CLINICAL STUDY PROTOCOL

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

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Otsuka Pharmaceutical Co., Ltd.

Investigational Medicinal Product

ASTX660

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A Phase 1/2 Trial of ASTX660 in Patients with Relapsed/Refractory T-cell Lymphoma

Protocol No. 401-102-00001

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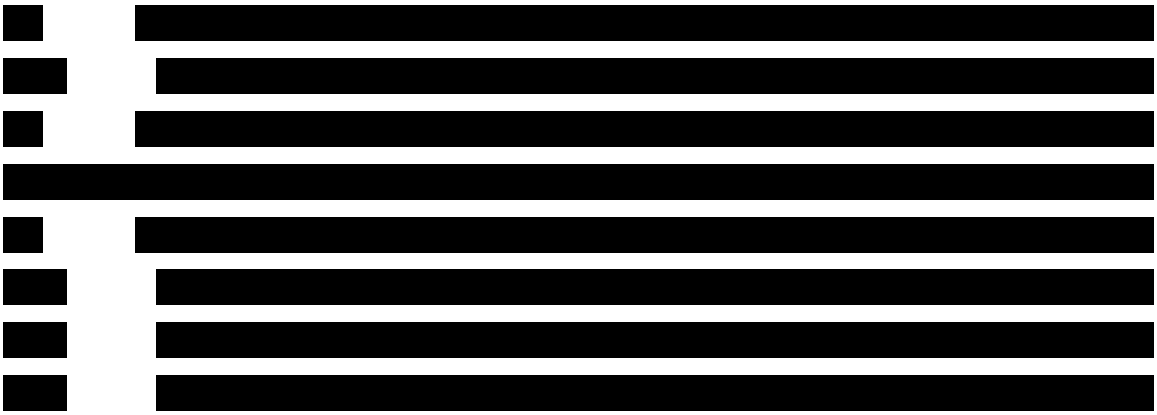

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1 Protocol Summary

1.1 Synopsis

Name of Sponsor:

Otsuka Pharmaceutical Co., Ltd.

Name of Investigational Medicinal Product:

ASTX660

Protocol No.:

401-102-00001

Protocol Title:

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

Protocol Lay Person Short Title:

A phase 1/2 trial of ASTX660 in patients with relapsed/refractory T-cell lymphoma

Clinical Phase/Trial Type:

Phase 1/2 trial/clinical pharmacology trial

Treatment/Indication:

Patients with relapsed/refractory peripheral T-cell lymphoma (r/r PTCL), patients with relapsed/refractory cutaneous T-cell lymphoma (r/r CTCL), and patients with relapsed/refractory adult T-cell leukemia/lymphoma (r/r ATLL)

Objectives and Endpoints:

Primary Objectives:

Phase 1 (dose escalation part): To evaluate the tolerability and safety of ASTX660 in patients with r/r PTCL and patients with 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 r/r ATLL

Phase 2: To evaluate the efficacy of ASTX660 at the RD in patients with r/r PTCL

Secondary Objectives:

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

[redacted]

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 left ventricular ejection fraction (LVEF)

Phase 1 (ATLL expansion part): Safety (AEs, clinical laboratory values, vital signs, body weight, ECOG PS, 12-lead ECGs, and 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) proposed by the International Working Group (IWG).

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]

Trial Design:

Multicenter, open-label, uncontrolled

Trial Population:

The following male or female patients, 20 years of age or older, will be enrolled: a maximum of 18 patients with r/r PTCL or r/r CTCL combined (3 to 6 subjects/cohort) in phase 1 (dose escalation part); 6 to 10 patients with r/r ATLL in phase 1 (ATLL expansion part); and 33 patients with r/r PTCL as efficacy-evaluable subjects in phase 2.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

1) Patients 20 years of age or older at the time of informed consent and who provide written consent to participate in the trial using the informed consent form approved by the institutional review board.
2) Patients with T-cell lymphoma with a histopathologic diagnosis of any of the following based on the World Health Organization (WHO) Classification (2017):

<Peripheral T-cell lymphoma>: Phase 1 (dose escalation part) and phase 2

For the purpose of this trial, peripheral T-cell lymphoma is defined as mature T- or natural killer (NK) cell neoplasms listed in the WHO Classification that fall under any of the following subtypes (for phase 2, submission of specimens is required for central pathological diagnosis):

- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Peripheral T-cell lymphoma, not otherwise specified (NOS)
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma
- Nodal peripheral T-cell lymphoma with T-follicular helper cells phenotype
- Anaplastic large cell lymphoma, anaplastic lymphoma kinase (ALK) positive
- Anaplastic large cell lymphoma, ALK negative

<Cutaneous T-cell lymphoma>: Phase 1 (dose escalation part)

For the purpose of this trial, cutaneous T-cell lymphoma is defined as mature T- or NK cell neoplasms listed in the WHO Classification that fall under any of the following subtypes:

- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
- Primary cutaneous peripheral T-cell lymphoma, rare subtypes

<Adult T-cell leukemia/lymphoma>: Phase 1 (ATLL expansion part)

Patients with a diagnosis of ATLL classified into acute, lymphoma, or chronic type with unfavorable prognostic factors who are positive for serum anti-human T-cell leukemia virus type 1 antibody.

3) Patients who previously received systemic antineoplastics to treat the primary disease as indicated below.

<Peripheral T-cell lymphoma>: Phase 1 (dose escalation part)

Relapsed or refractory patients who previously received at least 1 regimen of antineoplastics (oral corticosteroid monotherapy is not included in this category). Patients with CD30-positive anaplastic large cell lymphoma must have a history of treatment with brentuximab vedotin.[a]

<Peripheral T-cell lymphoma>: Phase 2

Relapsed or refractory patients who previously received at least 2 regimens of antineoplastics (oral corticosteroid monotherapy is not included in this category). Patients with CD30-positive anaplastic large cell lymphoma must have a history of treatment with brentuximab vedotin.[a]

<Cutaneous T-cell lymphoma>

Relapsed or refractory patients who previously received at least 1 regimen of systemic antineoplastics (oral corticosteroid monotherapy is not included in this category). Patients with mycosis fungoides or Sézary syndrome must have a history of treatment with mogamulizumab.[a]

<Adult T-cell leukemia/lymphoma>

Relapsed or refractory patients who previously received at least 1 regimen of antineoplastics. Patients who are positive for CCR4 must have a history of treatment with mogamulizumab.[a]

[a]This criterion does not apply to patients for whom treatment has been judged to be inappropriate or those who refused to receive the treatment.

4) Patients with the following lesion(s) at screening:

<Peripheral T-cell lymphoma>: Phase 1 (dose escalation part)

Swollen lymph nodes or extranodal lesions identified by positron emission tomography-computed tomography (PET-CT) or computed tomography (CT) during screening or within 28 days prior to the first dose of trial treatment.

<Peripheral T-cell lymphoma>: Phase 2

Swollen lymph nodes or extranodal lesions measurable in 2 perpendicular diameters by CT scan during screening or within 28 days prior to the first dose of trial treatment, with the longest diameter exceeding 1.5 cm (swollen lymph nodes) or 1.0 cm (extranodal lesions).

<Cutaneous T-cell lymphoma>

Lesions that can be considered skin lesions during screening.

<Adult T-cell leukemia/lymphoma>

At least one of measurable lesions identified by CT scan during screening or within 28 days prior to the first dose of trial treatment or skin lesions identified during screening.

5) Patients with an ECOG PS score of 0 or 1. For phase 2, patients with a PS score of 2 are eligible to be enrolled in the trial only if their physical activities are restricted by symptoms associated with the primary disease such as accumulation of pleural or ascitic fluid.
6) Patients with acceptable organ function as indicated below.

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.0 × institutional upper limit of normal (ULN) (≤ 3.0 × institutional ULN for subjects with hepatic involvement).
- Total bilirubin ≤ 1.5 × institutional ULN.
- Absolute neutrophil count (ANC) ≥ 1,000/mm^3 (≥ 750/mm^3 for subjects with bone marrow involvement) (Administration of granulocyte colony-stimulating factor [G-CSF] within 14 days prior to the test is not allowed).
- Platelet count ≥ 50,000/mm^3 (≥ 25,000/mm^3 for subjects with bone marrow involvement) (Platelet transfusion within 14 days prior to the test is not allowed).
- Serum creatinine ≤ 1.5 × institutional ULN or creatinine clearance (calculated by Cockcroft & Gault formula) ≥ 50 mL/min.
- Amylase and lipase ≤ 1.0 × institutional ULN.

7) Patients who are able to orally receive the investigational medicinal product (IMP).
8) Patients who are expected to live for at least 3 months.
9) Fertile, sexually active male patients (excluding those who have had a bilateral orchiectomy) or sexually active female patients of childbearing potential, who agree to practice 2 different contraceptive measures during the trial and for 3 months after the last dose of IMP. If birth control is employed, 2 of the following methods must be used: vasectomy, tubal ligation, intrauterine device, oral contraceptive, and condom (all methods approved or certified in Japan).

Exclusion Criteria:

All phase 1 and 2 of the trial

1) Patients with hypersensitivity to ASTX660 or excipients of the drug product.
2) Patients with active infection(s) requiring antibacterial, antifungal, or antiviral therapies.
3) Patients with cardiac disease that meets any of the following criteria:

a) Left ventricular ejection fraction (LVEF) < 50% by echocardiography or multiple-gated acquisition (MUGA) scan.
b) Congestive cardiac failure (Grade 3 or 4 according to New York Heart Association [NYHA] functional classification).
c) Inadequately controlled cardiac disease including unstable angina or hypertension requiring hospitalization within the past 3 months (90 days).
d) History or presence of complete left bundle branch block, third-degree (complete) atrioventricular block, cardiac pacemaker, or inadequately controlled arrhythmia requiring treatment.
e) History or presence of long QT syndrome.
f) History or presence of ventricular arrhythmia requiring aggressive treatment.
g) Screening 12-lead ECG with QTc interval of ≥ 470 msec.
h) Any other condition that is medically considered to have the potential to put the subject at increased cardiac risk.

