STATISTICAL ANALYSIS PLAN

A Phase 1/2, Multicenter, Open-label, Uncontrolled Trial to Evaluate the Tolerability and Safety of ASTX660 and the Efficacy at the Recommended Dose in Patients with Relapsed/Refractory T-cell Lymphoma

NCT Number: NCT04362007
Protocol No. 401-102-00001
Version Date: Dec 18, 2024

Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product
ASTX660

Protocol No. 401-102-00001

A Phase 1/2, Multicenter, Open-label, Uncontrolled Trial to Evaluate the Tolerability and Safety of ASTX660 and the Efficacy at the Recommended Dose in Patients with Relapsed/Refractory T-cell Lymphoma

Statistical Analysis Plan

Version: 1.0
Issue date: Dec 18, 2024
Clinical Protocol Amendment 4 Approval: Dec 5, 2022

Confidential

Table of Contents

List of Appendices

List of Abbreviations and Definition of Terms

Abbreviation	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
ATLL	Adult T-cell leukemia /lymphoma
AUC	Area under the concentration time curve
AUC_%Extrap	Percentage of AUC due to extrapolation from t_{last} to infinity [(AUC_∞ - AUC_t) / $AUC_\infty \times 100$]
AUC_∞	Area under the concentration time curve from time zero to infinity
AUC_{24h}	Area under the concentration-time curve from time zero to 24 hours
AUC_{24h}/D	AUC_{24h} normalized by dose
AUC_t	Area under the concentration time curve calculated to the last observable concentration at time t
AUC_t/D	AUC_t normalized by dose
[redacted]	[redacted]
CL/F	Apparent clearance of drug from plasma after extravascular administration
CL/F/BW	CL/F normalized in body weight
C_{max}	Maximum (peak) plasma concentration of the drug
C_{max}/D	C_{max} normalized by dose
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
[redacted]	[redacted]
FAS	Full analysis set
[redacted]	[redacted]
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
INR	International normalized ratio
IPI	International prognostic index
JSCC	Japanese Society of Clinical Chemistry
λ_z	Apparent terminal-phase disposition rate constant (first-order)
λ_z(point)	Number of points used in computing λ_z

λ_z(lower)	Lower limit on time for values to be included in the calculation of λ_z
λ_z(upper)	Upper limit on time for values to be included in the calculation of λ_z
λ_z(Rsq)	Goodness of fit statistic for the terminal elimination phase, adjusted for the number of points used in the estimation of λ_z
LDH	Lactate (lactic acid) dehydrogenase
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
mSWAT	Modified severity weighted assessment tool
MUGA	Multiple gated acquisition
ORR	Overall response rate
OS	Overall survival
[redacted]	[redacted]
PD	Progressive disease
PET-CT	Positron emission tomography-computed tomography
PFS	Progression free survival
PR	Partial response
PS	Performance status
PTCL	Peripheral T-cell lymphoma
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate by Fridericia's formula
r/r	Relapsed/refractory
Rac(AUC_{24h})	Accumulation ratio of multiple dose to first dose at regular administration for AUC_{24h}
Rac(C_{max})	Accumulation ratio of multiple dose to first dose at regular administration for C_{max}
Rac(C_{trough})	Accumulation ratio of multiple dose to first dose at regular administration for C_{trough}
RD	Recommended dose
SpO2	Percutaneous oxygen saturation
$t_{1/2,z}$	Terminal phase elimination half life
TEAE	Treatment-emergent adverse event
t_{last}	Time of last measurable (positive) concentration
t_{max}	Time to maximum (peak) plasma concentration
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

1 Introduction

This statistical analysis plan (SAP) documents the detailed methods of tabulation/analysis or evaluation to perform the statistical analyses necessary for preparing the clinical study report of the concerned trial.

This trial consists of phase 1 (dose escalation part), phase 1 (ATLL expansion part), and phase 2, and this SAP was also prepared based on the premise that the trial will be conducted until phase 2. However, the trial was eventually ended after conducting phase 1 (dose escalation part) only, and tabulation/analysis will be performed on phase 1 (dose escalation part) only.

2 Trial Objectives

Primary:

- Phase 1 (dose escalation part): To evaluate the tolerability and safety of ASTX660 in patients with relapsed/refractory peripheral T-cell lymphoma (r/r PTCL) and patients with relapsed/refractory cutaneous T-cell lymphoma (r/r CTCL) and determine the recommended dose (RD) for phase 2
- Phase 1 (ATLL expansion part): To evaluate the safety of ASTX660 at the RD in patients with relapsed/refractory adult T-cell leukemia/lymphoma (r/r ATLL)
- Phase 2: To evaluate the efficacy of ASTX660 at the RD in patients with r/r PTCL

Secondary:

Phase 1 (dose escalation and ATLL expansion parts):

- To evaluate the pharmacokinetics (PK) of ASTX660
- To evaluate the efficacy of ASTX660

Phase 2:

- To evaluate the safety of ASTX660
- To evaluate the PK of ASTX660

3 Trial Design

3.1 Type/Design of Trial

This is a phase 1/2, multicenter, open-label, uncontrolled trial of ASTX660 in Japanese patients with relapsed/refractory (r/r) PTCL, r/r CTCL, and r/r ATLL. This trial comprises the following 3 parts: phase 1 (dose escalation part) for subjects with r/r PTCL and r/r CTCL, phase 1 (ATLL expansion part) for subjects with r/r ATLL, and phase 2 for subjects with r/r PTCL.

Phase 1 (dose escalation part) will assign 3 to 6 subjects to each dose cohort (see Table 3.1-1) to evaluate the tolerability and safety of ASTX660 and then determine the recommended dose (RD) based on the dose-limiting toxicity (DLT) observed during the DLT assessment period of Cycle 1 and its incidence. Once a tested dose is considered the RD of ASTX660 in a particular cohort, this cohort will be expanded to 6 subjects to evaluate safety, even if the initial 3 subjects in the cohort have not experienced DLT.

Table 3.1-1 Dose Levels in Phase 1 (Dose Escalation Part)

Dose Level	Daily Dose
Dose level 1	120 mg
Dose level 2	150 mg
Dose level 3	180 mg

Phase 1 (ATLL expansion part) will enroll 6 to 10 subjects with r/r ATLL to evaluate the safety of ASTX660 at the RD and explore efficacy.

Phase 2 is designed to evaluate the efficacy of ASTX660 in a single arm of subjects with r/r PTCL in consideration of the prevalence of PTCL in Japan. The primary endpoint is ORR (as assessed by the Central Efficacy Evaluation Committee) and secondary endpoints are duration of response (DOR), PFS, OS, time to response (TTR), time to progression (TTP), proportion of subjects who proceed to transplantation, and ORR as assessed by the investigator or subinvestigator. A total of 33 efficacy-evaluable subjects will be enrolled.

The DLT assessment period of phase 1 (dose escalation part) will begin on Cycle 1 Day 1 (when trial treatment begins) and end just before the start of Cycle 2 (or before withdrawal examination if the subject discontinued the trial before Cycle 2). Subjects can continue trial treatment if they do not meet any of the withdrawal criteria and wish to continue participation in the trial. Subjects will be hospitalized during Cycle 1 of phase 1 (dose escalation part) and of phase 1 (ATLL expansion part) and between Cycle 1 Day 1 and Cycle 1 Day 7 of phase 2.

