraded from 4.03 to 5.0 in Protocol Amendment 05 (03 May 2018).	6.7.2 Adverse Events
QTc Bazett is removed.	QTc Bazett was not included in Protocol.	6.7.5 Electrocardiograms

2 TABLE OF CONTENTS

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AE	adverse event
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
ADaM	Analysis Data Model
BP	blood pressure
BSA	body surface area
BOR	Best Overall Response
CBR	Clinical Benefit Rate
CRF	case report form
CI	confidence interval
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CR	complete response
CCR	clinical complete response
CTCAE	common terminology criteria for adverse events
CTCL	cutaneous T-cell lymphoma
CV	coefficient of variation
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EORTC	European Organization for Research and Treatment of Cancer
FACT-G	Functional Assessment of Cancer Therapy - General
FAS	Full Analysis Set
FDA	US Food and Drug Administration
GRS	Global Response Score
ICF	informed consent form
IRC	Independent Review Committee
IL-2	Interleukin-2

Abbreviation	Term
ISCL	International Society for Cutaneous Lymphomas
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
mSWAT	modified Severity Weighted Assessment Tool
NE	not evaluable
ORR	Objective Response Rate
PFS	progression-free survival
PK	pharmacokinetic
PR	Partial Response
PD	Progression disease
PT	preferred term
Q1	first quartile
Q3	third quartile
QoL	Quality of Life
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SE	standard error
SI	Système International
SOC	system organ class
TEAE	treatment-emergent adverse event
TLG	tables, listings, and graphs
$t_{1/2}$	Elimination half-life
t_{max}	Time to maximum concentration
TTP	Time to Progression
TTR	Time to Response
TNMB	tumor-node-metastasis-blood
UNK	unknown
VAS	visual analog scale
Vd_{ss}	Volume of distribution at steady state

Abbreviation	Term
WHO	World Health Organization

4 INTRODUCTION

Protocol E7777-G000-302 consists of an initial Lead-In part followed by the Main Study. The Lead-In part was conducted between May 2013 and August 2015 and a clinical study report (CSR) for lead-in part was completed in January 2019.

This statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for the Main Study. The primary efficacy population will include a subset of subjects from the Lead-in part as described in Protocol Amendment 06.

4.1 Study Objectives

The efficacy analyses will be performed primarily in the Stage I – III subjects from Main Study (approximately 65) plus the Stage I – III subjects from the 9 µg/kg/day dose group in Lead-In Study (approximately 5), and additional analyses will be performed in all subjects (both Main Study and Lead-In) who received study drug at 9 µg/kg/day dose.

4.1.1 Primary Objective(s)

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 [CR] and partial response [PR], according to International Society for Cutaneous Lymphomas (ISCL)/ European Organization for Research and Treatment of Cancer (EORTC) Global Response Score (GRS) [Olsen 2011])[1].

4.1.2 Secondary Objective(s)

- To determine the 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)[2]
- 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 9 µg/kg/day dose group
- To characterize the pharmacokinetics (PK) of E7777 and immunogenicity after treatment with E7777

4.1.3 Exploratory Objective(s)

- To assess the following efficacy endpoints for subjects treated with E7777: progression-free survival (PFS) and time to progression (TTP) (using GRS)
- To assess pruritus improvement reported by subjects treated with E7777

- To assess Quality of Life (QoL) for (1) all subjects (both Main Study and Lead-In) who received study drug at 9 μg/kg/day dose, (2) Stage I – III subjects from Main Study plus Stage I – III subjects from the 9 μg/kg/day dose group in Lead-In Study.

4.2 Overall Study Design and Plan

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

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 the Lead-In Study in the 9 μg/kg/day dose group with recurrent or persistent CTCL are treated with E7777 to assess efficacy. Safety will be evaluated in all subjects from the Main Study, and in Lead-In subjects from the 9μg/kg/day dose group. The dose of E7777 in the Main Study is selected from results of the Lead-In part of the study. The primary efficacy analysis will be based on Stage I – III subjects treated at 9 μg/kg/day, which includes subjects from both the Main Study plus the Lead-In.

Study Phases for Each Subject

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

- **Pretreatment Phase** includes a Screening Period and a Baseline Period:
  - **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 have been 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 met all the specified eligibility criteria.
  - **Baseline Period** is from Day -7 to the start of treatment. Subjects who completed the Baseline assessments and met the eligibility criteria began treatment in the Treatment Phase.
- **Treatment Phase** consists of the following periods:
  - **Treatment Period.** E7777 will be administered by intravenous (IV) infusion over 60 minutes (± 10 minutes) on 5 consecutive days every cycle of 21 days. Treatment with E7777 for up to 8 cycles; each cycle of 21 days is one Period. Subjects who attained skin tumor response and derived clinical benefit from E7777 treatment could continue receiving treatment beyond 8 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 will be 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 moved to the Extension Phase.

- **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 with attained skin tumor response and 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.

Pharmacokinetics and Immunogenicity

In the Lead-in, initial serial PK sampling at dose levels 6 to 15 μg/kg had been performed. Immunogenicity had also been assessed at these dose levels. In the Main Study, limited serial and sparse PK samples will be used to characterize PK, and the relationship of 9 μg/kg/day exposure and primary efficacy.