4) Patients who are positive for human immunodeficiency virus (HIV) antibody, hepatitis B virus (HBV)-deoxyribonucleic acid (DNA), or hepatitis C virus (HCV) antibody.
5) Patients with Grade 2 or greater neuropathy.
6) Patients with significant mental illness or other condition (alcohol or other substance abuse/addiction) that, in the opinion of the investigator or subinvestigator, predisposes the subject to high risk of noncompliance with the protocol.
7) Patients who received any of the following treatments for the primary disease prior to the first dose of trial treatment:
   a) Chemotherapy or radiotherapy within 3 weeks (6 weeks if nitrosoureas) prior to trial treatment.
   b) Skin directed therapy including topicals or radiation within 3 weeks prior to trial treatment.
   c) Monoclonal antibody therapy within 4 weeks prior to trial treatment.
   d) Other investigational drugs (small molecules or biologics) or investigational therapies (including cell-based therapies such as chimeric antigen receptor [CAR] T-cell therapy) within the longer of 3 weeks or 5 half-lives prior to trial treatment.
8) Patients with adverse reactions (except for alopecia) to the prior treatment that has not resolved to Grade 2.
9) Patients with concurrent malignancies, except appropriately treated squamous carcinoma or basal cell carcinoma of skin or carcinoma in situ of uterine cervix, breast or prostate cancer stable on endocrine therapy, and other previous cancers that have not relapsed for at least 5 years.
10) Patients with central nervous system involvement of lymphoma.

11) Patients with a history of allogenic hematopoietic stem cell transplantation, or those who underwent autologous stem cell transplantation within 14 weeks prior to the first dose of trial treatment.
12) Patients who received corticosteroids > 10 mg/day prednisone equivalent within 3 weeks prior to the first dose of trial treatment. However, patients without tumor decrease on stable corticosteroid therapy at low doses (≤ 10 mg/day prednisone equivalent) for more than 3 weeks prior to the first dose of trial treatment can be included. In that case, the corticosteroid therapy can be continued without dose increase until trial treatment is discontinued.
13) Patients with a history of gastrectomy.
14) Patients with a history or presence of pneumonitis (interstitial pneumonia) or pulmonary fibrosis. If screening CT scan suggests abnormal shadow of the pulmonary interstitium (eg, bilateral ground glass opacity), the investigator or subinvestigator should consult with a pulmonologist or a radiologist, as needed, to determine whether the patient has pneumonitis (interstitial pneumonia) or pulmonary fibrosis.
15) Patients with inadequately controlled diabetes mellitus.
16) Pregnant or nursing female patients or female patients with a positive pregnancy test at screening. Nursing patients cannot participate in the trial even if they discontinue breastfeeding. Female patients must undergo a pregnancy test to confirm that they are not pregnant at screening. However, a pregnancy test is not necessary for female patients without childbearing potential (ie, patients with a history of bilateral oophorectomy or hysterectomy or who have been postmenopausal for at least 12 months except for cases where menopause could be due to the effect of antineoplastic treatment).
17) Patients who, in the opinion of the investigator or subinvestigator, are otherwise ineligible to participate in the trial.

Trial Site(s):

Approximately 25 trial sites in Japan

Investigational Medicinal Product(s), Dose, Dosage Regimen, Treatment Duration, Formulation, Mode of Administration:

Investigational medicinal product and formulations:

ASTX660 capsules 30 mg and 90 mg (1 capsule contains 30 or 90 mg of ASTX660)

Dose, dosage regimen, and mode of administration:

Trial treatment will be conducted in repeated 28-day cycles comprising 7 days of 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 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 use the RD determined based on the results of phase 1 (dose escalation part).

Treatment duration:

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

Trial Assessments:

Assessments for Efficacy: Hematology, CT scan (PTCL subjects, CTCL subjects, and ATLL subjects), PET-CT scan (PTCL subjects), bone marrow aspiration or biopsy (PTCL subjects and ATLL subjects), modified severity weighted assessment tool (mSWAT) assessment (CTCL subjects), response review, investigation of new treatment for the primary disease, investigation of disease progression, and investigation of survival status

Assessments for Pharmacokinetics and [redacted]: Blood sampling for plasma drug concentrations and [redacted]

Assessments for Safety: AEs, clinical laboratory tests, vital signs, body weight, ECOG PS, 12-lead ECG (local), echocardiography, and lung field assessment by PET-CT and CT scans

[redacted]

Screening/Other: Subject demographics (prior treatment, disease stage [Lugano classification will be used for PTCL and ATLL and TNMB classification of mycosis fungoides and Sézary syndrome will be used for CTCL], and International Prognostic Index [IPI] [PTCL and ATLL]), medical history, viral tests, pregnancy test, and height

Efficacy and Safety Data Review Committee:

The Efficacy and Safety Data Review Committee will consist of individuals who are independent of the parties involved in the trial (eg, sponsor, medical expert, investigators, and subinvestigators) and are not directly involved in the trial. The committee will review the trial-related safety, serious or unexpected AEs, and efficacy from a third party standpoint, and will make recommendations, based on the obtained results of assessment, regarding the conduct and results of the trial, including continuation, modification, or discontinuation of the trial. For phase 1 (dose escalation part), the committee will also make recommendations about DLT assessment, dose, and whether to advance to phase 2. For phase 2, the committee will also serve as the Central Efficacy Evaluation Committee.

Statistical Methods:

For phase 2 efficacy analysis set, the ORR as assessed by the Central Efficacy Evaluation Committee and its two-sided 95% confidence interval (by Clopper-Pearson method) will be calculated and the frequency of the best overall response as assessed by the Central Efficacy Evaluation Committee will be summarized.

Trial Duration:

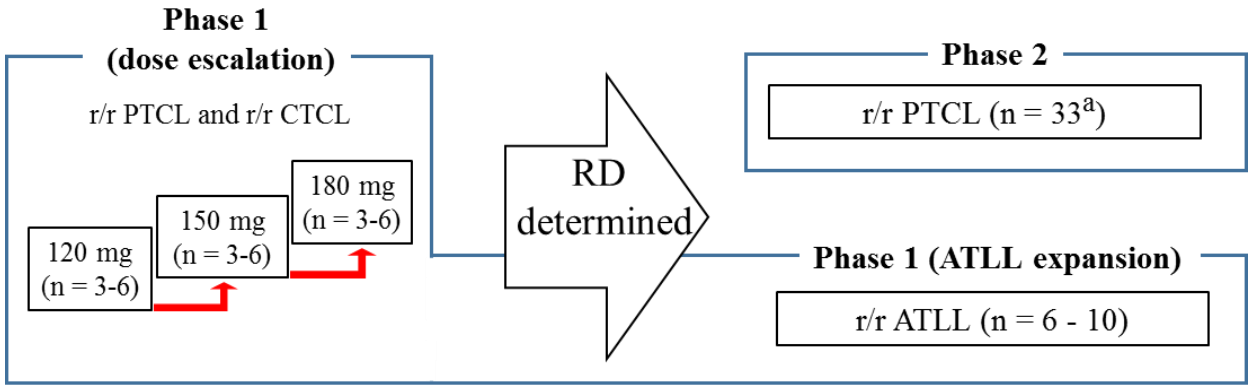
Each subject in this trial is expected to participate in the following periods of the trial (approximate durations listed):

- Screening period: Days −21 to −1
- IMP treatment period: Trial treatment can be continued until the withdrawal criteria are met.
- Follow-up period: 30 days after trial treatment discontinuation or the start of new treatment for the primary disease, whichever comes first.
- Investigation of survival status: Every 3 months following the end of the follow-up period.

Overall, the trial duration from signing of the first informed consent form to the final subject assessment is expected to be approximately 4 years and 6 months, including phase 1 (dose escalation part), phase 1 (ATLL expansion part), and phase 2.

1.2 Schema

Figure 1.2-1 Trial Design Schematic



[a]Phase 2 will enroll 33 subjects as efficacy-evaluable subjects.

1.3 Schedule of Assessments

Table 1.3-1 Schedule of Assessments, Phase 1 (Dose Escalation Part), Cycles 1 and 2

		Cycle 1											Cycle 2				
Week		**Week 1**				**Week 2**			**Week 3**			**Week 4**	**Week 1**		**Week 3**		**Week 4**
Cycle Day		1[a]	2	3	7	8	9	10	15	16	21	22	1[b]	7	15	21	22
Allowable Window[c]		-	-	-	-	-	-	-	-	-	-	-	-4	-	-2	-	±7
IMP administration[d]		←	—	—	→				←	—	→		←	—	→		
Hospitalization[e]		←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Trial Procedure	**Screening Period (D-21 to D-1)**																
Informed consent[f]	X												X				
Demographics	X																
Viral tests[g]	X												X				
Eligibility assessment	X																
Physical examination	X	X											X				
Height	X																
Body weight	X	X											X				
Vital signs (blood pressure, pulse rate, SpO_2, body temperature)	X	←	—	—	→				←	—	→		X		X		
Performance status (ECOG PS)	X												X				
12-Lead ECG (local)[h]	X								X		X		X				
[redacted]																	
Echocardiography or MUGA scan[i]	X																
AEs	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Concomitant medications/therapies	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Hematology[k]	X	X				X			X				X		X		
Serum chemistry[k,l]	X	X	X	X	X	X			X			X	X		X		
Urinalysis[k]	X	X							X				X		X		
Pregnancy test[m]	X												X				
[redacted]																	
Blood sampling for PK analysis[o]		X	X		X	X	X	X	X	X	X	X	X				
[redacted]																	
CT scan (PTCL subjects, CTCL subjects)[r]	X																X[r]
PET-CT scan (PTCL subjects)[s]	X																X[s]
Lung field assessment on CT images[t]	X																X[t]
Identification of lesions	X																
Bone marrow aspiration or biopsy (PTCL subjects)[u]	X																X[u]
mSWAT assessment (CTCL subjects)[v]	X																X[v]
Response review[w]																	X[w]
Chest X ray[x]		X											X				

SpO_2 = percutaneous oxygen saturation.

[a]Each scheduled test/assessment will be performed prior to IMP administration. Physical examination, body weight, hematology, serum chemistry, urinalysis, and chest X ray can be omitted on Cycle 1 Day 1 if they were performed within 4 days before Cycle 1 Day 1.

[b]Each test/assessment will be performed prior to IMP administration. Physical examination, body weight, 12-lead ECG (local), hematology, serum chemistry, urinalysis, and pregnancy test can be omitted on Cycle 2 Day 1 if they were performed within 4 days before Cycle 2 Day 1.

[c]This allowable window is only for tests, observations, and assessments. The IMP must be administered on the scheduled days.

[d]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 scheduled examinations. Subjects will fast for 2 hours before and 2 hours after IMP administration. 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.

[e]Subjects will be hospitalized during Cycle 1.

[f]Written informed consent will be obtained from potential subjects themselves prior to all trial-related procedures. Subjects who wish to continue their participation in Cycle 2 onward will provide additional written informed consent, no earlier than Cycle 1 Day 22 and prior to the start of Cycle 2, to continue participation.