Advancement to the next dose cohort in phase 1 (dose escalation part) will be determined according to the dose escalation plan as shown in Table 3.1-2. If the initial 3 subjects have not experienced DLT during the DLT assessment period of each dose cohort, then the next dose cohort will begin. If 1 of 3 subjects have experienced DLT, an additional 3 subjects will be enrolled in the current dose cohort to further investigate DLT in 6 subjects. Thereafter, advancement to the next dose cohort will be permitted only if DLT has occurred in no more than 1 of 6 subjects. If DLT has occurred in 2 or more of 3 subjects or 2 or more of 6 subjects, further dose increase will not be permitted.

Table 3.1-2 Dose Escalation Plan for the Dose Escalation Part

Number of Subjects With DLT	Dose Escalation Plan
0/3	Advance to the next dose cohort[a]
1/3	Expand the current dose cohort to a total of 6 subjects by enrolling additional subjects
1/6	Advance to the next dose cohort[a]
2/6	Judge the treatment to be intolerable and identify the one-level lower dose as the RD[b]
≥ 2/3	Discontinue subject enrollment in the current dose cohort and identify the one-level lower dose as the RD[b]

[a]The sponsor will consult with the medical expert and/or members of the Efficacy and Safety Data Review Committee and determine, as appropriate, dose increase and/or a next dose level to be tested in consideration of safety observed at the dose levels that have been tested.

[b]If the initial dose level is judged to be intolerable due to the occurrence of DLT, the sponsor will consult with the medical expert and/or members of the Efficacy and Safety Data Review Committee and consider assessment at the one-level lower dose.

Dose-limiting toxicities in this trial are defined as shown below. Advancement to the next dose cohort will be determined based on the occurrence of DLTs during the DLT assessment period of each cohort in consideration of recommendations of the Efficacy and Safety Data Review Committee.

<Definition of dose-limiting toxicities>

The DLT assessment period of phase 1 (dose escalation part) will begin on Cycle 1 Day 1 (when trial treatment begins) and end just before the start of Cycle 2 (or before withdrawal examination if the subjects discontinued the trial before Cycle 2). Dose-limiting toxicities are defined as adverse events (AEs) occurring during this period that meet any of the following criteria, are not related to the primary disease, complication(s), or concomitant medication(s), and has a reasonable relationship with ASTX660. The Common Terminology Criteria for Adverse Events Version 4.03 (CTCAE v4.03) will be used to determine severity.

1) Grade 4 thrombocytopenia, Grade 3 or higher clinically significant bleeding, or anemia requiring a new erythrocyte transfusion
2) Febrile neutropenia that does not resolve within 3 days or Grade 4 neutropenia that lasts for more than 7 days under appropriate treatment
3) Liver-associated abnormalities as listed below:

- Grade 3 or higher alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation except ALT or AST elevation < 8 × upper limit of normal (ULN) for less than 7 days
- ALT or AST > 3 × ULN and either total bilirubin > 2 × ULN or international normalized ratio (INR) > 1.5
- ALT or AST > 3 × ULN with clinical indications of liver toxicity (symptoms [eg, jaundice] or other clinical findings)

4) Excepting the above AEs, any other Grade 3 or higher nonhematologic or Grade 4 hematologic toxicity except Grade 3 nausea, vomiting, or diarrhea lasting less than 48 hours

Among Grade 3 nonhematologic toxicities, transient laboratory abnormalities, laboratory abnormalities in laboratory test items not specified in the protocol, symptoms and signs that can be controlled by symptomatic treatments, and so on will be discussed with the Efficacy and Safety Data Review Committee to determine whether or not these events are DLTs. Subjects with an ASTX660 compliance of < 85% (ie, less than 12 days of completed dosing in a cycle of 14 days of scheduled dosing) during the DLT assessment period for reasons other than AEs will be excluded from the DLT-evaluable population in the trial.

During the screening period of phase 2, tumor samples will be collected from subjects with r/r PTCL, and central pathological diagnoses will be made according to a separately prepared procedure during the trial. The central image review committee will read the computed tomography (CT) and positron emission tomography-computed tomography (PET-CT) images obtained during the screening period and the treatment and observation period and at the withdrawal examination based on the Lugano response criteria for non-Hodgkin lymphoma (2014)[1] proposed by the International Working Group (IWG), and then the Central Efficacy Evaluation Committee will centrally assess the reading results.

3.2 Trial Treatments

3.2.1 Dose and Regimen

Trial treatment will be conducted in repeated 28-day cycles comprising 7 days of investigational medicinal product (IMP) administration (Days 1 - 7 and Days 15 - 21) and 7 days of rest (Days 8 - 14 and Days 22 - 28).

After the dosing time is determined, the IMP will be orally administered once daily at approximately the same clock time on Days 1 to 7 and Days 15 to 21 of each cycle throughout the trial period. On scheduled visit days, subjects will return to the trial site without taking the IMP and receive the IMP after the scheduled examinations. Subjects will, in principle, fast for 2 hours before and 2 hours after IMP administration. In phase 1 (dose escalation and ATLL expansion parts), subjects will fast for at least 10 hours before IMP administration on Cycle 1 Day 1 and Cycle 1 Day 7. During fasting, consumption of tea, coffee, and water is permitted but other foods or beverages must not be consumed. In cases where a delay of 6 hours or longer has elapsed from the scheduled dosing time, IMP administration scheduled on that day will be skipped.

In phase 1 (dose escalation part), treatment will begin with a daily dose of 120 mg, which will then be increased to 150 mg and 180 mg according to the dose escalation plan. Dose increase in the same subject is prohibited. Phase 1 (ATLL expansion part) and phase 2 will adopt the RD determined based on the results of phase 1 (dose escalation part).

3.2.2 Treatment Duration

Trial treatment can be continued until the withdrawal criteria are met.

3.3 Trial Population

3.3.1 Sample Size and Target Population

Patients with r/r PTCL, patients with r/r CTCL, and patients with r/r ATLL

- Phase 1 (dose escalation part): A maximum of 18 subjects with r/r PTCL or r/r CTCL (3 to 6 subjects/cohort)
- Phase 1 (ATLL expansion part): 6 to 10 subjects with r/r ATLL

Phase 2: 33 subjects with r/r PTCL (as efficacy-evaluable subjects)

3.4 Handling of Timepoint

The baselines of clinical laboratory values, vital signs, body weight, and [redacted] are defined as the data prior to IMP administration on Cycle 1 Day 1 or, if the data of Cycle 1 Day 1 do not exist, the data at screening.

The baselines of 12-lead ECG, ECOG PS, and left ventricular ejection rate are defined as the data at screening.

In tabulation for each time point, nominal visits (visits in CRF) will be used without setting visit windows. In addition, the data at discontinuation and unscheduled data will

not be included in the analyses. (However, they will be used for tabulation independent from time points and displayed in listings.)

4 Sample Size

For phase 1, the sample size was not calculated statistically. In phase 1 (dose escalation part), DLT will be evaluated, with reference to section IV., Phase 1 Studies, of "Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs (PFSB/ELD Notification No. 1101001 dated 01 Nov 2005),[2]" in 3 to 6 subjects per cohort. In phase 1 (ATLL expansion part), the sample size will be 6 to 10 subjects to confirm the safety of ASTX660 at the RD for phase 2 study in patients with r/r ATLL.