PK assessment of E7777 will be based 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 obtained in the Main Study on the rest of the subjects on Day 1 of Cycle 1 will be assessed.

Immunogenicity (formation of antibodies to E7777 or Interleukin-2 (IL-2), and of neutralizing antibodies) will be assessed in all subjects in 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 tested positive at any time for anti-IL-2 will be followed up for immunogenicity testing for anti-IL-2 on a 6-month schedule for one year and every year thereafter until antibody titers decrease to baseline level or upon study termination.

Please see Table 4 of the Protocol (Schedule of Assessments) for more details on study procedures.

Timing of Primary Analysis for the Main Study

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 that).

5 DETERMINATION OF SAMPLE SIZE

The sample size of approximately 70 Stage I‐III subjects (including Stage I‐III subjects from both the Main Study and the Lead-In part 9ug/kg/day dose group combined) was estimated assuming that the lower bound of the 2-sided 95% Confidence Interval (CI) of ORR exceeding 25% which indicates clinical benefit in persistent and recurrent CTCL. With a sample size of 70, the 2-sided 95% exact Clopper-Pearson confidence interval of an

observed 36% ORR (i.e., 25 subjects with CR+PR among 70 subjects) would be with lower bound of 25% and upper bound of 48%.

Sample size estimates were calculated using PASS 2008 software.

6 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

6.1 Study Endpoints

Tumor responses (based on the Olsen criteria) assessed by an Independent Review Committee (IRC) will be used in the evaluation of primary efficacy endpoint, and the associated secondary and exploratory efficacy endpoints. In addition, the IRC will assess tumor responses using Prince criteria, which is a separate secondary endpoint. Investigator-assessed tumor response (based on the Olsen criteria) and the associated secondary and exploratory response endpoints will also be reported.

6.1.1 Primary Endpoint(s)

The primary efficacy endpoint is ORR assessed by IRC based on Global Response Score (GRS) (Olsen 2011)[1].

6.1.2 Secondary Endpoint(s)

- DOR based on GRS
- TTR based on GRS
- ORR assessed by investigator using GRS (Olsen 2011)[1]
- Objective response assessed by IRC using Prince (2010)[2]
- Skin response (according to modified Severity Weighted Assessment Tool (mSWAT))
- Duration of skin response
- Time to skin response
- Safety parameters
- PK parameters
- Immunogenicity

6.1.3 Exploratory Endpoint(s)

- PFS and TTP
- Clinical Benefit Rate (CBR)
- Pruritus improvement
- QoL using Skindex-29 and the FACT-G Questionnaire

6.2 Study Subjects

6.2.1 Analysis Sets

The definitions of the analysis sets are provided below:

All Enrolled Subjects: All subjects in Main Study who signed informed consent, and at Screening were assessed as meeting all inclusion criteria and not meeting any exclusion criteria.

Full Analysis Set: All subjects (both Main Study and Lead-In) who received study drug at 9 μg/kg/day dose.

Primary Efficacy Analysis Set: All Stage I – III subjects (both Main Study and Lead-In) who received study drug at 9μg/kg/day dose.

Safety Analysis Set: All subjects dose (both Main Study and Lead-In) who received study drug at 9 μg/kg/day. This will be the analysis set for all safety analyses.

Stage I-III Safety Analysis Set: All Stage I – III subjects (both Main Study and Lead-In) who received study drug at 9μg/kg/day dose.

Per Protocol Set: All subjects had a baseline and at least one post-dose tumor assessment and had no major protocol deviations in either Primary Efficacy Analysis Set or Full Analysis Set. The per protocol analysis set will be the secondary analysis set for efficacy endpoints.

PK Analysis Set: All subjects from whom at least one quantifiable concentration of E7777 was observed at 9 μg/kg/day dose (both Main Study and Lead-In) will comprise the analysis set for the PK data.

Population PK Analysis Set: All subjects from whom at least one quantifiable concentration of E7777 is available with a documented dosing history from both Lead-in and Main Study.

Population PK/PD Analysis Set: All subjects in the Population PK analysis set for whom efficacy and safety variables are also available from both Lead-in and Main Study.

The number (percentage) of subjects included in each analysis set will be presented.

Table 1 summarizes which analyses each analysis set will be primarily used for.

	Full	Primary Efficacy	Safety	Stage I-III Safety	Per Protocol	PK Analysis Set
Disposition	•	•				
Demography & Baseline Characteristics	•	•				
Disease History	•	•				
Prior & Concomitant Medications	•	•				
Tumor Response per Olsen criteria by Investigator assessment	•	•				
Tumor Response per Olsen criteria by IRC review	•	•			•	
Tumor Response per Prince criteria by IRC review		•				
Skin Response	•	•				
Progression-Free Survival	•	•				
Time to Progression	•	•				
Patient Pruritus	•	•				
Drug Exposure			•	•		
Adverse Events			•	•		
Laboratory Tests			•	•		
Vital Signs			•	•		
ECGs			•	•		
Pharmacokinetic serum/parameter						•
Immunogenicity			•			

6.2.2 Subject Disposition

Enrolled subjects include all subjects who signed informed consent forms in the Main Study. The number of subjects screened, the number (percentage) of subjects who failed screening and the reasons for screen failure, will be summarized based on data reported on the Screening Disposition CRF.