[g]Subjects will undergo viral tests (HBV-DNA quantification) from Cycle 2 onward only if they tested positive for HBc or HBs antibody at screening.

[h]12-Lead ECGs (local) will be performed at screening, predose and 2 hours postdose on Day 15 and Day 21 of Cycle 1, and from Cycle 2 Day 1 onward, predose on Day 1 of each cycle.

[redacted]

[j]Echocardiography or MUGA scan will be performed at screening, on Cycle 3 Day 1 (within −7 days), and thereafter, Day 1 (within −7 days) of each odd-numbered cycle.

[k]See Table 10.2-1 Clinical Laboratory Assessments for test items.

[l]KL-6 will be measured at screening and from Cycle 1 Day 1 onward, predose on Day 1 of each cycle.

[m]For females of childbearing potential (FOCBP) only.

[redacted]

[o]See Table 8.2.1-1 for the timing of blood sampling.

[redacted]

[r]CT scan will be performed at screening, Week 4 of Cycles 2, 4, and 6, and thereafter, Week 4 of every 3 cycles (Cycles 9, 12, 15…). The allowable window for Cycle ≥ 2 is ±7 days. Scan results obtained within 28 days before Cycle 1 Day 1 can be used as screening results if the subject agrees.

[s]PET-CT scan will be performed at screening and thereafter, at the earliest possible timing after complete response (CR) is confirmed by CT scan for efficacy evaluation. Scan results obtained within 28 days before Cycle 1 Day 1 can be used if the subject agrees.

[t]Lung field on CT images by PET-CT or CT scan will be reviewed for safety evaluation.

[u]Bone marrow aspiration or biopsy will be performed at screening and thereafter, as needed, such as when confirming CR at the time of efficacy evaluation. Results obtained within 28 days before Cycle 1 Day 1 can be used if the subject agrees.

[v]Skin lesions will be assessed using an mSWAT at screening, Week 4 of Cycles 2, 4, and 6, and thereafter, Week 4 of every 3 cycles (Cycles 9, 12, 15…). The allowable window is ±7 days.

[w]For PTCL, assessment is based on Lugano response criteria for non-Hodgkin lymphoma (2014)[1] by the IWG, and for CTCL, assessment is based on mSWAT.

[x]If the lung field was assessed on CT images within 7 days, its results can substitute for chest X ray.

Table 1.3-2 Schedule of Assessments, Phase 1 (Dose Escalation Part), From Cycle 3 Onward, Withdrawal Examination, Follow-up Period, Investigation of Survival Status

	Cycle 3				Cycles 4–6					Cycle ≥7					Withdrawal Examination[a]	Follow-up Period[b]	Survival Status
Week	1		3		1		3		4	1		3		4	Within 7 days after discontinuation	Within 30 days after last dose of treatment	Every 3 months
Cycle Day	1[c]	7	15	21	1[c]	7	15	21	22	1[c]	7	15	21	22			
Allowable Window[d]	-4	-	-4	-	-4	-	-4	-	±7	-4	-	-4	-	±7		+14	±14
IMP administration[e]	←	→	←	→	←	→	←	→		←	→	←	→				
Trial Procedure																	
Viral tests[f]	X				X					X					X		
Physical examination	X				X					X					X	X	
Body weight	X				X					X							
Vital signs (blood pressure, pulse rate, SpO_2, body temperature)	X		X		X		X			X		X			X	X	
Performance status (ECOG PS)	X				X										X	X	
12-Lead ECG (local)	X				X					X					X	X	
Echocardiography or MUGA scan[g]	X[g]				X[g]					X[g]					X		
AEs	←															→	
Concomitant medications/therapies	←															→	
Hematology[h]	X		X		X		X			X		X			X	X	
Serum chemistry[h,i]	X		X		X		X			X		X			X	X	
Urinalysis[h]	X		X		X		X			X		X			X		
Pregnancy test[j]	X				X					X					X		
CT scan (PTCL subjects, CTCL subjects)[k]									X[k]					X[k]	X		
PET-CT scan (PTCL subjects)[l]									X[l]					X[l]			
Lung field assessment on CT images[m]									X[m]					X[m]	X		
Bone marrow aspiration or biopsy (PTCL subjects)[n]									X[n]					X[n]	X[n]		
mSWAT assessment (CTCL subjects)[o]									X[o]					X[o]	X		
Response review[p]									X					X	X		
Chest X ray[q]	X				X					X							
Investigation of new treatment for the primary disease[r]																	X
Investigation of disease progression[s]																	X
Investigation of survival status[t]																	X

[a]Withdrawal examination will be performed within 7 days after trial treatment discontinuation is determined. Efficacy endpoints will be evaluated in consideration of the subject's general condition.

[b]The scheduled tests/assessments will be performed 30 days after trial treatment discontinuation or just before new treatment for the primary disease begins, whichever comes first. If withdrawal examination or scheduled tests/assessments were performed within 7 days, repeated tests/assessments can be omitted, and information on AEs and concomitant medications/therapies will be collected.

[c]Each test/assessment will be performed prior to IMP administration. Scheduled tests/assessments can be omitted on Day 1 if they were performed within 4 days before Day 1.

[d]This allowable window is only for tests, observations, and assessments. The IMP must be administered on the scheduled days.

[e]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 scheduled examinations. Subjects will fast for 2 hours before and 2 hours after IMP administration. 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.

[f]Subjects will undergo viral tests (HBV-DNA quantification) from Cycle 2 onward only if they tested positive for HBc or HBs antibody at screening.

[g]Echocardiography or MUGA scan will be performed at screening, on Cycle 3 Day 1 (within −7 days), and thereafter, Day 1 (within −7 days) of each odd-numbered cycle.

[h]See Table 10.2-1 Clinical Laboratory Assessments for test items.

[i]KL-6 will be measured at screening and from Cycle 1 Day 1 onward, predose on Day 1 of each cycle.

[j]For FOCBP only.

[k]CT scan will be performed at screening, Week 4 of Cycles 2, 4, and 6, and thereafter, Week 4 of every 3 cycles (Cycles 9, 12, 15…). The allowable window for Cycle ≥ 2 is ±7 days. Scan results obtained within 28 days before Cycle 1 Day 1 can be used if the subject agrees.

[l]PET-CT scan will be performed at screening and thereafter, at the earliest possible timing after CR is confirmed by CT scan for efficacy evaluation. Scan results obtained within 28 days before Cycle 1 Day 1 can be used if the subject agrees.

[m]Lung field on CT images by PET-CT or CT scan will be reviewed for safety evaluation.

[n]Bone marrow aspiration or biopsy will be performed at screening and thereafter, as needed, such as when confirming CR at the time of efficacy evaluation. Results obtained within 28 days before Cycle 1 Day 1 can be used if the subject agrees.

[o]Skin lesions will be assessed using an mSWAT at Week 4 of Cycles 2, 4, and 6 and thereafter, Week 4 of every 3 cycles (Cycles 9, 12, 15…). The allowable window is ±7 days.

[p]For PTCL, assessment is based on Lugano response criteria for non-Hodgkin lymphoma (2014)[1] by the IWG, and for CTCL, assessment is based on mSWAT.

[q]If the lung field was assessed on CT images within 7 days, its results can substitute for chest X ray.

[r]Investigation will be performed every 3 months following the end of the follow-up period. Only for subjects who have no disease progression at trial discontinuation, the investigation will be performed after trial discontinuation until the start of new treatment or the end of the trial. For subjects whose new

treatment for the primary disease is being investigated at the date of approval of protocol amendment 4, the investigation will be completed after the final investigation has been conducted, and for subjects receiving trial treatment at that time, the investigation will be performed and completed following the end of the follow-up period.

[s]Investigation will be performed every 3 months following the end of the follow-up period. Only for subjects who have no disease progression at trial discontinuation, progression of the primary disease will be investigated after trial discontinuation until disease progression (including the start of new treatment) or the end of the trial. For subjects whose disease progression is being investigated at the date of approval of protocol amendment 4, the investigation will be completed after the final investigation has been conducted, and for subjects receiving trial treatment at that time, the investigation will be performed and completed following the end of the follow-up period.

[t]Investigation will be performed every 3 months following the end of the follow-up period. For subjects whose survival status is being investigated at the date of approval of protocol amendment 4, the investigation of survival status will be completed after the final investigation has been conducted, and for subjects receiving trial treatment at that time, the investigation will be performed and completed following the end of the follow-up period.

Table 1.3-3 Schedule of Assessments, Phase 1 (ATLL Expansion Part)

		Cycle 1											Cycle 2					Cycle ≥3					Withdrawal Examination	Follow-up Period[c]	Survival Status
Week		**Week 1**				**Week 2**			**Week 3**			**Week 4**	**Week 1**		**Week 3**		**Week 4**	**Week 1**		**Week 3**		**Week 4**	**Within 7 days after discontin-uation[b]**	Within 30 days after last dose of treatment	Every 3 months
Cycle Day		**1[a]**	**2**	**3**	**7**	**8**	**9**	**10**	**15**	**16**	**21**	**22**	**1[a]**	**7**	**15**	**21**	**22**	**1[a]**	**7**	**15**	**21**	**22**			
Allowable Window[d]		-	-	-	-	-	-	-	-	-	-	-	**-4**	-	**-4**	-	**±7**	**-4**	-	**-4**	-	**±7**		+14	±14
IMP administration[e]		←	—	—	→				←	—	→		←	→	←	→		←	→	←	→				
Hospitalization[f]		→																							
Trial Procedure	**Screening Period (D-21 to D-1)**																								
Informed consent	X																								
Demographics	X																								
Viral tests[g]	X												X					X					X		
Eligibility assessment	X																								
Physical examination	X	X											X					X					X	X	
Height	X																								
Body weight	X	X											X					X							
Vital signs (blood pressure, pulse rate, SpO_2, body temperature)	X	X							X				X		X			X		X			X	X	
Performance status (ECOG PS)	X	X											X					X					X	X	
12-Lead ECG (local)[h]	X	X			X				X		X		X					X					X	X	
Echocardiography or MUGA scan[i]	X																	X[i]					X		
AEs	←	—	—	—	→																			→	
Concomitant medications/therapies	←	—	—	—	→																			→	
Hematology[j]	X	X							X			X	X		X			X		X			X	X	
Serum chemistry[j,k]	X	X			X				X			X	X		X			X		X			X	X	
Urinalysis[j]	X	X							X			X	X		X			X		X			X		
Pregnancy test[l]	X												X					X					X		
Blood sampling for PK analysis[m]		X	X		X	X	X	X	X	X	X	X	X													
CT scan[o]	X																X^o					X^o	X		
Lung field assessment on CT images[p]	X																X^p					X^p	X		
Identification of lesions	X																								
Bone marrow aspiration or biopsy[q]	X^q																X^q					X^q	X^q		
Response review[r]																	X^r					X^r	X		
Chest X ray[s]		X											X					X							
Investigation of new treatment for the primary disease[t]																									X
Investigation of disease progression[u]																									X
Investigation of survival status[v]																									X

[a]Each test/assessment will be performed prior to IMP administration. Scheduled tests/assessments can be omitted on Day 1 if they were performed within 4 days before Cycle 1 Day 1 and from Cycle 2 onward, within 4 days before Day 1 of the relevant cycle.