For phase 2, a threshold response rate (P0) of 10%, an ASTX660 expected response rate of 30%, and at one-sided 2.5% level of significance will be used to test the null hypothesis H0 of P = P0 against the alternative hypothesis H1 of P > P0 (where, P is the response rate of ASTX660) by a proportion test (by Clopper-Pearson method). Under these conditions, the sample size needed to achieve a power of 80% was determined to be ≥ 33 efficacy-evaluable subjects.

5 Statistical Analysis Datasets

5.1 Safety Analysis Set

The safety analysis set includes all subjects that were administered at least 1 dose of IMP.

5.2 DLT Analysis Set

The DLT analysis set include all subjects who received at least 1 dose of IMP and have available data necessary for DLT assessment during the DLT assessment period.

Subjects with an ASTX660 compliance of < 85% (ie, less than 12 days of completed dosing in a cycle of 14 days of scheduled dosing) during the DLT assessment period for reasons other than AEs will be excluded from the DLT-evaluable population in the trial; therefore, such subjects will be excluded from the DLT analysis set.

5.3 Efficacy Analysis Set

The efficacy analysis set is defined as the full analysis set (FAS) and includes all subjects that were administered at least 1 dose of IMP. If subjects enrolled in phase 2 are not diagnosed with PTCL by central pathological diagnosis, the subjects will not be included in the efficacy analysis set.

5.4 Pharmacokinetic Analysis Set

The PK analysis set includes all subjects who received at least 1 dose of IMP and have available ASTX660 concentration measurement data for at least 1 time point.

5.5 Handling of Missing Data

For primary, secondary, or PK endpoint analysis, missing data will not be imputed.

Regarding time-to-event type endpoints, calculation of disease duration (Section 7.3 Baseline Disease Evaluation), and determination of concomitant medications (Section 7.5 Prior and Concomitant Medications), dates may be missed partially (eg, 2020-09-UN). Concrete handling methods are defined in the specifications.

6 Primary and Secondary Endpoints

6.1 Primary Endpoints

Phase 1 (dose escalation part): Dose-limiting toxicity (DLT) and safety (adverse events [AEs], clinical laboratory values, vital signs, body weight, Eastern Cooperative Oncology Group [ECOG] Performance Status [PS], 12-lead ECGs, and echocardiography)

Phase 1 (ATLL expansion part): Safety (AEs, clinical laboratory values, vital signs, body weight, ECOG PS, 12-lead ECGs, and left ventricular ejection fraction [LVEF])

Phase 2: Overall response rate (ORR) as assessed by the Central Efficacy Evaluation Committee based on Lugano response criteria for non-Hodgkin lymphoma (2014)[1] proposed by the International Working Group (IWG)

6.2 Secondary Endpoints

Phase 1 (dose escalation and ATLL expansion parts):

[Pharmacokinetic endpoints]

- Plasma ASTX660 concentrations over time and PK parameters. Dose proportionality will only be assessed in the dose escalation part.

[Efficacy endpoints]

- ORR as assessed by the investigator or subinvestigator
- Duration of response (DOR)
- Progression free survival (PFS)
- Overall survival (OS)
- Time to response (TTR)
- Time to progression (TTP)

- Proportion of subjects who proceed to transplantation

Phase 2:

[Efficacy endpoints]

- DOR
- PFS
- OS
- TTR
- TTP
- Proportion of subjects who proceed to transplantation
- ORR as assessed by the investigator or subinvestigator

[Safety endpoints]

AEs, clinical laboratory values, vital signs, body weight, ECOG PS, 12-lead ECGs, and LVEF

[Pharmacokinetic endpoints]

- Plasma ASTX660 concentrations over time

[redacted]

7 Disposition and Demographic Analysis

Except for Section 7.1 and Section 7.6, the safety analysis set, efficacy analysis set, and PK analysis set will be included.

Except for Section 7.1, tabulations will be performed for each of phase 1 (dose escalation part), phase 1 (ATLL expansion part), and phase 2, and the tabulation for phase 1 (dose escalation part) will be performed by cohort.

7.1 Subject Disposition

The disposition of subjects will be tabulated.

The number of subjects with informed consent and the number of enrolled subjects will be calculated.

For overall and each part, cohort, and target disease (PTCL, CTCL) (phase 1 dose escalation part only), the numbers and proportions (the denominator is enrolled subjects) of subjects of each disease type (phase 2), enrolled subjects, subjects with trial treatment discontinuation, subjects with trial discontinuation, and subjects of each analysis set will be calculated. Regarding subjects with trial treatment discontinuation and subjects with trial discontinuation, the number and proportion (the denominator is enrolled subjects) of subjects will be calculated for each discontinuation reason.

7.2 Demographic and Other Baseline Characteristics

Continuous variables (age, height, and body weight [at screening]), will be summarized in respect of descriptive statistics (the number of subjects, mean, standard deviation, minimum, median, and maximum), and categorical variables (sex, race, ethnicity, ECOG PS [screening period], and the presence of concurrent/prior diseases) will be summarized in respect of the number and proportion of subjects.

Concurrent/prior diseases will be coded by system organ class (SOC) and ICH Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT), and the number and proportion of subjects will be calculated for each SOC and PT.

7.3 Baseline Disease Evaluation

The number and proportion of subjects will be calculated by diagnosis, disease stage (stages based on the Lugano classification for PTCL and ATLL and the TNMB classification for CTCL will be used), international prognostic index (IPI) (for PTCL and ATLL only), CD30 positive (for PTCL only), prior chemotherapy for the primary disease, number of regimens of chemotherapy for the primary disease, best overall response after chemotherapy for the primary disease, best overall response after the latest chemotherapy, prior hematopoietic stem cell transplantation, and prior radiotherapy for the primary disease. In tabulation for PTCL or ATLL only, proportions will be calculated by using the number of PTCL patients as a denominator.

Regarding disease period (the length of the period from the day of initial diagnosis until the start day of IMP administration [years]), descriptive statistics will be calculated, and the number and proportion of subjects will be summarized for each category (< 1 year, ≥ 1 and < 3 years, ≥ 3 and < 5 years, ≥ 5 and < 10 years, and ≥10 years) after classification.

7.4 Treatment Compliance

For IMP compliance rate (proportion of the number of actual days of IMP administration to the number of scheduled days of IMP administration), descriptive statistics will be calculated, and frequency tabulation will be performed.

In addition, as for relative dose intensity (the proportion of the actual total dose to the planned total dose), descriptive statistics will be calculated, and frequencies will be tabulated. The planned dose will be calculated by multiplying the planned dose in CRF with the number of days, and the actual dose will be calculated by using the actual dose in CRF.

Categories in frequency tabulation are defined as shown in Table 7.4-1.

Table 7.4-1 Categories of IMP Compliance Rate

Item	Level
Compliance rate	• < 50% • ≥ 50% and < 80% • ≥ 80% and < 100% • 100% • 100% <
Relative dose intensity	• < 50% • ≥ 50% and < 80% • ≥ 80% and < 100% • 100% • 100% <

7.5 Prior and Concomitant Medications

The number and proportion of subjects will be calculated for each of all regimens or medications used and therapies conducted for the primary disease (the "Prior Chemotherapy or Other Therapy for Primary Diagnosis" form in CRF).