The disposition status of subjects for both the Primary Efficacy Analysis Set and Full Analysis Set will be summarized based on data reported on the Study Disposition Treatment Phase CRF. Also, subjects discontinued from treatment but on survival follow-up at the data cutoff date will be summarized. In addition, subjects discontinued study and the reasons for discontinuation will also be summarized.

A distribution of the number of subjects by each country and site will be provided.

6.2.3 Protocol Deviations

All protocol deviations will be identified by reviewing the data prior to database lock for primary analysis. Major protocol deviations will be appropriately summarized by site and grouped into different categories. All major protocol deviations identified according to study entry criteria and during treatment will be listed. All protocol deviations related to COVID-19 will be listed.

6.2.4 Demographic and Other Baseline Characteristics

Demographic and Baseline characteristics will be presented using summary statistics and listings for both the Primary Efficacy Analysis Set and Full Analysis Set.

6.2.4.1 Demography

Continuous demographic and Baseline variables include:

- Age (year)
- Height (cm)
- Weight (kg)
- Body Surface Area (BSA)(m^2): BSA = SQRT([Height(cm) x Weight(kg)]/ 3600)

Categorical variables include:

- Sex (male/female)
- Age group (year): <65 years, ≥65
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino
- Country: Australia and United States
- Race
  - White
  - Black or African American
  - Asian
    - Japanese
    - Other Asian
  - American Indian or Alaska Native
  - Native Hawaiian or other Pacific Islander
  - Other
- Race group: White, Asian and all others
- ECOG performance status (0 to 2)

6.2.4.2 Disease characteristics

Disease history and characteristics at study entry including type of CTCL (Mycosis Fungoides (MF)/Sezary Syndrome (SS)), CTCL disease stage at baseline, CTCL disease staging, tumor-

node-metastasis-blood (TNMB) stage at study entry, mSWAT (modified Severity Weighted Assessment Tool) score at baseline and pruritus VAS at baseline will be summarized.

6.2.5 Medical history

A subject data listing of medical and surgical history will be provided. Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 24.0 or most recent version).

6.2.6 Prior Anticancer Therapy

Prior anticancer therapies tables will be presented for both Primary Efficacy Analysis Set and Full Analysis Set, also listings will be provided.

Number of subjects with prior anti-cancer therapies, number of therapies (including medication and non-medication) and duration of last therapy, and best response to the last therapy, and non-medication therapy category will be summarized for prior anticancer therapies. Prior anti-cancer medications and non-medication therapies will be summarized separately.

6.2.7 Prior and Concomitant Medications

Prior and concomitant medications tables will be presented for both Primary Efficacy Analysis Set and Full Analysis Set, also listings will be provided.

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) version of March 2021 or most recent version. The number (percentage) of subjects who took prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) Classification and WHO drug preferred term. Prior medications include medications that started prior to 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 but within 30 days after the end date of exposure of study drug.

Premedication for E7777 is required in cycles 1 to 3 and is optional from cycle 4 onward. Premedications will be listed based on an indication of "Premedication" on prior and concomitant CRF. Steroid premedications during study will also be summarized by number (percentage) of subjects who took steroid premedication in total and during each cycle.

6.3 Data Analysis General Considerations

6.3.1 Pooling of Centers

Subject data from all centers will be pooled for all analyses. Center will not be considered as a factor in the analyses.

6.3.2 Adjustments for Covariates

No adjustment for covariates will be made for this study.

6.3.3 Multiple Comparisons/Multiplicity

Not applicable.

6.3.4 Examination of Subgroups

Baseline disease stage subgroup analysis for efficacy endpoints ORR, DOR, TTR, CBR, skin response, duration of skin response and time to skin response may be provided as appropriate.

For Primary Analysis Set, disease stage subgroup categories may include IA/IB/IIA; IIB; and IIIA/IIIB as appropriate; for Full Analysis Set, disease stage grouping categories may include IA/IB/IIA; IIB; IIIA/IIIB; and IVA/IVA1/IVA2 as appropriate.

Additional subgroup analyses may also be conducted, if deemed appropriate.

6.3.5 Handling of Missing Data, Dropouts, and Outliers

Adverse Events with incomplete start dates will be considered treatment emergent if:

a) Day and month are missing and the year is equal to or after the year of the first dose date;

b) Day is missing, and the year is after the year of the first dose;

c) Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date;

d) Year is missing; or

e) Complete date is missing.

Medications will be considered concomitant if:

a) Day and month are missing and the year is equal to or after the year of the first dose date;

b) Day is missing, and the year is after the year of the first dose;

c) Day is missing and the year is equal to the year of the first dose date and the month is equal to or after the month of the first dose date; or

d) Year is missing; or

e) Complete date is missing.

For incomplete dates involving efficacy and other safety data, a conservative imputation will be used for calculation if needed. More details of imputation rules will be specified in study analysis dataset specification.

6.4 Efficacy Assessments

6.4.1 Best Overall Response (BOR) based on GRS

The best overall response (BOR) based on the GRS according to Olsen (2011)[1] criteria is described as follows.