[b]Withdrawal examination will be performed within 7 days after trial treatment discontinuation is determined. Efficacy endpoints will be evaluated in consideration of the subject's general condition.

[c]The scheduled tests/assessments will be performed 30 days after trial treatment discontinuation or just before new treatment for the primary disease begins, whichever comes first. If withdrawal examination or scheduled tests/assessments were performed within 7 days, repeated tests/assessments can be omitted, and information on AEs and concomitant medications/therapies will be collected.

[d]This allowable window is only for tests, observations, and assessments. The IMP must be administered on the scheduled days.

[e]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 scheduled examinations. Subjects will fast for 2 hours before and 2 hours after IMP administration. 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.

[f]Subjects will be hospitalized during Cycle 1.

[g]Subjects will undergo viral tests (HBV-DNA quantification) from Cycle 2 onward only if they tested positive for HBc or HBs antibody at screening.

[h]12-Lead ECGs (local) will be performed at screening, predose and 2 hours postdose on Day 1, Day 7, Day 15, and Day 21 of Cycle 1, and from Cycle 2 Day 1 onward, predose on Day 1 of each cycle. 12-Lead ECG on Cycle 1 Day 1 must not be omitted even if it was performed within 4 days.

[i]Echocardiography or MUGA scan will be performed at screening, on Cycle 3 Day 1 (within −7 days), and thereafter, Day 1 (within −7 days) of each odd-numbered cycle.

[j]See Table 10.2-1 Clinical Laboratory Assessments for test items.

[k]KL-6 will be measured at screening and from Cycle 1 Day 1 onward, predose on Day 1 of each cycle.

[l]For FOCBP only.

[m]See Table 8.2.1-1 for the timing of blood sampling.

[redacted]

[o]CT scan will be performed at screening, Week 4 of Cycles 2, 4, and 6, and thereafter, Week 4 of every 3 cycles (Cycles 9, 12, 15…). The allowable window for Cycle ≥ 2 is ±7 days. Scan results obtained within 28 days before Cycle 1 Day 1 can be used if the subject agrees.

[p]Lung field on CT images by CT scan will be reviewed for safety evaluation.

[q]Bone marrow aspiration or biopsy will be performed at screening and thereafter, as needed, such as when confirming CR at the time of efficacy evaluation. Bone marrow involvement identified during prior treatment of the primary disease can be used as screening results only if the subject agrees.

[r]Assessment is based on the Japan Clinical Oncology Group (JCOG) response criteria for ATLL (2009).

[s]If the lung field was assessed on CT images within 7 days, its results can substitute for chest X ray.

[t]Investigation will be performed every 3 months following the end of the follow-up period. Only for subjects who have no disease progression at trial discontinuation, investigation will be performed after trial discontinuation until the start of new treatment or the end of the trial.

[u]Investigation will be performed every 3 months following the end of the follow-up period. Only for subjects who have no disease progression at trial discontinuation, progression of the primary disease will be investigated after trial discontinuation until disease progression (including the start of new treatment) or the end of the trial.

[v]Investigation will be performed every 3 months following the end of the follow-up period.

Table 1.3-4 Schedule of Assessments, Phase 2

		Cycle 1						Cycle 2					Cycle ≥3					Withdrawal Examination	Follow-up period[c]	Survival status
Week		Week 1		Week 2	Week 3		Week 4	Week 1		Week 3		Week 4	Week 1		Week 3		Week 4	Within 7 days after discontinuation[b]	Within 30 days after last dose of treatment	Every 3 months
Cycle Day		1[a]	7	8	15	21	22	1[a]	7	15	21	22	1[a]	7	15	21	22			
Allowable Window[d]		-	-	-	-4	-	-	-4	-	-4	-	±7	-4	-	-4	-	±7		+14	±14
IMP administration[e]		←	→		←	→		←	→	←	→		←	→	←	→				
Hospitalization[f]		→																		
Trial Procedure	**Screening Period (D-21 to D-1)**																			
Informed consent	X																			
Demographics	X																			
Viral tests[g]	X							X					X					X		
Eligibility assessment	X																			
Physical examination	X	X						X					X					X	X	
Height	X																			
Body weight	X	X						X					X							
Vital signs (blood pressure, pulse rate, SpO_2, body temperature)	X	X			X			X		X			X		X			X	X	
Performance status (ECOG PS)	X	X						X					X					X	X	
12-Lead ECG (local)[h]	X		X					X					X					X	X	
Echocardiography or MUGA scan[i]	X												X[i]					X		
AEs	←																		→	
Concomitant medications/therapies	←																		→	
Hematology[j]	X	X			X		X	X		X			X		X			X	X	
Serum chemistry[j,k]	X	X	X		X		X	X		X			X		X			X	X	
Urinalysis[j]	X	X			X		X	X		X			X		X			X		
Pregnancy test[l]	X							X					X					X		
Blood sampling for PK analysis[m]		X	X	X		X	X													
[redacted]																				
Submission of samples for central pathological diagnosis[o]	X																			
CT scan[p]	X											X[p]					X[p]	X		
PET-CT scan[q]	X											X[q]					X[q]			
Lung field assessment on CT images[r]	X											X[r]					X[r]	X		
Identification of lesions	X																			
Bone marrow aspiration or biopsy[s]	X											X[s]					X[s]	X[s]		
Response review[t]												X[t]					X[t]	X		
Chest X ray[u]		X						X					X							
Investigation of new treatment for the primary disease[v]																				X
Investigation of disease progression[w]																				X
Investigation of survival status[x]																				X

[a]Each test/assessment will be performed prior to IMP administration. Scheduled tests/assessments can be omitted on Day 1 if they were performed within 4 days before Cycle 1 Day 1 and from Cycle 2 onward, within 4 days before Day 1 of the relevant cycle.

[b]Withdrawal examination will be performed within 7 days after trial treatment discontinuation is determined. Efficacy endpoints will be evaluated in consideration of the subject's general condition.

[c]The scheduled tests/assessments will be performed 30 days after trial treatment discontinuation or just before new treatment for the primary disease begins, whichever comes first. If withdrawal examination or scheduled tests/assessments were performed within 7 days, repeated tests/assessments can be omitted, and information on AEs and concomitant medications/therapies will be collected.

[d]This allowable window is only for tests, observations, and assessments. The IMP must be administered on the scheduled days.

[e]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 scheduled examinations. Subjects will fast for 2 hours before and 2 hours after IMP administration. 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.

[f]Subjects will be hospitalized from Cycle 1 Day 1 through Cycle 1 Day 7.

[g]Subjects will undergo viral tests (HBV-DNA quantification) from Cycle 2 onward only if they tested positive for HBc or HBs antibody at screening.

[h]12-Lead ECGs (local) will be performed at screening, predose and 2 hours postdose on Cycle 1 Day 7, and from Cycle 2 Day 1 onward, predose on Day 1 of each cycle.

[i]Echocardiography or MUGA scan will be performed at screening, on Cycle 3 Day 1 (within −7 days), and thereafter, Day 1 (within −7 days) of each odd-numbered cycle.

[j]See Table 10.2-1 Clinical Laboratory Assessments for test items.

[k]KL-6 will be measured at screening and from Cycle 1 Day 1 onward, predose on Day 1 of each cycle.

[l]For FOCBP only.

[m]See Table 8.2.1-2 for the timing of blood sampling.

[redacted].

[o]Tumor samples will be submitted by the end of Cycle 1 according to a separately prepared procedure for central pathological diagnosis.

[p]CT scan will be performed at screening, Week 4 of Cycles 2, 4, and 6, and thereafter, Week 4 of every 3 cycles (Cycles 9, 12, 15…). The allowable window for Cycle ≥ 2 is ±7 days. Scan results obtained within 28 days before Cycle 1 Day 1 can be used as screening results if the subject agrees.

[q]PET-CT scan will be performed at screening and thereafter, at the earliest possible timing after CR is confirmed by CT scan for efficacy evaluation. Scan results obtained within 28 days before Cycle 1 Day 1 can be used if the subject agrees.

[r]Lung field on CT images by PET-CT or CT scan will be reviewed for safety evaluation.

[s]Bone marrow aspiration or biopsy will be performed at screening and thereafter, as needed, such as when confirming CR at the time of efficacy evaluation. Results obtained within 28 days before Cycle 1 Day 1 can be used if the subject agrees.

[t]Assessment is based on Lugano response criteria for non-Hodgkin lymphoma (2014)[1] by the IWG.

[u]If the lung field was assessed on CT images within 7 days, its results can substitute for chest X ray.

[v]Investigation will be performed every 3 months following the end of the follow-up period. Only for subjects who have no disease progression at trial discontinuation, investigation will be performed after trial discontinuation until the start of new treatment or the end of the trial.

[w]Investigation will be performed every 3 months following the end of the follow-up period. Only for subjects who have no disease progression at trial discontinuation, progression of the primary disease will be investigated after trial discontinuation until disease progression (including the start of new treatment) or the end of the trial.

[x]Investigation will be performed every 3 months following the end of the follow-up period.

1.3.1 Screening Period

The investigator or subinvestigator will obtain written informed consent from each subject him/herself prior to the screening procedure. Following acquisition of informed consent, the subject identifier and the date of signed informed consent will be recorded in the subject screening log.

The investigator or subinvestigator will then screen consented subjects and select those who meet all the inclusion criteria and do not fall under any of the exclusion criteria. The investigations and examinations specified in Section 1.3, Schedule of Assessments will be conducted, and the result of eligibility assessment will be recorded in the case report form (CRF).

At the screening visit, the following information will be recorded in the CRF: subject demographics (collection date, date of birth, sex, childbearing potential, race, ethnicity, country, disease type, date of initial diagnosis, prior chemotherapy for the primary disease [names of regimens or medications, treatment period, and best overall response], prior hematopoietic stem cell transplantation [if yes, date of treatment], prior radiotherapy for the primary disease [if yes, date of treatment and location of treatment], other prior treatment for the primary disease [if yes, medications/therapies, treatment period, and best overall response], disease stage [Lugano classification[1] for PTCL and ATLL and TNMB classification[2] of mycosis fungoides/Sézary syndrome for CTCL], IPI[3] [PTCL and ATLL]), and medical history (prior diseases within 5 years before informed consent and concurrent diseases).