Regarding prior medications and concomitant medications (the "Concomitant Medications" form in CRF), the number and proportion of subjects will be calculated for each medication by using the ATC level 2 and preferred name of World Health Organization Drug Dictionary (WHO-DD). Prior therapies and concomitant therapies will not be tabulated.

7.6 Protocol Deviations

Regarding significant protocol deviations, the number and proportion of subjects among enrolled subjects will be calculated for each of the following categories:

- Subjects who were enrolled in the trial although the inclusion criteria were not fulfilled
- Subjects who were not discontinued although the discontinuation criteria became fulfilled during the trial
- Subjects in whom a deviation of implementation procedures (that may affect the primary endpoints) was found
- Subjects who received IMP at an inappropriate dose
- Subjects who received a prohibited concomitant therapy

8 Efficacy Analysis

The efficacy analysis set will be included.

Except for Section 8.2, tabulation will be performed for each of phase 1 (dose escalation part), phase 1 (ATLL expansion part), and phase 2 part, and the tabulation for phase 1 (dose escalation part) will be performed by cohort and target disease (PTCL, CTCL).

The primary efficacy analysis is the ORR and its two-sided 95% CI (by Clopper-Pearson method) in phase 2. No multiplicity adjustment will be applied for the primary or other efficacy analyses.

8.1 Efficacy Endpoint

8.1.1 Efficacy Analyses

8.1.1.1 Overall Response Rate

Regarding the ORR (phase 2) as assessed by the Central Efficacy Evaluation Committee, the ORR and its two-sided 95% confidence interval (CI) (by Clopper-Pearson method) will be calculated. The response rate is defined as the proportion of responders (subjects who have a best overall response of complete response [CR] or partial response [PR]) over the analysis set.

The frequency of the best overall response (CR, PR, stable disease[SD], progressive disease [PD], or inevaluable [NE]) as assessed by the Central Efficacy Evaluation Committee will be summarized. In addition, a swimmer plot will be prepared.

For PTCL and ATLL, a waterfall plot of the sum of the product of perpendicular diameters for the target lesion will be prepared.

Overall response rate (phase 1 and phase 2) as assessed by the investigator or subinvestigator will also be analyzed in the same manner.

8.1.1.2 Duration of Response

Kaplan–Meier plots will be provided for DOR, and the median and two-sided 95% CI will be estimated using the Kaplan–Meier method. The CI will be calculated based on Greenwood's formula.

Duration of response is defined as the period from the date of documented CR or PR as the overall response to:

- The date of documented PD as the overall response
- The date of the start of new treatment for the primary disease
- The date of death due to any cause

whichever occurs earlier. Censoring will be conducted on the last assessment day of overall response, or responders who undergo transplantation will be censored on the date of transplant.

Subjects for whom neither CR nor PR was documented as the overall response will not be included in the analysis of DOR.

Overall response for the definitions of DOR will be based on assessment by the investigator or subinvestigator.

8.1.1.3 Progression-free Survival

Kaplan–Meier plots will be provided for PFS, and the median and two-sided 95% CI will be estimated using the Kaplan–Meier method. The CI will be calculated based on Greenwood's formula.

Progression-free survival is defined as the period from the date of the start of ASTX660 treatment to:

- The date of documented PD as the overall response
- The date of the start of new treatment for the primary disease
- The date of death due to any cause

whichever occurs earlier. Censoring will be conducted on the last assessment day of overall response, or responders who undergo transplantation will be censored on the date of transplant.

Overall response for the definitions of PFS will be based on assessment by the investigator or subinvestigator.

8.1.1.4 Overall Survival

Kaplan–Meier plots will be provided for OS, and the median and two-sided 95% CI will be estimated using the Kaplan–Meier method. The CI will be calculated based on Greenwood's formula.

Overall survival is defined as the period from the date of the start of ASTX660 treatment to the date of death due to any cause. Subjects without a documented death date will be censored on the last date they were known to be alive.

In addition, the median of the period from the start date of ASTX660 treatment to the date of death (for subjects with death) or the last date they were known to be alive (for subjects without death) will be calculated as the median follow-up time.

8.1.1.5 Time to Response

Kaplan–Meier plots will be provided for TTR, and the median and two-sided 95% CI will be estimated using the Kaplan–Meier method. The CI will be calculated based on Greenwood's formula. Only the Kaplan–Meier plots for TTR will have a shape wherein percentage starts from 0% and increases when response is obtained.

Time to response is defined as the period from the date of the start of ASTX660 treatment to the date of the earliest documented CR or PR as the overall response. Subjects for whom neither CR nor PR was documented as the overall response will be censored on the last assessment day of overall response.

Overall response for the definitions of TTR will be based on assessment by the investigator or subinvestigator.

8.1.1.6 Time to Progression

Kaplan–Meier plots will be provided for TTP, and the median and two-sided 95% CI will be estimated using the Kaplan–Meier method. The CI will be calculated based on Greenwood's formula.

Time to progression is defined as the period from the date of the start of ASTX660 treatment to:

- The date of documented PD as the overall response
- The date of the start of new treatment for the primary disease
- The date of death due to the progression of the primary disease

whichever occurs earlier. Censoring will be conducted on the last assessment day of overall response, or responders who undergo transplantation will be censored on the date of transplant.

Overall response for the definitions of TTP will be based on assessment by the investigator or subinvestigator.

8.1.1.7 Proportion of Subjects Who Proceed to Transplantation

The proportion of subjects who undergo transplantation after IMP treatment will be calculated.

8.1.2 Sensitivity Analyses

Not to be performed.

8.1.3 Technical Computational Details for Efficacy Analysis

The supplemental information about time-to-event type endpoints is described.

- For subjects continuing the trial treatment, the last date they were known to be alive is defined as the latest date of survival state investigation or hospital visit. In addition, for subjects with trial treatment discontinuation, it is defined as the date of trial treatment discontinuation, the data of trial discontinuation, the date of visit during the follow-up period, or the date of survival state investigation, whichever occurs later.
- The overall response assessment date obtained from "8.1 Efficacy Assessments" of the protocol, the disease progression investigation date obtained from "1.3.5 Investigation of Survival Status" of the protocol, or the date of treatment discontinuation (if the obvious aggravation or relapse of the primary disease requiring alternative treatments was observed), whichever occurs earlier, will be used as the date of documented PD as the overall response.
- The overall response obtained from "8.1 Efficacy Assessments" of the protocol or the results of the disease progression investigation obtained from "1.3.5 Investigation of Survival Status" of the protocol will be used as the last assessment day of overall response.
- If a subject discontinued the trial treatment without once receiving the judgment of overall response ("8.1 Efficacy Assessments" of the protocol), and if the reason for treatment discontinuation is not included in the cases where "the obvious exacerbation or relapse of the primary disease requiring an alternative therapy was observed," the PFS and TTP of the subject will be censored on the start date of ASTX660 treatment.
- If a subject discontinued the trial treatment without once receiving the judgment of overall response ("8.1 Efficacy Assessments" of the protocol), the TTR of the subject will be censored on the start date of ASTX660 treatment.