Tumor assessment and response criteria will be according ISCL/EORTC response criteria described in Olsen (2011)[1] criteria. This is a composite measure of tumor burden in skin, lymph node, blood, and viscera. The documented date of CR/PR/SD/PD for GRS will be based on the corresponding mSWAT score assessment date (implemented for IRC assessment by IRC and derived programmatically for Investigator assessment). Assessments showing non-PD after a single PD, or assessments showing non-PD after two consecutive PD evaluations within 7 days of each other, will be included in the determination of BOR. The key points of BOR derivation are described as follows.

- **Complete Response (CR)**. BOR of CR can be achieved by the following situations:
  - BOR is CR when the duration between the two CRs is ≥ 3 weeks for two consecutive CRs or two CRs with "unknown" or "missing" assessments in between.

  The documented start date of CR is defined as the date of mSWAT score assessment date corresponding to the initial CR.

- **Partial Response (PR).** When BOR of CR is not achieved, BOR of PR can be achieved by one of the following situations:
  - BOR is PR when the duration between the two responses (PR or CR) is ≥ 3 weeks for two consecutive PRs, the order of CR, PR, or the order of PR, CR, without intervening of SD/UNK or missing assessments.
  - BOR is PR when the duration between the two responses (PR or CR) is ≥ 3 weeks for two PRs, or the order of PR, CR, with up to two intervening SD assessments in between.
  - BOR is PR when the duration between the two responses (PR or CR) is ≥ 3 weeks for two PRs, the order of CR, PR, or the order of PR, CR, with "unknown" or "missing" assessments in between.

  The documented start date of PR is the date of mSWAT score assessment date corresponding to the initial PR or CR

- **Stable Disease (SD).** When BOR of CR/PR is not achieved, BOR of SD can be achieved by the following:

  If subject at least once had an overall timepoint evaluation of CR/PR/SD that was recorded ≥3 weeks after the first dose of study drug.

- **Progressive Disease (PD).** When BOR of CR/PR/SD is not achieved, if subject at least once had an overall time point evaluation of PD, then the BOR is PD.

  The date of documented PD is:

- If subject is not treated beyond the initial PD, date of PD should be used.
- If subject is treated beyond the initial PD (per protocol), date of the initial PD should be used if consecutive PDs; if there are intervening SD/PR/CR between the two PDs, date of the later PD should be used.

- **Unknown (UNK).**
  - No baseline assessment
  - No post-baseline evaluations GRS assessment
  - Early SD (SD <21 days from first dose date)
  - Subject has only UNK (assessment not possible) for Global Response Score for all postbaseline Tumor Timepoint Response Assessment.

More details regarding BOR derivation can be found in the Analysis Data Model (ADaM) Data Specification document.

6.4.2 Best Overall Response (BOR) for Skin Response

BOR for skin response will follow the same approach as described in section 6.4.1 based on timepoint skin response instead of GRS assessment.

6.4.3 Best Overall Response (BOR) using Prince (2010)[2]

The IRC will also assess timepoint tumor responses using Prince (2010)[2] criteria. The BOR based on Prince criteria at subject level will be derived. BOR will fall into the following categories: CR+CCR (Clinical Complete Response), PR, SD, PD, and UNK.

The key point regarding Prince (2010)[2] criteria is that, according to Prince (2010)[2] criteria, the documented response (i.e., CR, CCR, PR) required confirmation by two additional tumor burden assessments over a period of at least 6 weeks. Documented responses for all end points had to be confirmed at three consecutive visits (i.e., maintained for 6 weeks after the initial documentation).

Assessments showing non-PD after a single PD, or assessments showing non-PD after two consecutive PD evaluations within 7 days of each other, will be included in the determination of BOR.

The details of derivation can be found in the ADaM Data Specification document.

6.5 Efficacy Analyses

All efficacy analyses will be performed on the Primary Efficacy Analysis Set (i.e., in the Stage I – III subjects from Main Study plus the Stage I – III subjects from the 9 µg/kg/day dose group in Lead-In Study), and additionally on Full Analysis Set. Tumor response assessed by IRC based on Olsen (2011)[1] criteria will also be summarized using the Per Protocol Set.

6.5.1 Primary Efficacy Analysis

The primary endpoint is the ORR based on Olsen (2011)[1] criteria, using response assessment data by IRC. The ORR is the proportion of subjects achieving a BOR of confirmed CR or PR. The Primary Efficacy Analysis Set will be used for analysis.

The 2-sided, exact 95% CI of ORR will be calculated using the Clopper-Pearson method. The treatment will be considered efficacious and demonstrating the clinical benefit of E7777 if the lower bound of the 2-sided 95% exact CI of the observed ORR exceeds 25%.

6.5.2 Secondary Efficacy Analyses

6.5.2.1 Duration of Response

The DOR is defined as the time from the date that a confirmed objective response (CR or PR) was first met until the date of documented PD or death due to any cause for those subjects with a confirmed PR or CR. For subjects who did not experience PD or death by the end of data cut off, censoring rules for DOR are the same as those of PFS.

- Duration of objective response (months) = (Date of PD/Death or Censor Date – Date of first objective response+ 1) × 12/365.25, for subjects with objective response.