Table 1.3-5 Disease Stage (Lugano Classification)

Disease Stage		Involvement	Extranodal Status
Limited	I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
	II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
	II bulky[a]	II as above with "bulky" disease	Not applicable
Advanced	III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	Not applicable
	IV	Additional noncontiguous extralymphatic involvement	Not applicable

Tonsils, Waldeyer's ring, and spleen are considered nodal tissue.

[a]Whether stage II bulky is treated as limited or advanced disease may be determined by histology and a number of prognostic factors. Since the definition of bulky disease differs depending on histology, the longest diameter, instead of "X," should be recorded.

Table 1.3-6	**Disease Stage (TNMB Classification of Mycosis Fungoides/Sézary Syndrome)**	
Skin: T	T1	Limited patches, papules, and/or plaques covering < 10% of the skin surface (Patch is a lesion without significant elevation or induration. Plaque is a lesion that is elevated or indurated.) T1a (patch only), T1b (plaque ± patch)
	T2	Patches, papules, or plaques covering ≥ 10% of the skin surface T2a (patch only), T2b (plaque ± patch)
	T3	One or more tumors (≥ 1 cm diameter)
	T4	Confluence of erythema covering ≥ 80% of the body surface area
Node: N	N0	No clinically abnormal lymph nodes; biopsy not required
	N1 N1a N1b	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN0-2[a] Clone negative Clone positive
	N2 N2a N2b	Clinically abnormal lymph nodes; histopathology Dutch grade 2 or NCI LN3[a] Clone negative Clone positive
	N3 Nx	Clinically abnormal lymph nodes; histopathology Dutch grade 3-4 or NCI LN4[a] Clone positive or negative Clinically abnormal lymph nodes; no histologic confirmation or strict N grading impossible
Visceral: M	M0	No visceral organ involvement
	M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood: B	B0 B0a B0b	Absence of significant blood involvement: ≤ 5% of peripheral blood lymphocytes are atypical (Sézary) cells Clone negative Clone positive
	B1 B1a B1b	> 5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2 Clone negative Clone positive
	B_2	≥ 1000/μL Sézary cells (clone positive) in peripheral blood leukocytes plus one of the following: CD4/CD8 ≥ 10, CD4 + CD7– cells ≥ 40%, or CD4+ CD26– cells ≥ 30%

[a]NCI classification for lymph node

NCI LN0 No atypical lymphocytes
NCI LN1 Occasional and isolated atypical lymphocytes not arranged in clusters
NCI LN2 Many atypical lymphocytes or in 3 to 6 cell clusters
NCI LN3 Aggregates of atypical lymphocytes: nodal architecture preserved
NCI LN4 Partial/complete effacement of nodal architecture by atypical lymphocytes or frankly neoplastic cells

Stage	T	N	M	B
I A	1	0	0	0, 1
I B	2	0	0	0, 1
II A	1, 2	1, 2, X	0	0, 1
II B	3	0-2, X	0	0, 1
III A	4	0-2, X	0	0
III B	4	0-2, X	0	1
IV A1	1-4	0-2, X	0	2
IV A2	1-4	3	0	0-2
IV B	1-4	0-3, X	1	0-2

X: Clinically abnormal enlargement of lymph nodes is not histologically confirmed, or strict N grading is impossible.

Table 1.3-7 International Prognostic Index (IPI)

Prognostic Factor	Adverse Prognostic Factor
Age	> 60 years
Serum lactate dehydrogenase (LDH) level	Above normal
Performance Status	2 - 4
Disease stage	III or IV
Number of extranodal sites of involvement	≥ 2
Prognostic factor score of 0 or 1: Low risk Prognostic factor score of 2: Low-Intermediate risk Prognostic factor score of 3: High-Intermediate risk Prognostic factor score of 4 or 5: High risk	

1.3.2 Treatment and Observation Period

The treatment and observation period will be from Cycle 1 Day 1 through determination of trial treatment discontinuation. On treatment days, the scheduled tests/assessments will be performed prior to IMP administration as specified in Section 1.3, Schedule of Assessments. Subjects with suspected interstitial lung disease based on percutaneous oxygen saturation (SpO_2), auscultation, chest X ray, or lung field assessment on CT images will undergo additional examinations at the discretion of the investigator or subinvestigator and receive appropriate treatment as necessary. Likewise, subjects with suspected pancreatitis based on elevated amylase or lipase levels identified by serum chemistry and objective/subjective symptoms will also undergo additional examinations at the discretion of the investigator or subinvestigator and receive appropriate treatment as necessary.

1.3.3 Withdrawal Examination

Withdrawal examination will be performed within 7 days after trial treatment discontinuation is determined. Efficacy endpoints will be evaluated in consideration of the subject's general condition.

1.3.4 Follow-up Period

The scheduled tests/assessments will be performed 30 days after trial treatment discontinuation or just before new treatment for the primary disease begins, whichever comes first. If withdrawal examination or scheduled tests/assessments were performed within 7 days of the last day of the follow-up period, repeated tests/assessments can be omitted, and information on AEs and concomitant medications/therapies will be collected.

1.3.5 Investigation of Survival Status

The subject's survival status will be investigated every 3 months following the end of the follow-up period. Only for subjects who have no disease progression at trial discontinuation, new treatment for the primary disease and disease progression will be investigated. The results will be recorded in the CRF. These visits may be conducted by telephone. In phase 1 (dose escalation part), for subjects whose survival status is being investigated at the date of approval of protocol amendment 4, the investigation will be completed after the final investigation of survival status has been conducted (including investigation of new treatment for the primary disease and investigation of disease progression), and for subjects receiving trial treatment at that time, the investigation of survival status (including investigation of new treatment for the primary disease and investigation of disease progression) will be performed and completed following the end of the follow-up period.

2 Introduction

ASTX660 is a synthetic small molecule that was developed using the fragment-based drug discovery platform of Astex Pharmaceuticals Inc. (hereinafter referred to as "ASTEX"). It is known that the inhibitor of the apoptosis protein (IAP) family, which engages in evasion of apoptosis, includes the X-linked inhibitor of apoptosis protein (XIAP) and the cellular inhibitor of apoptosis protein (cIAP), and overexpression of these IAPs in numerous tumors has been reported.[4] The XIAP suppresses the apoptosis pathway by directly inhibiting caspases primarily through the intrinsic pathway, while cIAP suppresses the extracellular ligand-mediated extrinsic apoptosis pathway through binding to tumor necrosis factor (TNF) receptor-associated factor-2 (TRAF2) or other factors thereby forming complexes. It have been reported that overexpression of IAPs in cells inhibits apoptosis and is associated with resistance to chemotherapy and radiotherapy.[4,5] ASTX660 represents a novel structural class of nonpeptidomimetic IAP antagonists. ASTX660 has been shown to have tumour growth inhibitory activity and

potent proapoptotic activity in nonclinical studies.[6] ASTX660 has an inhibitory profile for both cIAP1 and XIAP and therefore is expected to be effective in blocking the pathways that circumvent apoptosis. ASTEX has been conducting a phase 1/2 clinical trial (hereinafter referred to as "ASTX660-01 trial") since 2015 in the United States and other foreign countries. After a recommended dose (RD) of 180 mg was identified in phase 1, the trial proceeded to phase 2 for solid tumor and lymphoma. Phase 2 has demonstrated that ASTX660 has promising efficacy in the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL), and further efficacy evaluation is ongoing in additionally enrolled patients with PTCL and CTCL. Against this backdrop, Otsuka Pharmaceutical Co., Ltd. (hereinafter referred to as "Otsuka") embarked on the development of ASTX660 for patients with PTCL in Japan, where the prevalence of this illness is comparable to that in the United States[7] and has planned a phase 1/2 trial to evaluate the tolerability, safety, efficacy, and pharmacokinetics (PK) of ASTX660 in Japanese patients. In patients with adult T-cell leukemia/lymphoma [ATLL] as well, a disease that affects a relatively large number of individuals in Japan[7] but is not included in the overseas trial, phase 1 (ATLL expansion part) of this trial is designed to evaluate the safety of ASTX660 at the RD.

PTCL, CTCL, and ATLL, which are derived from mature T-cells and natural killer (NK) cells, are categorized as "mature T- and NK cell neoplasms" by the World Health Organization (WHO) Classification (2017) and are associated with a variety of symptoms including systemic lymphadenopathy, hepatosplenomegaly, weight loss, fever, and night sweats.[8]

"Mature T- and NK cell neoplasms" are rare illnesses, and the number of patients in Japan is estimated to be approximately 2000 according to Portal Site of Official Statistics of Japan 2017 (https://www.e-stat.go.jp/).

The WHO Classification divides "mature T- and NK cell neoplasms" into approximately 30 subtypes, and the relative frequency of the subtypes varies among regions across the world. A comparative study of the incidence of hematopoietic malignancies between Japan and the United States has found that the proportion of "mature T- and NK cell neoplasms" in diagnosed malignant lymphomas between 2003 and 2008 is 18.1% in Japan and 6.8% in the United States.[7] This difference is due to ATLL caused by human T-cell leukemia virus type 1 (HTLV-1), which affects individuals predominantly in the southwest area of Japan. Excluding ATLL, the proportion of "mature T- and NK cell neoplasms" was 9.8% in Japan and 6.6% in the United States.