8.2 Subgroup Analyses

For phase 2, the analyses in Sections 8.1.1.1 to 8.1.1.6 will be performed on the subject demographics shown in Table 8.2-1.

Table 8.2-1 Factors Included in Subgroup Analyses	
Demographic Item	**Level**
Disease stage (Lugano classification)	• Limited (stage I, stage II) • Advanced (stage III, stage IV)
International prognostic index (IPI)	• Low to low-intermediate risk • High-intermediate to high risk
Disease type	• Peripheral T-cell lymphoma, NOS • Angioimmunoblastic T-cell lymphoma • Anaplastic large cell lymphoma, ALK positive • Anaplastic large cell lymphoma, ALK negative • Other

9 Safety Analyses

Except for Section 9.2, the safety analysis set will be included.

Except for Section 9.2, tabulations will be performed for each of phase 1 (dose escalation part), phase 1 (ATLL expansion part), and phase 2, and the tabulation for phase 1 (dose escalation part) will be performed by cohort.

9.1 Extent of Exposure

The descriptive statistics of the total dose and treatment duration (= last treatment date − treatment start date + 1) of IMP will be calculated. For the number of treatment cycles for each subject, descriptive statistics and frequency distribution will be calculated.

As for the cycles whose start was postponed and cycles during which dose reduction was required, the numbers of those cycles and the proportions of them to the total number of treatment cycles will be calculated.

9.2 Dose Limiting Toxicity

For phase 1 (dose escalation part), the frequencies of DLTs (number and proportion of subjects with DLT) will be summarized by cohort in the DLT analysis set. The results of assessment by the Efficacy and Safety Data Review Committee will be used for the tabulation.

9.3 Adverse Events

All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. The incidence of the following events will be summarized. Severity will be tabulated based on CTCAE version 4.03. However, in

tabulation by CTCAE Grade, if there are 2 or more onsets of the same event in the same subject, the most severe AE will be included in tabulation.

- Treatment-emergent AEs (TEAEs)
- TEAEs occurring in 2 or more subjects
- TEAEs by CTCAE grade
- TEAEs by the initial onset time
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP
- Grade ≥ 3 TEAEs
- TEAEs of special interest

TEAEs causally related to the IMP will also be tabulated in the same manner.

The categories of the initial onset time are defined as Cycle 1 Day 1 to 3, Cycle 1 Day 4 to 7, Cycle 1 Week 2, Cycle 1 Week 3 to 4, Cycle 2, Cycle 3, Cycle 4 to 6, Cycle 7 to 9, and Cycle 10 or later.

TEAEs of special interest are defined as pneumonitis, rash maculo-papular, and pancreatitis.

9.4 Clinical Laboratory Data

The clinical laboratory assessments included in hematology, serum chemistry, urinalysis, and coagulation in Appendix 2 of the protocol will be included in tabulation, whereas those in virus test and pregnancy test will not be included in tabulation.

Descriptive statistics will be calculated for actual measurements and changes from baseline at each time point (except for urine qualitative tests). Measurements obtained at each trial site will be used for the clinical laboratory data in this trial; therefore, the units of measurements may differ depending on trial sites. Unit conversion is stipulated in the specifications. Regarding WBC differential, both percentages and absolute values will be tabulated.

For urine qualitative tests, a shift table of each time point in comparison to baseline will be prepared.

By using institutional reference values, data will be classified as “within reference range,” “below reference range,” or “above reference range,” and a shift table of each time point in comparison to baseline will be prepared. In hematology and serum chemistry tests, shift tables of baseline versus each time point and baseline versus the worst value (the worst value after the start of IMP administration) will be prepared based

on the severity classification of CTCAE version 4.03, and the proportion of subjects in whom Grade ≥ 3 laboratory abnormalities were observed after the start of IMP administration will be calculated.

Regarding LDH, the results of the JSCC and IFCC methods will be tabulated as a whole; regarding ALP, the results of the JSCC and IFCC methods will be tabulated as a whole after conversion to the IFCC method. Regarding amylase isozymes, although data will be tabulated as either percentages or absolute values depending on trial sites, percentages and absolute values will not be tabulated as a whole after conversion.

9.5 Vital Sign Data

For vital signs (blood pressure, pulse rate, SpO_2, and body temperature), descriptive statistics will be calculated for actual measurements and changes from baseline at each time point.

9.6 Physical Examination Data

Physical findings will be shown in a listing.

9.7 Electrocardiogram Data

For tabulation in this section, the results measured and judged by trial sites will be used.

For the parameters of 12-lead ECG (heart rate, RR interval, PR interval, QRS width, QT interval, and QTcF interval), descriptive statistics will be calculated for actual measurements at each time point and changes from baseline.

As for QTcF interval, the number and proportion of subjects who met the following criteria during the trial will be calculated.

- A measured value was "> 450 msec," "> 480 msec," or "> 500 msec."
- A change from baseline was "> 30 msec" and "> 60 msec."

As for ECG assessment of normality/abnormality, a shift table of each time point in comparison to baseline will be prepared.

9.8 Other Safety Data

9.8.1 ECOG Performance Status

For US Eastern Cooperative Oncology Group Performance Status (ECOG PS), a shift table of each time point in comparison to baseline will be prepared.

9.8.2 Body Weight

For body weight, descriptive statistics will be calculated for actual measurements and changes from baseline at each time point.

9.8.3 Left Ventricular Ejection Rate

For left ventricular ejection rate measured by echocardiography or multiple-gated acquisition (MUGA) scan, descriptive statistics will be calculated for actual measurements and changes from baseline at each time point.

9.8.4 Lung Field Assessment by PET-CT or CT Scans

The results of lug field assessment will be shown in a listing.

9.8.5 Chest X-Ray

The results of chest X-Ray will be shown in a listing.

10 Pharmacokinetic Analyses

10.1 Pharmacokinetic Analysis

The PK analysis set will be included. The overview of the contents of analyses is shown in this section, and the detail items related to analyses (data handling and calculation and analysis methods of pharmacokinetic parameters) are shown in Section 10.2, Section 10.3, and Section 10.4.

10.1.1 Plasma ASTX660 Concentration

1) Phase 1 (dose escalation part and ATLL expansion part)
The following analyses will be performed for each part:

- Plasma ASTX660 concentration will be tabulated for each assessment time (each Day of each cycle), blood sampling time point, and dose level.
- (Dose escalation part only) For each of Cycle 1 Days 1 and 7, a figure to compare plasma concentrations over time between dose levels (mean ± standard deviation and median) will be prepared.
- As for each dose level during Cycle 1 (Days 1, 7, 15, and 21), a figure to compare plasma concentrations over time between subjects will be prepared.
- A figure to compare plasma concentrations over time between Cycle 1 Days 1 and 7 and a figure to compare plasma concentrations over time between Days 15 and 21 will be prepared for each dose level (mean ± standard deviation and median). Those figures for each subject will also be prepared.

2) Phase 2

- Plasma ASTX660 concentration will be tabulated for each assessment time (each Day of Cycle 1) and blood sampling time point.
- For each Day in Cycle 1 (Days 1, 7, and 21), a figure to compare plasma concentrations over time between subjects will be prepared.
- As for Cycle 1, a figure to compare plasma concentrations over time between Days 1, 7, and 21 (mean ± standard deviation and median) will be prepared. That figure for each subject will also be prepared.