For subjects with confirmed PR or CR, the DOR will be analyzed using Kaplan-Meier (KM) product-limit estimates. Probabilities of DOR ≥ 6 and 12 months will be presented with 2-sided 95% CIs as appropriate, if they can be estimated from the model. The median and quartiles of DOR from KM estimation will be provided with 95% CIs if estimable. The DOR curve from KM method will be provided.

For subjects with confirmed PR or CR, the number and percentage of subjects with DOR ≥ 6 and 12 months will also be summarized as descriptive statistics as appropriate.

The swimmer plot will be plotted demonstrating the treatment duration and timepoint responses over time.

6.5.2.2 Time to Response

The TTR is defined as the elapsed time from the date of the first study drug dose until the date of first documented confirmed CR or PR, whichever occurs first. Summary statistics of TTR for subjects with confirmed CR or PR (objective response) will be presented.

TTR will also be summarized by treatment cycles completed when the first documented response occurred.

TTR for subjects with confirmed CR or PR will be analyzed using KM method. The median and quartiles of TTR from KM estimation will be provided with 2-sided 95% CIs if estimable. The cumulative probabilities will be plotted over time.

6.5.2.3 ORR Using Prince (2010)[2]

The ORR is the proportion of subjects achieving a BOR of confirmed CR+CCR or PR per Prince (2010)[2] criteria. The Primary Efficacy Analysis Set will be used for analysis. See Section 6.4.3 for the derivation of BOR.

The 2-sided, exact 95% CI of ORR will be calculated using the Clopper-Pearson method.

6.5.2.4 Skin Response (according to mSWAT)

ORR for skin response based on the mSWAT score, is defined as the proportion of subjects with best skin response of CR or PR. See Section 6.4.2 for the derivation of the BOR for skin response.

The 2-sided, exact 95% CI of ORR will be calculated using the Clopper-Pearson method.

In addition, waterfall plot presenting each subject's percentage change in mSWAT from baseline at postbaseline nadir before data cutoff will be provided.

6.5.2.5 Duration of Skin Response

The duration of skin response based on the mSWAT score is defined as time from the date when criteria for confirmed skin response (CR or PR) was first met until the date of documented PD or death due to any cause for those subjects with a confirmed PR or CR. For subjects who did not experience PD or death by the end of data cut off, censoring rules for duration of skin response are the same as those of PFS.

Duration of skin response will be analyzed following the same approach in Section 6.5.2.1.

6.5.2.6 Time to Skin Response

The 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 confirmed skin response (CR or PR) are first met.

Time to skin response will be analyzed following the same approach in Section 6.5.2.2.

6.5.3 Other Efficacy Analyses

6.5.3.1 Exploratory Efficacy Analyses

PROGRESSION FREE SURVIVAL

The PFS is defined as the date of first dosing to the date of documented PD or death as a result of any cause (whichever occurs first).

PFS will be analyzed for the Primary Efficacy Analysis Set and Full Analysis Set.

PFS will be analyzed using KM method. The median, quartiles and the PFS rates at 3, 6, 9, 12 months and so on (depending on data adequacy) will be calculated using KM method and

presented with 2-sided 95% CIs if estimable. The cumulative probabilities of PFS will be plotted over time.

The PFS censoring rules in this SAP and definition of progression date will follow the Food and Drug Administration (FDA) "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2007)"

Table 2 Censoring Rules for Analysis of Progression-Free Survival

No.	Situation	Date of Event (Progression/Death) or Censoring	Outcome
1	No baseline tumor or postbaseline GRS assessments	Date of first dose	Censored
2	Progression documented between scheduled visits*	Date of PD by GRS assessment	Event
3	No progression at the time of data cutoff	Date of last adequate GRS assessment prior to or on date of data cutoff	Censored
4	New anticancer treatment started	Date of last adequate GRS assessment prior to or on date of new anticancer treatment	Censored
5	Death before first PD by GRS assessment	Date of death	Event
6	Death between adequate GRS assessment visits**	Date of death	Event
7	Death or progression after more than one missed visit/GRS assessment***	Date of last adequate GRS assessment before missed GRS assessments	Censored

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

Any GRS assessments after new anticancer treatment starts will not be considered in the definition of PFS.

*If subject is not treated beyond initial PD, date of PD should be used. If subject is treated beyond initial PD (per protocol), date of initial PD should be used if consecutive PDs; if there are intervening SD/PR/CR between two PDs, date of the later PD should be used.** Adequate GRS assessment is assessment of CR, PR, SD and PD at regular interval.

***More than one missed visits is defined as having the duration between the last tumor assessment and death or PD longer than 44 days which is (3) ×2×7+3-1days for subjects on every 3 weeks (-3 days window) for subjects on every 3 weeks tumor assessment schedule during treatment; after date of end of treatment date, 69 days which is (4+1) ×2×7-1days for subjects on every 4 weeks (± 1 week) for 1 year after end of study treatment; 209 days which is (12+3) ×2×7-1 days for subjects on every 12 weeks (± 3 weeks) tumor assessment schedule from 1 year after end of study treatment up to 3 years.