Among "mature T- and NK cell neoplasms," the most frequent of all lymphoma subtypes (including B-cell lymphoma and Hodgkin's lymphoma) in Japan is ATLL (10.00%), followed by angioimmunoblastic T-cell lymphoma (5.13%), peripheral T-cell lymphoma, not otherwise specified (NOS) (4.51%), anaplastic large-cell lymphoma, anaplastic lymphoma kinase (ALK) negative (1.59%), and extranodal NK/T-cell lymphoma, nasal type (1.55%).[9]

Regarding the prognosis of PTCL, a study by the International T-Cell Lymphoma Project[10] reported a 5-year survival rate of 70% for anaplastic large-cell lymphoma, ALK positive (ALK-positive ALCL), 49% for anaplastic large-cell lymphoma, ALK negative (ALK-negative ALCL), 32% for both angioimmunoblastic T-cell lymphoma (AITL) and peripheral T-cell lymphoma, NOS (PTCL NOS), and prognosis varies substantially among subtypes. Peripheral T-cell lymphoma is classified as aggressive lymphoma (intermediate-grade lymphoma) that progresses monthly without treatment, and a multinational retrospective study designed to evaluate clinical utility of Revised European American Lymphoma (REAL) Classification prior to introduction of rituximab revealed that all PTCL subtypes combined excluding ALCL had a poorer prognosis compared with diffuse large B-cell lymphoma (DLBCL).[11,12]

Concerning treatment for PTCL, the Practical Guidelines for Hematological Malignancies (2018) presents separate therapeutic strategies for ALK-positive ALCL and other PTCL subtypes. For ALK-positive ALCL, the guidelines recommend the CHOP protocol as the primary treatment based on treatment outcomes in patients with ALK-positive ALCL being comparable to that in patients with DLBCL. For other subtypes including PTCL NOS, AITL, and ALK-negative ALCL, the guidelines also recommend, as the primary treatment, combination chemotherapy such as the CHOP protocol, the treatment outcomes of which have been widely reported. For patients with partial or no response to the primary treatment, salvage therapy or clinical trials are recommended, and subsequent recommended treatment regimens include salvage therapy, clinical trials, and autologous or allogeneic transplantation, as well as palliative therapy and best supportive care. The guidelines do not specify regimens or drugs for salvage therapy to be used as secondary or subsequent treatments.

With regard to the prognosis of ATLL, a study of the above International T-Cell Lymphoma Project reported a 5-year survival rate of 14%.[10] As treatment for ATLL, the Practical Guidelines for Hematological Malignancies (2018) recommend VCAP-AMP-VECP-based combination chemotherapy for acute subtype, lymphoma subtype, and chronic subtype with unfavorable prognostic factors (abnormal values of at least 1 of lactate dehydrogenase [LDH], albumin, and blood urea nitrogen [BUN]), all categorized

as aggressive ATLL. For patients responsive to treatment without issues of age, general condition, or major organ function, allogeneic hematopoietic stem cell transplantation is considered if an appropriate donor is available. For patients unresponsive to treatment, the guidelines recommend salvage therapy, clinical trials, allogeneic transplantation, palliative radiotherapy, and best supportive care. The guidelines[13] do not specify regimens or drugs for salvage therapy to be used as secondary or subsequent treatments. Various chemotherapy regimens have been tried to date in the treatment of relapsed or refractory aggressive ATLL, often resulting in a brief response followed by the rapid progression of the disease.

For the smoldering subtype and chronic subtype without unfavorable prognostic factors, both categorized as indolent ATLL, the guidelines recommend observation without treatment until progression to aggressive ATLL and, after exacerbation of the disease, introduction of similar treatment regimens to those for initial aggressive ATLL.

Although multiple approved agents are available for relapsed or refractory PTCL in Japan, there is no established standard of care with evidence of prolonged survival. Some patients respond to the existing therapies but their progression free survival (PFS) is as short as approximately 1 to 4 months.[14] Given that ASTX660 has a novel mechanism of action that differs from that of the existing drugs and that the interim results of an overseas trial suggest that ASTX660 monotherapy has a certain level of efficacy in patients with PTCL, Otsuka believes that ASTX660 may represent a new treatment option for relapsed or refractory PTCL.

Please refer to the ASTX660 Investigator's Brochure (IB) for more detailed information.

2.1 Trial Rationale

Encouraged by the interim results of an ongoing foreign phase 1/2 clinical trial (ASTX660-01 trial) suggesting that ASTX660 is effective in patients with PTCL and CTCL, Otsuka has designed this trial protocol with the aim of evaluating the tolerability, safety, efficacy, and PK of ASTX660 in Japanese patients. This trial has been designed with due consideration given to subject safety, and Otsuka has determined that provided the trial is conducted in accordance with the protocol, it is appropriate from scientific and ethical perspectives. See Section 4.2 for scientific rationale for the trial design.

2.2 Background

At the present time, the ASTX660-01 trial, an ongoing phase 1/2 first-in-human trial, is the only clinical trial of ASTX660. The primary objectives of phase 1 of the ASTX660-01 trial are to evaluate safety and identify the maximum tolerated dose (MTD), the

recommended phase 2 dose (RP2D), and the recommended dosing regimen of ASTX660 in subjects with advanced solid tumors or lymphoma for whom standard life-prolonging measures are not available and who receive ASTX660 on Days 1 to 7 and Days 15 to 21 in repeated 28-day cycles. Subject enrollment in phase 1 has been completed and all subjects have completed trial treatment. Phase 1 has identified 210 mg/day as the MTD and 180 mg/day as the RP2D.

The primary objectives of phase 2 of the ASTX660-01 trial are to explore the single-agent antitumor activity of ASTX660 in selected tumor types that are characterized by a molecular feature that may confer sensitivity to ASTX660. Phase 2 is designed to enroll patients with head and neck squamous cell carcinoma (HNSCC), DLBCL, PTCL, CTCL, and cervical carcinoma, as well as other tumor types that are characterized by a molecular feature that may confer sensitivity to ASTX660 (eg, oncogenic activation of the NF-κB pathway or documented amplification of the gene loci encoding cIAP1 or cIAP2), pending confirmation by the Astex medical monitor. It is designed to initially enroll 14 subjects in each of 6 patient populations (6 tumor types) (the first stage) and then if 1 or more responses are observed in any cohort, the cohort could be expanded to a total of 30 subjects (the second stage). Responses have been observed in the PTCL and CTCL cohorts in the first stage, and only these 2 cohorts have entered the second stage and enrollment of additional subjects in these cohorts is under way.

As mentioned earlier, PTCL comprises a variety of tumor types and prognosis varies greatly among them. The 5-year survival rate of PTCL NOS and AITL, which are both relatively common in Japan, is approximately 30% and the median overall survival (OS) is approximately 2 to 3 years. The prognosis of relapsed or refractory PTCL is worse than that. Lately, multiple agents have been approved in Japan for the treatment of relapsed or refractory PTCL. Although all these drugs achieve a certain overall response rate (ORR), which has been used as the primary endpoint in clinical trials, none of them are recommended as established standard of care, and there remains limited treatment options for relapsed or refractory PTCL. Based on the convenience of an oral formulation and a novel mechanism of action that differs from that of the existing agents, ASTX660 has the potential to become a new therapeutic option for patients with relapsed or refractory PTCL.

2.3 Known and Potential Risks and Benefits

As of data cutoff date (04 Jun 2019), 152 subjects were exposed to ASTX660 in phase 1 and 2 of the ASTX660-01 trial. Frequently reported investigational medicinal product (IMP)-related adverse events (AEs) (incidence of ≥ 10%) included lipase increased (23%), amylase increased (22%), nausea (16%), fatigue (14%), rash/rash maculo-papular

(12%/14%), diarrhoea (13%), pruritis (12%), anaemia (11%), and alanine aminotransferase increased (11%). Frequently reported IMP-related AEs of ≥ Grade 3 (incidence of ≥ 5%) included lipase increased (11%), amylase increased (7%), and rash maculo-papular (7%). IMP-related serious AEs (SAEs) that occurred in more than 1 subject included pneumonitis (5 subjects, 3.3%), rash maculo-papular (3 subjects, 2.0%), and pancreatitis (2 subjects, 1.3%). These events represent potential risks of exposure to ASTX660 in the present trial.

Exposure to ASTX660 and participation in the present trial are expected to provide clinical benefits including tumor decrease and suppression of primary disease exacerbation.

3 Objectives and Endpoints

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
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	Primary: Phase 1 (dose escalation part): Dose-limiting toxicity (DLT) and safety Phase 1 (ATLL expansion part): Safety Phase 2: 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) Phase 2: Secondary efficacy: • Duration of response (DOR) • PFS • OS • Time to response (TTR) • Time to progression (TTP) • Proportion of subjects who proceed to transplantation • ORR as assessed by the investigator or subinvestigator

Table 3-1 Trial Objectives and Endpoints

Objectives	Endpoints
Secondary: Phase 1 (dose escalation and ATLL expansion parts): • To evaluate the PK of ASTX660 • To evaluate the efficacy of ASTX660 Phase 2: • To evaluate the safety of ASTX660 • To evaluate the PK of ASTX660	Pharmacokinetics: Plasma ASTX660 concentrations over time, PK parameters[a] (see below for details), and dose proportionality[b,c] • Day 1: C_{max}, AUC_{∞}, AUC_t, t_{max}, λ_z, AUC_%Extrap, $t_{1/2,z}$, CL/F, CL/F/BW, t_{last}, C_{max}/D,[b] AUC_{∞}/D,[b] AUC_t/D[b] • Day 7: C_{max}, AUC_{24h}, t_{max}, λ_z, $t_{1/2,z}$, CL/F, CL/F/BW, t_{last}, C_{max}/D,[b] AUC_{24h}/D,[b] Rac(AUC_{24h}), Rac(C_{max}), Rac(C_{trough}) [a]For phase 1 only, [b]For the dose escalation part only, [c]Only when dosing is performed at 3 or more dose levels. Secondary efficacy: • ORR as assessed by the investigator or subinvestigator • DOR • PFS • OS • TTR • TTP • Proportion of subjects who proceed to transplantation Safety: AEs, clinical laboratory values, vital signs, body weight, Eastern Cooperative Oncology Group Performance Status (ECOG PS), 12-lead electrocardiograms (ECGs), and left ventricular ejection fraction (LVEF)
[redacted]	[redacted]

Section 9.4 describes the statistical analysis of the endpoints.

4 Trial Design

4.1 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 4.1-1) 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 4.1-1 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 4.1-2. 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 4.1-2 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 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.

4.2 Scientific Rationale for Trial Design

4.2.1 Phase 1 (Dose Escalation Part)

Phase 1 (dose escalation part) is designed to evaluate the tolerability and safety of ASTX660 in patients with r/r PTCL and r/r CTCL and determine the RD for phase 2. As

mentioned earlier, the initial dose is 120 mg/day, and 3 to 6 subjects will be enrolled in each cohort with a 3 + 3 dose escalation design. The RD will be determined based on the DLT observed during the DLT assessment period of Cycle 1 of each cohort and its incidence. The tolerability of ASTX660 will be carefully assessed in each cohort with due consideration given to subject safety, and advancement to the next cohort will be determined according to the dose escalation plan. Hospitalization during Cycle 1 is mandatory so that the trial will be conducted with close monitoring of the subject's condition. Treatment interruption criteria and criteria for starting the next cycle are in place for possible occurrences of toxicities of ASTX660 to ensure subject safety.