10.1.2 Pharmacokinetic Parameters of ASTX660

Pharmacokinetic parameters will be calculated only for Cycle 1 Days 1 and 7 in phase 1 (dose escalation part and ATLL expansion part).

The following analyses will be performed for each part:

- Each pharmacokinetic parameter will be tabulated by assessment time and dose level.
  - Cycle 1 Day 1
    C_{max}, AUC_{24h}, AUC_t, AUC_∞, t_{max}, λ_z, AUC_%Extrap, $t_{1/2,z}$, CL/F, CL/F/BW, t_{last}, C_{max}/D^a, AUC_t/D^a, AUC_∞/D^a
  - Cycle 1 Day 7
    C_{max}, AUC_{24h}, t_{max}, λ_z, $t_{1/2,z}$, CL/F, CL/F/BW, t_{last}, C_{max}/D^a, AUC_{24h}/D^a, $R_{ac}(AUC_{24h})$, $R_{ac}(C_{max})$, $R_{ac}(C_{trough})$

  [a]To be calculated for the dose escalation part only.

10.1.3 Dose Proportionality of ASTX660

Dose proportionality analyses will be performed only for Cycle 1 Day 7 in phase 1 (dose escalation part).

Only when 3 or more doses are administered, the following parameters will be investigated:

- C_{max} and AUC_{24h} on Cycle 1 Day 7

10.2 Handing of Data

- If vomiting occurred after ASTX660 administration (if vomiting occurred before twice the median of t_{max} in the group to which the concerned subject was assigned [the subject will be excluded from calculation]), every plasma drug concentration

after IMP administration in the Week corresponding to the first vomiting and pharmacokinetic parameters using the concentration will be rejected.

- The plasma drug concentrations collected at the time point out of the allowable window (refer to the Section 8.2.1 of the protocol) will not be adopted in calculation of descriptive statistics at the concerned time point. However, they will be used for calculation of pharmacokinetic parameters, and the parameters whose calculation was judged as inappropriate will be rejected.
- The plasma drug concentrations within the same Week after the time point of IMP nonadministration will be rejected, and the pharmacokinetic parameters calculated by using the rejected concentrations will also be rejected.
- Other than those above, the plasma drug concentrations or pharmacokinetic parameters that were judged as inappropriate by a clinical pharmacology representative will be rejected. In that case, the reasons for judging as inappropriate will be recorded separately.
- Plasma drug concentrations below the lower limit of quantitation[a] on each administration day will be handled as 0 (ng/mL) until the first measurable time point, and those after the first measurable time point will be handled as missing.
  [a]The lower limit of quantitation of plasma ASTX660 concentration is 1.00 ng/mL.
- Concentrations reported as "not analyzed (NA)" and "not determined (ND)" will be handled as missing.

10.3 Calculation Methods of Pharmacokinetic Parameters

- Pharmacokinetic parameters will be calculated by the noncompartmental model analysis for each subject and administration day. However, pharmacokinetic parameters will not be calculated for the subjects in whom plasma drug concentrations are below the lower limit of quantitation at all time points.
- For postdose time, actual postdose time will be used. However, predose will be handled as "0 hours."
- As for dose, the administered doses of ASTX660 (120 mg, 150 mg, or 180 mg) will be used.
- The linear trapezoidal rule will be used for calculation of AUC.
- AUC_{24h} will be calculated by using the plasma concentration obtained from actual blood sampling at 24 hours postdose. If blood sampling was not conducted at 24 hours postdose, or if the concentration at that time was below the lower limit of quantitation, the data will be handled as follows:
  - If a concentration no less than the lower limit of quantitation was obtained at the time point later than 24 hours postdose:
    The plasma concentration at 24 hours postdose obtained by linear extrapolation with the concentrations at the time points right before and after 24 hours postdose will be used.

  - If a concentration no less than the lower limit of quantitation was not obtained at the time point later than 24 hours postdose:
    The plasma concentration at 24 hours postdose obtained with log linear extrapolation by using λ_z calculated from concentrations before 24 hours postdose will be used. If λ_z is incalculable, AUC_{24h} will also be handled as incalculable.
- If C_{max} was observed at multiple time points, the earliest time after administration will be adopted as t_{max}. In addition, C_{max} for multiple dose is defined as the maximum concentration during the dosing interval.
- The range of measuring points to be used for calculation of λ_z is defined as the last 3 points. However, if the slope of the regression line in that case is not negative, or if λ_z(Rsq) is less than 0.800, measurement points will be added until a time point exceeding t_{max}[a] and the range with which λ_z(Rsq) is first 0.800 or more will be selected. If the slope of the regression line does not become negative even after the range of measurement points is added until the time point shortly after t_{max}[a], and if λ_z(Rsq) is not 0.800 or more, λ_z will be handled as incalculable. When estimating λ_z, weighting of the regression equation will not be conducted.
  [a]Time point of reaching the maximum concentration during concentration transition. If there are multiple applicable time points, the latest time point after administration will be adopted.
- Other than the pharmacokinetic parameters shown in Section 10.1.2, λ_z(lower), λ_z(upper), λ_z(point), and λ_z(Rsq) will also be calculated. However, these parameters will not be tabulated.
- CL/F/BW on Cycle 1 Days 1 and 7 will be calculated by dividing CL/F on each Day by the body weight before IMP administration on Cycle 1 Day 1. Regarding body weight, if the value on Cycle 1 Day 1 is missing, and if the day of screening is within −4 days from Cycle 1 Day 1, the value at screening will be used.
- Parameters corrected for dose (each parameter/D) will be calculated by dividing each parameter by dose (120 mg, 150 mg, or 180 mg).
- $R_{ac}(AUC_{24h})$ and $R_{ac}(C_{max})$ will be calculated by dividing AUC_{24h} and C_{max}, respectively, on Cycle 1 Day 7 by the same parameter on Cycle 1 Day 1.
- $R_{ac}(C_{trough})$ will be calculated by dividing the plasma drug concentration at 24 hours postdose on Cycle 1 Day 7 by that on Cycle 1 Day 1.

10.4 Analysis Methods

1) Calculation of Descriptive Statistics

- Descriptive statistics will be calculated only for the time points (items) for which subjects to be tabulated account for over half of subjects to be analyzed.
- The descriptive statistics to be calculated for plasma drug concentration will be the number of subjects to be analyzed, number of subjects to be tabulated,

arithmetic mean, standard deviation, coefficient of variation, minimum, median, and maximum.

- Descriptive statistics to be calculated for pharmacokinetic parameters (except for t_{max} and t_{last}) will be the number of subjects to be analyzed, number of subjects to be tabulated, arithmetic mean, standard deviation, coefficient of variation, geometric mean, minimum, median, and maximum.
- Descriptive statistics to be calculated for t_{max} and t_{last} will be the number of subjects to be analyzed, number of subjects to be tabulated, minimum, median, and maximum.
- The number of digits of the descriptive statistics of plasma drug concentration and pharmacokinetic parameters will be as follows:
  - Arithmetic mean, geometric mean, standard deviation, and median: To be rounded to the same number of digits as that of the values of individual subjects for the concerned data
  - Minimum and maximum: To be displayed as they are with the same number of digits as that of the values of individual subjects for the concerned data
  - Coefficient of variation: To be rounded to 1 decimal place

2) Dose Proportionality

   To be analyzed using the regression equation expressed by (I) to determine the estimate of b with a two-sided 95% CI.