The priority of the censoring rules is as follows:

1. If the subject had PD or death, the following sequence will be applied:

- If a subject did not have a baseline tumor assessment (No. 1), the subject will be censored on the date of first dose. However, if the subject died within 41 days (6 weeks-1day) after first dose and did not receive a new anticancer treatment, it will be

counted as PFS event at the date of death. If a subject had new anticancer treatment before PD or death (No. 4), the subject will be censored on the date of the last adequate GRS assessment prior to or on the date of new anticancer treatment.

- If a subject missed two or more tumor assessments before PD or death (No. 7), the subject will be censored on the date of the last adequate GRS assessment before PD or death. Note that if a subject is censored by both this criterion and the anticancer treatment criterion, the earliest censoring date will be used.
- Otherwise, if a subject had an event (No. 2, No. 5, or No. 6), the earliest event date will be used.

2. If a subject did not have PD or death, the censoring date will be the earliest censoring date if the subject met multiple censoring criteria (No. 1, No. 3, No. 4, No. 7).

TIME TO PROGRESSION (TTP)

TTP is defined as the time from the date of first dosing to the date of documented PD or death as a result of CTCL. The same censoring rules, except for death (other cause), as in the analysis of PFS will be applied in calculation of TTP.

TTP will be analyzed following the same approach as for PFS in Section 6.5.3.1.

CLINICAL BENEFIT RATE (CBR)

The CBR is defined as the proportion of subjects who had best overall response of CR or PR or Durable SD by IRC or investigator assessment.

Durable Stable disease must be achieved at ≥ 23 weeks after first dose of study drug to be considered best overall response based on Olsen (2011)[1] criteria.

The 2-sided, exact 95% CI of CBR will be calculated using the Clopper-Pearson method.

PRURITUS IMPROVEMENT

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. Subject's pruritus improvement rate is defined as the proportion of subjects with a clinically significant improvement in pruritus. The 2-sided, exact 95% CI of pruritus improvement rate will be calculated using the Clopper-Pearson method.

In addition, the percentages of subjects who have ≥ 20% and ≥ 50% improvements (decreases) relative to baseline will be tabulated.

SENSITIVITY ANALYSES

Sensitivity analyses for ORR in subjects receiving versus subjects not receiving steroid medication for any cycle during the study will be performed. ORR (the proportion of

subjects achieving a BOR of confirmed CR or PR) will be summarized along with the 2-sided, exact 95% CI, using the Clopper-Pearson method.

6.6 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

6.6.1 Pharmacokinetic Analyses

Analyses will be based on the pharmacokinetic analysis set.

The PK Analysis Set will be defined as:

> The PK Analysis Set includes subjects from whom at least one quantifiable concentration of E7777 was observed at 9 μg/kg/day dose (both Main Study and Lead-In).

Serial PK assessment of E7777 will be performed on all subjects in the Lead-In 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 rest of the subjects on Day 1 of Cycle 1.

The PK analysis will be done using PK Analysis Set.

Serum concentration data for E7777 will be analyzed and summarized using descriptive statistics (n, mean, standard deviation (SD), median, minimum and maximum) by time point.

PK parameters will be derived for subjects with serial blood PK sampling using non-compartmental methods for E7777 on Day 1 of Cycles 1, 3 and 5. These include as data permit:

- Time to maximum concentration (t_{max})
- Maximum concentration (C_{max})
- Area under the curve from 0 to t ($AUC_{(0-t)}$)
- Area under the curve from 0 to infinity ($AUC_{(0-inf)}$)
- Elimination half-life ($t_{1/2}$)
- Total body clearance (CL)
- Volume of distribution at steady state (Vd_{ss})

Descriptive statistics (n, mean, standard deviation (SD), median, minimum and maximum, geometric mean (%CV)) will be used to summarize PK parameters.Geometric mean (%CV) will not be computed for t_{max}.

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

The following figures will be prepared:

- Linear and semi-log plots of individual E7777 serum concentration versus time at each cycle and day for subjects with serial blood PK sampling
- Linear and semi-log plots of mean and SD for E7777 serum concentration versus time by cycle and day for subjects with serial blood PK sampling
- Box plot of pharmacokinetic parameters ($C_{max,}$ $AUC_{(0\text{-}t),\ and}$ $AUC_{(0\text{-}inf)}$) by cycle for subjects with serial blood PK sampling
- Relationship of Drug Exposure on Cycles ($C_{max,}$ $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}inf)}$) (AbImpact = 0 Only) if applicable

Based on the immunogenicity (antibody positive, negative, etc.) additional PK analyses may be prepared.

Serum concentration data from the sparse PK sampling time points and the intense PK sampling time points from both lead-in and main phase will be analyzed using a population PK approach incorporating data from all studies of the E7777 program. The relationship of E7777 exposure and key efficacy and safety endpoints will also be assessed (as part of population PK/PD analyses). Details concerning the objectives and methods of these exploratory analyses will not be described in this SAP but will be described in a separate population analysis plan (PAP) authored by Modeling and Simulation of Clinical Pharmacology Science (M&S, CPhS), Medicine Development Center (MDC)-Eisai.

6.6.2 Immunogenicity Analysis

Analyses will be based on the safety analysis set.