Target subjects are r/r PTCL and r/r CTCL patients who were previously treated with antineoplastics. Both PTCL and CTCL are lymphomas derived from mature T-cells and NK cells, and the interim results of an overseas trial suggest that ASTX660 has a certain level of efficacy at the RD in subjects with PTCL and CTCL. Considering that the safety of ASTX660 has been studied at the same dose level in a few patients with PTCL and CTCL in an overseas trial, Otsuka has decided that evaluating the tolerability, safety, and PK of ASTX660 in PTCL and CTCL patients is appropriate.

For PTCL, as mentioned earlier, the Practical Guidelines for Hematological Malignancies[13] lists salvage therapy, clinical trials, and autologous or allogeneic transplantation, as well as palliative therapy and best supportive care as secondary and subsequent treatments for PTCL but does not specify regimens or drugs for salvage therapy to be used as secondary or subsequent treatments. For CTCL, the Evidence-based Clinical Guidelines for Skin Malignancies Version 2 (2015)[15] has no description of secondary and subsequent treatments. Under such circumstances, Otsuka believes that the eligibility criteria defined in this protocol will ensure appropriate selection of subjects who meet the target patient criteria as specified in the Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs (PFSB/ELD Notification No. 1101001 dated 01 Nov 2005).[16]

Subjects who experience neither AEs that make it difficult to continue the trial nor exacerbation of the primary disease during Cycle 1, which is in the DLT assessment period of the trial, and are expected to benefit from continued treatment with ASTX660 will be allowed from an ethical point of view to continue trial treatment after the DLT assessment period if they wish to carry on the treatment. Safety and efficacy will also continue to be evaluated in these subjects.

In conclusion, the conduct of phase 1 (dose escalation part) in r/r PTCL and r/r CTCL patients is justified scientifically and ethically.

4.2.2 Phase 1 (ATLL Expansion Part)

Phase 1 (ATLL expansion part) is designed to evaluate the safety of ASTX660 at the RD in patients with r/r ATLL and explore efficacy. Aggressive ATLL, the target disease in this part of the trial, often follows the rapid progression. Relapsed patients after chemotherapy or refractory patients, the target population of the trial, have an even worse prognosis. For this reason, Otsuka has decided to conduct an ATLL expansion part for ATLL patients after the RD is determined, in addition to a dose escalation part for PTCL and CTCL patients.

Adult T-cell leukemia/lymphoma, listed in "mature T- and NK cell neoplasms" categorized by the WHO Classification, is more prevalent in the southwest area of Japan compared with other regions in the world. In view of the current lack of adequate response of r/r ATLL to the existing treatments, the ATLL expansion part has been designed to evaluate the safety of ASTX660 monotherapy, the efficacy of which has been shown in PTCL and CTCL patients, in Japanese patients and explore the efficacy as well.

As in phase 1 (dose escalation part), hospitalization during Cycle 1 is mandatory, treatment interruption criteria and criteria for starting the next cycle are in place to ensure subject safety, and each examination will be required before advancing to the next cycle.

In conclusion, the conduct of phase 1 (ATLL expansion part) in r/r ATLL patients is justified scientifically and ethically.

4.2.3 Phase 2

Phase 2 is designed to evaluate the efficacy of ASTX660 at the RD in patients with r/r PTCL who were previously treated with at least 2 regimens of antineoplastics. For the purpose of minimizing interinstitutional differences in tumor type classification and efficacy evaluation and ensuring coherent objective evaluation across trial sites, a central pathological diagnosis committee and a central image review committee will be organized to conduct central assessments. The primary endpoint is ORR as assessed by the Central Efficacy Evaluation Committee based on assessments by the central image review committee according to the Lugano response criteria for non-Hodgkin lymphoma (2014)[1] by the IWG. The threshold response rate and the expected response rate are set at 10% and 30%, respectively, and the target sample size is set at 33 subjects as evaluable subjects (see Section 9.1, Sample Size). Given that no standard of care has been established for the target disease and the unavailability of trial results for ASTX660 monotherapy in PTCL patients who previously received secondary treatment, 10% is selected as a threshold response rate that could represent a certain level of efficacy. The expected response rate is selected based on ORRs observed in patients who previously

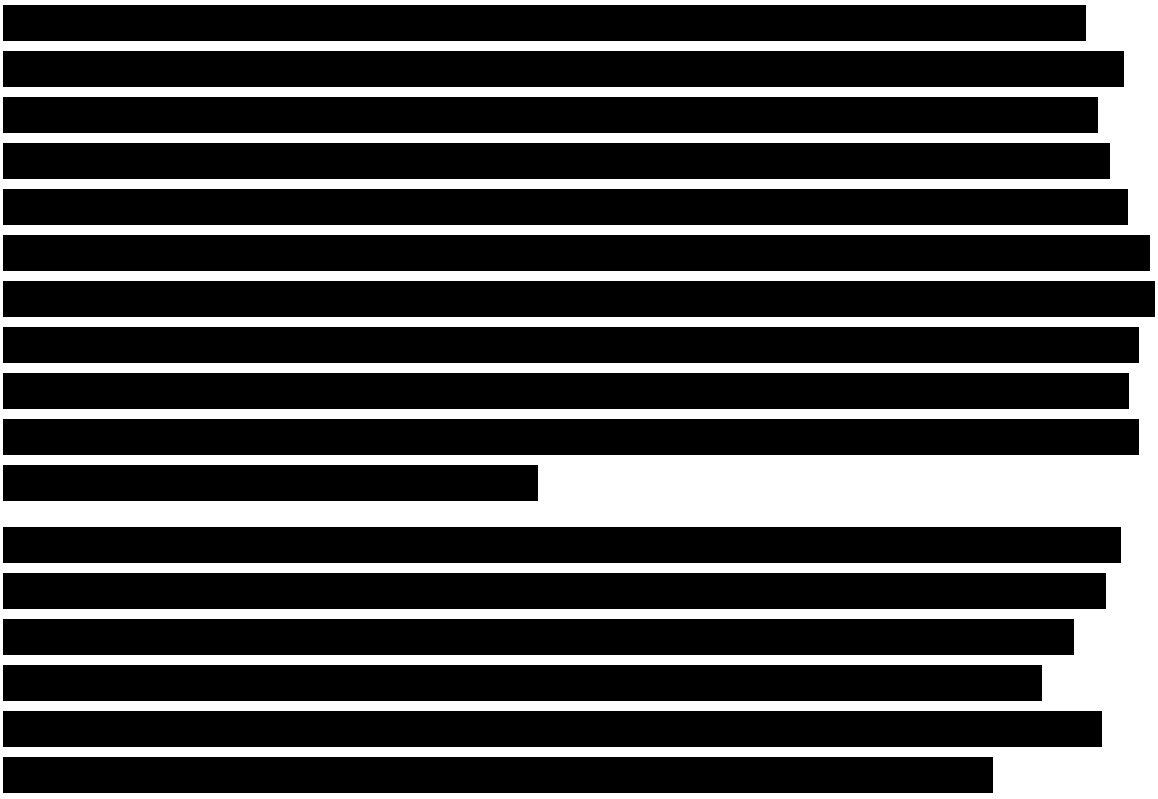
received at least 1 regimen of antineoplastic therapies in Japanese trials conducted for gaining approval of antineoplastics that are currently approved for the indication of r/r PTCL[17,18,19,20], as well as on the expectation that ASTX660 may also yield a similar response rate in r/r PTCL patients who previously received at least 2 regimens of antineoplastics.

The eligibility criteria have been determined in consultation with the Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs (PFSB/ELD Notification No. 1101001 dated 01 Nov 2005)[16] to ensure that the patients selected for the trial are appropriate.

As in phase 1 (dose escalation part), hospitalization during Cycle 1 is mandatory, treatment interruption criteria and criteria for starting the next cycle are in place to ensure subject safety, and each examination will be required before advancing to the next cycle. Hospitalization for 7 days from the first IMP administration through Cycle 1 Day 7 is mandatory.

In conclusion, the conduct of phase 2 in r/r PTCL patients is justified scientifically and ethically.

4.3 Dosing Rationale



4.4 End of Trial Definition

The end of trial date is defined as the last date of contact or the date of final contact attempt from the end of trial electronic case report form (eCRF) page for the last subject completing or withdrawing from the trial.

5 Trial 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)

[redacted]

5.2 Eligibility Criteria

5.2.1 Inclusion Criteria

Exceptions for eligibility criteria will not be permitted during the trial by the investigator or subinvestigator.

Subjects are required to meet the following inclusion criteria during the screening period as specified in the schedule of assessments (see Table 1.3-1, Table 1.3-3, and Table 1.3-4):

1) Patients 20 years of age or older at the time of informed consent and who provide written consent to participate in the trial using the informed consent form (ICF) approved by the institutional review board (IRB).
2) Patients with T-cell lymphoma with a histopathologic diagnosis of any of the following based on the WHO Classification (2017):

<Peripheral T-cell lymphoma>: Phase 1 (dose escalation part) and phase 2

For the purpose of this trial, peripheral T-cell lymphoma is defined as mature T- or NK cell neoplasms listed in the WHO Classification that fall under any of the following subtypes (for phase 2, submission of specimens is required for central pathological diagnosis):

- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Monomorphic epitheliotropic intestinal T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Follicular T-cell lymphoma
- Nodal peripheral T-cell lymphoma with T-follicular helper cells phenotype
- Anaplastic large cell lymphoma, ALK positive
- Anaplastic large cell lymphoma, ALK negative

<Cutaneous T-cell lymphoma>: Phase 1 (dose escalation part)

For the purpose of this trial, cutaneous T-cell lymphoma is defined as mature T- or NK cell neoplasms listed in the WHO Classification that fall under any of the following subtypes:

- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
- Primary cutaneous peripheral T-cell lymphoma, rare subtypes

<Adult T-cell leukemia/lymphoma>: Phase 1 (ATLL expansion part)

Patients with a diagnosis of ATLL classified into acute, lymphoma, or chronic type with unfavorable prognostic factors who are positive for serum anti-human T-cell leukemia virus type 1 antibody.

3) Patients who previously received systemic antineoplastics to treat the primary disease as indicated below.

<Peripheral T-cell lymphoma>: Phase 1 (dose escalation part)

Relapsed or refractory patients who previously received at least 1 regimen of antineoplastics (oral corticosteroid monotherapy is not included in this category). Patients with CD30-positive anaplastic large cell lymphoma must have a history of treatment with brentuximab vedotin.[a]

<Peripheral T-cell lymphoma>: Phase 2

Relapsed or refractory patients who previously received at least 2 regimens of antineoplastics (oral corticosteroid monotherapy is not included in this category).