   $\ln Y = a + b \cdot \ln X \cdots (I)$

   X: Dose

   Y: Parameters (C_{max} and AUC_{24h})

   Dose proportionality is considered to be statistically demonstrated, when the two-sided 95% CI of the estimate of b includes 1.

3) Figure of plasma concentrations over time

- Regarding the figures containing plasma concentrations over time of Cycle 1 Days 1 and 7 in phase 1, both of those using actual measurements and log-converted values as the Y axis will be prepared. In figures using log-converted values, standard deviation will not be displayed.
- Regarding the figures containing plasma concentrations over time of Cycle 1 Days 15 and 21 in phase 1 and plasma concentrations over time in phase 2, only those using actual measurements as the Y axis will be prepared.
- For the X axis, planned postdose time will be used in the figures of mean ± standard deviation, whereas actual postdose time will be used in the figures of individual subjects. In both cases, predose will be handled as “0 hours.”

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]		
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

14 Interim Analysis

Not applicable.

[redacted]

[redacted]

16 References

1 Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32:3059-68.

2 Ministry of Health, Labour and Welfare. Revision to the "Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs." PFSB/ELD Notification No. 1101001. 01 Nov 2005.

3 Japanese Society of Nephrology, ed. Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease 2012. 2012.

Appendix 1 List of Summary Tables

- CT-1 : Subject Disposition, Phase I Part (Dose-escalation Part), All Screened Subject
- CT-2.1 : Reasons for Discontinuation, Phase I Part (Dose-escalation Part), All Enrolled Subject
- CT-2.2 : Summary of Major Protocol Deviations by Type of Deviation, Phase I Part (Dose-escalation Part), All Enrolled Subject
- CT-3.1.1 : Demographic and Baseline Characteristics, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-3.1.2 : Demographic and Baseline Characteristics, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-3.1.3 : Demographic and Baseline Characteristics, Phase I Part (Dose-escalation Part), PK Analysis Set
- CT-3.2.1 : Baseline Disease Evaluation, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-3.2.2 : Baseline Disease Evaluation, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-3.2.3 : Baseline Disease Evaluation, Phase I Part (Dose-escalation Part), PK Analysis Set
- CT-3.3.1 : Medical History, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-3.3.2 : Medical History, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-3.3.3 : Medical History, Phase I Part (Dose-escalation Part), PK Analysis Set
- CT-3.4.1 : Complications, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-3.4.2 : Complications, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-3.4.3 : Complications, Phase I Part (Dose-escalation Part), PK Analysis Set
- CT-4.1.1 : Prior Medications and Therapies for T-Cell Lymphoma, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-4.1.2 : Prior Medications and Therapies for T-Cell Lymphoma, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-4.1.3 : Prior Medications and Therapies for T-Cell Lymphoma, Phase I Part (Dose-escalation Part), PK Analysis Set
- CT-4.2.1 : Prior Medications, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-4.2.2 : Prior Medications, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-4.2.3 : Prior Medications, Phase I Part (Dose-escalation Part), PK Analysis Set
- CT-4.3.1 : Concomitant Medications, Phase I Part (Dose-escalation Part), Safety Analysis Set

- CT-4.3.2 : Concomitant Medications, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-4.3.3 : Concomitant Medications, Phase I Part (Dose-escalation Part), PK Analysis Set
- CT-5.1 : Overall Response Rate by Investigator, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-5.2 : Duration of Response by Investigator, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-5.3 : Progression Free Survival by Investigator, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-5.4 : Overall Survival, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-5.5 : Time to Response by Investigator, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-5.6 : Time to Progression by Investigator, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-5.7 : Percentage of Patients Who Switch to Transplantation, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-7.1 : Extent of Exposure to Investigational Medicine Product, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-7.2.1 : Treatment Compliance, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-7.2.2 : Treatment Compliance, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CT-7.2.3 : Treatment Compliance, Phase I Part (Dose-escalation Part), PK Analysis Set
- CT-8.1 : Overall Summary of Adverse Events, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.2 : Incidence of Dose Limiting Toxicity, Phase I Part (Dose-escalation Part), DLT Analysis Set
- CT-8.3.1 : Incidence of TEAEs by MedDRA System Organ Class and Preferred Term, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.3.2 : Incidence of TEAEs by MedDRA System Organ Class and Preferred Term in 2 or More Subjects in Total, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.4.1 : Incidence of IMP-related TEAEs by MedDRA System Organ Class and Preferred Term, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.4.2 : Incidence of IMP-related TEAEs by MedDRA System Organ Class and Preferred Term in 2 or More Subjects in Total, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.5 : Incidence of TEAEs by MedDRA System Organ Class, Preferred Term and CTCAE Grade, Phase I Part (Dose-escalation Part), Safety Analysis Set

- CT-8.6 : Incidence of IMP-related TEAEs by MedDRA System Organ Class, Preferred Term and CTCAE Grade, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.7 : Incidence of TEAEs by MedDRA System Organ Class, Preferred Term and Period of Onset, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.8 : Incidence of IMP-related TEAEs by MedDRA System Organ Class, Preferred Term and Period of Onset, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.9 : Incidence of CTCAE Grade 3 or More TEAEs by MedDRA System Organ Class and Preferred Term, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.10 : Incidence of CTCAE Grade 3 or More IMP-related TEAEs by MedDRA System Organ Class and Preferred Term, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.11 : Incidence of TEAEs Leading to Deaths by MedDRA System Organ Class and Preferred Term, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.12 : Incidence of IMP-related TEAEs Leading to Deaths by MedDRA System Organ Class and Preferred Term, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.13 : Incidence of Serious TEAEs by MedDRA System Organ Class and Preferred Term, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.14 : Incidence of IMP-related Serious TEAEs by MedDRA System Organ Class and Preferred Term, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.15 : Incidence of TEAEs Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.16 : Incidence of IMP-related TEAEs Leading to Discontinuation of Investigational Medicinal Product Administration by MedDRA System Organ Class and Preferred Term, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.17.1 : Incidence of TEAEs by MedDRA System Organ Class and Preferred Term (Pneumonitis Related TEAEs), Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.17.2 : Incidence of IMP-related TEAEs by MedDRA System Organ Class and Preferred Term (Pneumonitis Related TEAEs), Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.18.1 : Incidence of TEAEs by MedDRA System Organ Class and Preferred Term (Rash Maculopapular Related TEAEs), Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.18.2 : Incidence of IMP-related TEAEs by MedDRA System Organ Class and Preferred Term (Rash Maculopapular Related TEAEs), Phase I Part (Dose-escalation Part), Safety Analysis Set