Immunogenicity (formation of antibodies to E7777 or IL-2, and of neutralizing antibodies) will be assessed in all subjects in both the Lead-In 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 to be followed up for immunogenicity testing for anti- LI 2 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.

Anti-E7777/IL-2 antibodies results (negative/positive) will be summarized by number of subjects and percentage by visit. For subjects with positive anti-E7777/IL-2 antibodies, the titer levels will be summarized using descriptive statistics (n, mean (SD), Q1, Q3, median, minimum and maximum) by visit. In addition, neutralizing anti-E7777/IL-2 antibodies results (negative/positive) will be summarized by visit.

The following figures will be prepared:

- Semi-log box plot of Anti-E7777 and Anti-Il-2 titers by cycle

6.6.3 Pharmacodynamics, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

6.7 Safety Analyses

All safety analyses will be performed for the Safety Analysis Set and the Stage I-III Safety Analysis Set. Safety data will be summarized using descriptive statistics (eg, n, mean, standard deviation (SD), median, Q1, Q3, minimum and maximum for continuous variables; number and percentage for categorical variables). Safety data to be evaluated include adverse event (AEs), clinical laboratory results, vital signs, ECGs.

6.7.1 Extent of Exposure

The number of cycles/infusions on treatment, quantity of study drug administered, and duration of study drug treatment will be presented. The number of subjects requiring dose reductions, treatment interruption will be summarized.

- The number of cycles received and the number of infusions by cycle and overall will be summarized with descriptive statistics. Subject is considered to have received one cycle if the subject received at least one dose on any of days 1, 2, 3, 4 or 5 of a cycle during the cycle.
- The duration of study drug in weeks will be (Date of the last dose – Date of the first dose + 1) / 7, including drug interruption days.
- Total dose (ug/kg) of study drug is the summarization of all the actual doses received during study. Actual dose (ug/kg) is calculated using planned dose (ug/kg) × (actual volume(ml)/planned volume(ml)).
- Received dose as percentage of planned starting dose (%) = total dose (ug/kg) / (number of cycles × 5 (day) ×9 (ug/kg/day)) ×100.
- Number of subject weeks = summation over all subjects' exposure durations.

Subject data listings will be provided for all dosing records, and for the summary statistics calculated above.

Study drug interruption and dose reduction instructions for subjects who experience an E7777-related toxicity are presented in Table 1 per protocol amendment 6 section 9.4.1.5. The number of subjects with dose reductions and treatment interruption will be summarized by counts and percentages.

6.7.2 Adverse Events

Adverse events will be summarized for the Safety Analysis Set and Stage I-III Safety Analysis Set. Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or version 5.0. CTCAE version was upgraded from 4.03 to 5.0 in Protocol Amendment 05 (03 May 2018). 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 using the Medical Dictionary for Regulatory Activities (MedDRA version 24.0 or most recent version). AEs will be summarized by preferred term (PT) nested within system organ class (SOC). All AEs will be listed.

A TEAE is defined as an AE that emerged during treatment or up to 30 days (also 30 days for serious TEAEs) following last dose of study drug; AEs that emerge during study drug treatment, having been absent at pretreatment (Baseline), or those that:

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

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

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 from study drug, dose reduction or drug interruption, will be provided. The incidence of TEAEs will be summarized by SOC, PT, CTCAE grade, and relatedness to study drug (possibly related or probably related). 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). Treatment-related TEAEs includes TEAEs considered by the Investigator to be possibly or probably related to study drug or TEAEs with missing causality.

Separate summary tables and listings will be provided for all TEAEs, treatment-emergent SAEs, TEAEs reported as treatment-related, treatment-emergent SAEs reported as treatment-related, TEAEs by CTCAE grade, and TEAEs leading to treatment discontinuation.

In summary, the following TEAE tables will be provided:

- Overview of TEAEs
- Overview of treatment-related TEAEs
- TEAEs by SOC and PT and Worst CTCAE Grade
- TEAEs by PT in decreasing frequency
- Treatment-related TEAEs by SOC and PT and Worst CTCAE Grade
- Treatment-related TEAEs by PT in decreasing frequency
- Treatment-emergent serious TEAEs by SOC and PT
- Treatment-emergent serious TEAEs by PT in decreasing frequency
- Treatment-related serious TEAEs by SOC and PT
- Treatment-related serious TEAEs by PT in decreasing frequency
- TEAEs leading to discontinuation from study drug by SOC and PT

- TEAEs Leading to dose reduction or drug interruption by SOC and PT
- TEAEs leading to dose reduction by SOC and PT
- TEAEs leading to drug interruption by SOC and PT

The following listings of deaths and AEs will be prepared:

- All AEs
- Adverse events with CTCAE grade 3 or higher
- All Serious adverse events
- All deaths
- Adverse Events leading to study drug discontinuation
- Adverse Events leading to dose reduction or drug interruption

Note that for summary tables, if data are not adequate for summary, only listings will be provided.

6.7.2.1 Treatment-Emergent Adverse Events of Clinical Interest

TEAEs of special interest (AESI) for E7777 will be identified based on the review of safety data by Clinical and Pharmacovigilance.

AESI will be summarized by preferred terms and worst CTCAE grade.

6.7.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units, as appropriate.