- CT-8.19.1 : Incidence of TEAEs by MedDRA System Organ Class and Preferred Term (Pancreatitis Related TEAEs), Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-8.19.2 : Incidence of IMP-related TEAEs by MedDRA System Organ Class and Preferred Term (Pancreatitis Related TEAEs), Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-9.1 : Listing of Deaths, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-9.2 : Listing of Subjects With Serious Adverse Events Other Than Death, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-9.3 : Listing of Subjects With TEAEs Leading to Discontinuation of Investigational Medicinal Product Administration, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-9.4 : Listing of Dose Limiting Toxicity, Phase I Part (Dose-escalation Part), DLT Analysis Set
- CT-10.1 : Mean Change From Baseline in Clinical Laboratory Test Results - Serum Chemistry -, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-10.2 : Mean Change From Baseline in Clinical Laboratory Test Results - Hematology -, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-10.3 : Mean Change From Baseline in Clinical Laboratory Test Results - Urinalysis -, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-10.4 : Mean Change From Baseline in Clinical Laboratory Test Results - Blood Coagulation Test -, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-10.5 : Shift Tables of Clinical Laboratory Test Results - Serum Chemistry -, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-10.6 : Shift Tables of Clinical Laboratory Test Results - Hematology -, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-10.7 : Shift Tables of Clinical Laboratory Test Results - Urinalysis -, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-10.8 : Shift Tables of Clinical Laboratory Test Results - Blood Coagulation Test -, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-10.9 : Shift Tables of Clinical Laboratory Test Results by CTCAE Grade - Serum Chemistry -, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-10.10 : Shift Tables of Clinical Laboratory Test Results by CTCAE Grade - Hematology -, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-10.11 : Incidence of Clinical Laboratory Test Results with CTCAE Grade 3 or 4 - Serum Chemistry -, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-10.12 : Incidence of Clinical Laboratory Test Results with CTCAE Grade 3 or 4 - Hematology -, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-10.13: Listing of Clinical Laboratory Test Results with CTCAE Grade 3 or 4, Phase I Part (Dose-escalation Part), Safety Analysis Set

- CT-11 : Mean Change From Baseline in Vital Signs, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-12.1.1 : Mean Change From Baseline in Electrocardiogram Results (Local Assessment), Phase I Part (Dose-escalation Part), Safety Analysis Set
- [redacted]
- CT-12.2.1 : Incidence of Categorical Changes in ECG Evaluations (Local Assessment), Phase I Part (Dose-escalation Part), Safety Analysis Set
- [redacted]
- CT-12.3 : Shift Table of ECG Findings, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-13.1 : Shift Table of ECOG Performance Status, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-13.2 : Mean Change From Baseline in Body Weight, Phase I Part (Dose-escalation Part), Safety Analysis Set
- CT-13.3 : Mean Change From Baseline in Left Ventricular Ejection Fraction, Phase I Part (Dose-escalation Part), Safety Analysis Set
- [redacted]
- [redacted]
- PKT-1 : Individual and Summary of Plasma ASTX660 Concentrations Following Oral Administration, Phase I Part (Dose-escalation Part), Pharmacokinetic Analysis Set
- PKT-2 : Individual and Summary of Plasma ASTX660 Pharmacokinetic Parameters Following Oral Administration, Phase I Part (Dose-escalation Part), Pharmacokinetic Analysis Set

- CF-1 : Swimmer Plot of Treatment Response Assessment by Investigator, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CF-2 : Waterfall Plot of Results of Target Lesions, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CF-3 : Kaplan-Meier Plot of Duration of Response by Investigator, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CF-4 : Kaplan-Meier Plot of Progression Free Survival by Investigator, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CF-5 : Kaplan-Meier Plot of Overall Survival, Phase I Part (Dose-escalation Part), Efficacy Analysis Set

- CF-6 : Kaplan-Meier Plot of Time to Response by Investigator, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- CF-7 : Kaplan-Meier Plot of Time to Progression by Investigator, Phase I Part (Dose-escalation Part), Efficacy Analysis Set
- PKF-1.1 : Mean Plasma Concentrations Following Oral Administration, Phase I Part (Dose-escalation Part), Pharmacokinetic Analysis Set
- PKF-1.2 : Median Plasma Concentrations Following Oral Administration, Phase I Part (Dose-escalation Part), Pharmacokinetic Analysis Set
- PKF-2 : Plasma Concentrations Following Oral Administration, Phase I Part (Dose-escalation Part), Pharmacokinetic Analysis Set
- PKF-3.1 : Mean Plasma Concentrations Following Single and Multiple Oral Administration, Phase I Part (Dose-escalation Part), Pharmacokinetic Analysis Set
- PKF-3.2 : Median Plasma Concentrations Following Single and Multiple Oral Administration, Phase I Part (Dose-escalation Part), Pharmacokinetic Analysis Set
- PKF-4 : Individual Plasma Concentrations Following Single and Multiple Oral Administration, Phase I Part (Dose-escalation Part), Pharmacokinetic Analysis Set
- [redacted]
- [redacted]

Appendix 2 List of Subject Data Listings

- DEMOG-1 : Demographics
- DEMOG-2 : Informed Consent
- PDATA-1 : Primary Diagnosis
- PDATA-2 : Primary Diagnosis (PTCL)
- PDATA-3 : Primary Diagnosis (CTCL)
- PDATA-4 : Prior Autologous Hematopoietic Stem Cell Transplantation for Primary Diagnosis
- PDATA-5 : Prior Radiotherapy for Primary Diagnosis
- PDATA-6 : Prior Chemotherapy or Other Therapy for Primary Diagnosis
- PDATA-7 : Medical History
- PDATA-8 : Inclusion and Exclusion Criteria
- PDATA-9 : Screen Failure
- PDATA-10 : Physical Examination
- PDATA-11 : Height and Body Weight
- PDATA-12 : Vital Signs
- PDATA-13 : ECOG PS
- PDATA-14 : ECG Test Results (Local)
- [redacted]
- PDATA-16 : ECHO or MUGA
- LAB-1 : Local Lab Results (Chemistry)
- LAB-2 : Local Lab Results (Hematology)
- [redacted]
- LAB-4 : Local Lab Results (Urinalysis)
- LAB-5 : Pregnancy Test
- LAB-6 : Virus Test
- LAB-7 : Virus Test (HBV-DNA)
- PDATA-17 : Pharmacokinetics
- [redacted]
- [redacted]
- PDATA-21 : Chest X-Ray
- PDATA-22 : Lung Field Evaluation by CT Scan
- EFF-1 : Tumor Identification/Results of Target Lesions
- EFF-2 : Tumor Identification/Results of Non-Target Lesions
- EFF-3 : Bone Marrow Aspiration/Biopsy

- EFF-4 : CT Scan (CTCL)
- EFF-5 : mSWAT
- EFF-6 : Disease Response (PTCL)
- EFF-7 : Disease Response (CTCL)
- DREAS-1 : Listing of Discontinued Subjects
- AE-1 : Adverse Events
- PDATA-23 : Concomitant Medications
- PDATA-24 : Concomitant Therapy
- PDEV-1 : Protocol Deviation
- EFF-8 : Best Overall Response
- EFF-9 : Duration of Response
- EFF-10 : Progression Free Survival
- EFF-11 : Overall Survival
- EFF-12 : Time to Response
- EFF-13 : Time to Progression
- [redacted]
- PDATA-25 : Post-treatment Therapy for Primary Diagnosis
- PDATA-26 : Progressive Disease After End of Study Treatment
- PDATA-27 : Survival Follow-up
- PDATA-28 : End of Study
- SMED-1 : Exposure
- SMED-2 : Investigational Medicinal Product Compliance
- SUBEX-1 : Subjects Excluded From Analysis Population