On-treatment laboratory tests will be defined as laboratory tests conducted from the start of treatment to no more than 30 days after the last dose of study treatment. Central laboratory test results will be primary data source for laboratory analyses. Only when the central laboratory tests results are missing, the local laboratory test results will be used as substitute.

For all quantitative parameters listed in Table 3 (protocol Section 9.5.4.3) the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on treatment value) will be summarized by visit using descriptive statistics. Qualitative parameters listed in Table 3 (protocol Section 9.5.4.3) will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

6.7.3.1 Hematology and Clinical Chemistry

Laboratory parameters that are graded in CTCAE v5.0 will be summarized by CTCAE grade. In the summary of laboratory parameters by CTCAE grade, for parameters with CTCAE grading in both high and low direction, CTCAE in high and low directions will be summarized separately. Subjects with treatment-emergent markedly abnormal laboratory

values (TEMAV) will also be summarized. Markedly abnormal is defined as a value that is above or below the normal range and the CTCAE grade increased from baseline by 2 or more grades.

Laboratory test results will be reported in the following methods: hematology and blood chemistry.

- Summary of values at each visit and changes from baseline.
- Shifts from baseline to the worst postbaseline CTCAE grade.
- Summary of Treatment-emergent markedly abnormal laboratory results by cycle

6.7.3.2 Urinalysis

A listing of urinalysis results will be provided.

6.7.4 Vital Signs

Descriptive statistics for vital signs parameters (systolic and diastolic blood pressure (BP), heart rate, respiratory rate, body temperature and weight) and their change from baseline value will be presented by visit.

6.7.5 Electrocardiograms

Prior to Amendment 05 ECG QT/QTcF interval was read centrally, and triplicate ECG measurements were required. Amendment 05 resulted in the following changes for ECG monitoring:

- Triplicate ECGs were no longer required
- QT/QTcF interval was no longer be assessed by a central laboratory
- Single 12-Lead ECGs will be performed during Screening, Day 1 of each cycle, and End of Treatment

Shift tables for overall ECG findings categorized as normal and abnormal will be presented from baseline to worst postbaseline values by visit.

In addition, the number (percentage) of subjects with at least one postbaseline abnormal ECG result in QTc Fridericia during the treatment phase will be summarized. Centrally-read pre-Amendment 05 data will be combined with post-Amendment 05 non-centrally-read data. 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

6.7.6 Other Safety Analyses

No other safety analyses are planned for this study.

6.8 Other Analyses

6.8.1 Quality of Life

QoL will be assessed using the Skindex-29 and FACT-G questionnaires. Details of QoL analyses will be presented in a separate SAP.

6.8.2 COVID-19 Impact

Protocol deviations and adverse events associated with COVID-19 (coronavirus disease 2019) will be presented.

6.9 Exploratory Analyses

See Section 6.5.3 Other Efficacy Analyses

7 INTERIM ANALYSES

No interim analyses are planned for this study.

8 CHANGES IN THE PLANNED ANALYSES

8.1 Changes in the Planned Analyses from those in the Protocol

Clinical Benefit Rate (CBR), defined as the proportion of subjects who have best overall response of Complete Response + Partial Response + Durable Stable Disease, will be an additional exploratory efficacy analysis. This was not specified in protocol.

FAS and Safety Analysis Set are updated to include all 9 ug/kg/day Lead-In subjects in the analysis.

Full Analysis Set: All subjects who received study drug at 9 µg/kg/day dose (both Main Study and Lead-In).

Safety Analysis Set: All subjects who received study drug at 9 µg/kg/day dose (both Main Study and Lead-In). This will be the analysis set for all safety analyses.

Changes were presented in revision history table.

9 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

Baseline

Baseline is defined as the non-missing value most recently collected before the first dose of any study.

In the analyses of ORR and CBR, subjects without baseline or postbaseline tumor assessment will be considered as non-responders and will be included in the denominator when calculating ORR and CBR. Non-responders will be excluded in the analysis of DOR.

Study Day 1

Study Day 1 is defined as the day of the first dose of study drug administrated.

By-visit analysis

All by-visit analyses will be performed using assessment at corresponding scheduled visits recorded in the eCRF (not including unscheduled).

The unscheduled visits will be included in the analyses that involve definition of worst post-baseline assessment.

Time Conversion Factors

The following factors will be used to convert days to months or years:

1 month = 30.4375 days; 1 year = 365.25 days.

Missing/Partial Dates

Refer to programming specifications for details to handle any missing or partial dates.

10 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

11 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS v 9.4 or higher.

12 MOCK TABLES, LISTINGS, AND GRAPHS

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

13 REFERENCES

1. 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.
2. Prince HM, Duvic M, Martin A, Sterry W, Assaf C, Sun Y, et al. Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. J Clin Oncol. 2010;28(11):1870-7.

SIGNATURE PAGE

Author:

PPD

2/25/2022

PPD PPD PPD PPD

Date

Oncology Business Group, Eisai Inc.

Approval:

PPD

2/25/2022

PPD PPD PPD PPD PPD

Date

Oncology Business Group, Eisai Inc.

PPD

2/25/2022

PPD PPD PPD PPD PPD

Date

Oncology Business Group, Eisai Ltd.