Patients with CD30-positive anaplastic large cell lymphoma must have a history of treatment with brentuximab vedotin.[a]

<Cutaneous T-cell lymphoma>

Relapsed or refractory patients who previously received at least 1 regimen of systemic antineoplastics (oral corticosteroid monotherapy is not included in this category). Patients with mycosis fungoides or Sézary syndrome must have a history of treatment with mogamulizumab.[a]

<Adult T-cell leukemia/lymphoma>

Relapsed or refractory patients who previously received at least 1 regimen of antineoplastics. Patients who are positive for CCR4 must have a history of treatment with mogamulizumab.[a]

[a]This criterion does not apply to patients for whom treatment has been judged to be inappropriate or those who refused to receive the treatment.

4) Patients with the following lesion(s) at screening:
<Peripheral T-cell lymphoma>: Phase 1 (dose escalation part)

Swollen lymph nodes or extranodal lesions identified by PET-CT or CT during screening or within 28 days prior to the first dose of trial treatment.

<Peripheral T-cell lymphoma>: Phase 2

Swollen lymph nodes or extranodal lesions measurable in 2 perpendicular diameters by CT scan during screening or within 28 days prior to the first dose of trial treatment, with the longest diameter exceeding 1.5 cm (swollen lymph nodes) or 1.0 cm (extranodal lesions).

<Cutaneous T-cell lymphoma>

Lesions that can be considered skin lesions during screening.

<Adult T-cell leukemia/lymphoma>

At least one of measurable lesions identified by CT scan during screening or within 28 days prior to the first dose of trial treatment or skin lesions identified during screening.

5) Patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score of 0 or 1. For phase 2, patients with a PS score of 2 are eligible to be enrolled in the trial only if their physical activities are restricted by symptoms associated with the primary disease such as accumulation of pleural or ascitic fluid.

6) Patients with acceptable organ function as indicated below.

- AST and ALT ≤ 2.0 × ULN (≤ 3.0 × institutional ULN for subjects with hepatic involvement).
- Total bilirubin ≤ 1.5 × institutional ULN.
- ANC ≥ 1,000/mm^3 (≥ 750/mm^3 for subjects with bone marrow involvement) (Administration of granulocyte colony-stimulating factor [G-CSF] within 14 days prior to the test is not allowed).
- Platelet count ≥ 50,000/mm^3 (≥ 25,000/mm^3 for subjects with bone marrow involvement) (Platelet transfusion within 14 days prior to the test is not allowed).
- Serum creatinine ≤ 1.5 × institutional ULN or creatinine clearance (calculated by Cockcroft & Gault formula) ≥ 50 mL/min.
- Amylase and lipase ≤ 1.0 × institutional ULN.

7) Patients who are able to orally receive the IMP.

8) Patients who are expected to live for at least 3 months.

9) Fertile, sexually active male patients (excluding those who have had a bilateral orchiectomy) or sexually active female patients of childbearing potential, who agree to practice 2 different contraceptive measures during the trial and for 3 months after the last dose of IMP. If birth control is employed, 2 of the following methods must be used: vasectomy, tubal ligation, intrauterine device, oral contraceptive, and condom (all methods approved or certified in Japan).

A definition of childbearing potential can be found in Section 10.3.

[Rationale for Inclusion Criteria]

1) The age of 20 years was selected as the lower limit because individuals at this age can give consent by themselves, and due to ethical considerations based on Good Clinical Practice (GCP).

2), 3), 5), and 6) These criteria were set to define the target population of the trial with reference to the Guidelines for Clinical Evaluation of Antimalignant Tumor Drugs (PFSB/ELD Notification No. 1101001 dated 01 Nov 2005).[16]

4) This criterion was set to evaluate tumor response.

7) This criterion was set because ASTX660 is an oral formulation.

8) This criterion was set in consideration of the expected length of time to complete the safety evaluation.

9) This criterion was set in consideration of the safety of subjects and their partners

5.2.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following exclusion criteria at screening as specified in the schedule of assessments (Table 1.3-1, Table 1.3-3, and Table 1.3-4):

All phase 1 and 2 of the trial

1) Patients with hypersensitivity to ASTX660 or excipients of the drug product.
2) Patients with active infection(s) requiring antibacterial, antifungal, or antiviral therapies.
3) Patients with cardiac disease that meets any of the following criteria:
    a) Left ventricular ejection fraction (LVEF) < 50% by echocardiography or multiple-gated acquisition (MUGA) scan.
    b) Congestive cardiac failure (Grade 3 or 4 according to New York Heart Association [NYHA] functional classification).
    c) Inadequately controlled cardiac disease including unstable angina or hypertension requiring hospitalization within the past 3 months (90 days).
    d) History or presence of complete left bundle branch block, third-degree (complete) atrioventricular block, cardiac pacemaker, or inadequately controlled arrhythmia requiring treatment.
    e) History or presence of long QT syndrome.
    f) History or presence of ventricular arrhythmia requiring aggressive treatment.
    g) Screening 12-lead electrocardiogram (ECG) with QTc interval of ≥ 470 msec.
    h) Any other condition that is medically considered to have the potential to put the subject at increased cardiac risk.
4) Patients who are positive for human immunodeficiency virus (HIV) antibody, hepatitis B virus (HBV)-DNA, or hepatitis C virus (HCV) antibody.
5) Patients with Grade 2 or greater neuropathy.
6) Patients with significant mental illness or other condition (alcohol or other substance abuse/addiction) that, in the opinion of the investigator or subinvestigator, predisposes the subject to high risk of noncompliance with the protocol.
7) Patients who received any of the following treatments for the primary disease prior to the first dose of trial treatment:
    a) Chemotherapy or radiotherapy within 3 weeks (6 weeks if nitrosoureas) prior to trial treatment.
    b) Skin directed therapy including topicals or radiation within 3 weeks prior to trial treatment.
    c) Monoclonal antibody therapy within 4 weeks prior to trial treatment.
    d) Other investigational drugs (small molecules or biologics) or investigational therapies (including cell-based therapies such as chimeric antigen receptor [CAR] T-cell therapy) within the longer of 3 weeks or 5 half-lives prior to trial treatment.
8) Patients with adverse reactions (except for alopecia) to the prior treatment that has not resolved to Grade 2.
9) Patients with concurrent malignancies, except appropriately treated squamous carcinoma or basal cell carcinoma of skin or carcinoma in situ of uterine cervix,

breast or prostate cancer stable on endocrine therapy, and other previous cancers that have not relapsed for at least 5 years.

10) Patients with central nervous system involvement of lymphoma.
11) Patients with a history of allogenic hematopoietic stem cell transplantation, or those who underwent autologous stem cell transplantation within 14 weeks prior to the first dose of trial treatment.
12) Patients who received corticosteroids > 10 mg/day prednisone equivalent within 3 weeks prior to the first dose of trial treatment. However, patients without tumor decrease on stable corticosteroid therapy at low doses (≤ 10 mg/day prednisone equivalent) for more than 3 weeks prior to the first dose of trial treatment can be included. In that case, the corticosteroid therapy can be continued without dose increase until trial treatment is discontinued.
13) Patients with a history of gastrectomy.
14) Patients with a history or presence of pneumonitis (interstitial pneumonia) or pulmonary fibrosis. If screening CT scan suggests abnormal shadow of the pulmonary interstitium (eg, bilateral ground glass opacity), the investigator or subinvestigator should consult with a pulmonologist or a radiologist, as need, to determine whether the patient has pneumonitis (interstitial pneumonia) or pulmonary fibrosis.
15) Patients with inadequately controlled diabetes mellitus.
16) Pregnant or nursing female patients or female patients with a positive pregnancy test at screening. Nursing patients cannot participate in the trial even if they discontinue breastfeeding. Female patients must undergo a pregnancy test to confirm that they are not pregnant at screening. However, a pregnancy test is not necessary for female patients without childbearing potential (ie, patients with a history of bilateral oophorectomy or hysterectomy or who have been postmenopausal for at least 12 months except for cases where menopause could be due to the effect of antineoplastic treatment).
17) Patients who, in the opinion of the investigator or subinvestigator, are otherwise ineligible to participate in the trial

Subjects must agree to restrictions to medications and lifestyle described in Section 6.4 and Section 5.3, respectively.

[Rationale for Exclusion Criteria]

1), 2), 3), 4), 5), 8), 14), 15), and 16) These criteria were set in consideration of subject safety.

6), 7), 9), 10), 11), and 13) These criteria were set in consideration of the possible effects on safety and efficacy evaluations of ASTX660.

12) This criterion was set to ensure appropriate efficacy evaluation of ASTX660.

17) This criterion was set to allow the investigator or subinvestigator to exercise his/her discretion in judging if subjects are ineligible for trial participation.

5.4 Screen Failures

A screen failure is a subject from whom informed consent is obtained and is documented in writing (ie, subject signs an ICF), but who is not administered the IMP.

Subjects who fail to meet the eligibility criteria at screening may be rescreened for the test item(s) that did not meet the eligibility criteria at the first screening, and those who meet the eligibility criteria at rescreening can be enrolled. New consent is not required if rescreening takes place during the allowable window of the screening period, and only test item(s) for which variables have changed will be retested. Screening failures due to inability to be rescreened within the allowable window of the screening period must provide new written consent prior to rescreening and will be assigned a new subject ID.

If the subject meets the definition of a screen failure in this trial, the following information will be recorded in the CRF:

- Date of informed consent
- Visit date (screening visit)
- Demographics (collection date, birth date, sex, race, ethnicity, country)
- Result of eligibility assessment
- Screen failure date
- Reason for screen failure

6 Trial Treatments

6.1 Trial Treatments Administered

For information regarding the dose regimen and treatment period, including the follow-up period, for each treatment group of the trial, see Section 1.3 and Section 4.1.

6.1.1 Dose and Regimen and Treatment Duration

1) Investigational Medicinal Product
ASTX660 capsules: 30 mg and 90 mg (1 capsule contains 30 or 90 mg of ASTX660)

2) Dose and Regimen
Trial treatment will be conducted in repeated 28-day cycles comprising 7 days of 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) Treatment Duration
Trial treatment can be continued until the withdrawal criteria are met.

6.1.2 Treatment Interruption Criteria

In phase 1 (dose escalation part), if a DLT occurs in Cycle 1, trial treatment will be discontinued. If any AE corresponding to a DLT occurs in and after Cycle 2, trial treatment will be suspended, and if the event fails to improve by 1 or more grades (eg,

from Grade 3 to Grade 2) within 3 weeks following the onset of the event, trial treatment will be discontinued. If the event improves to the point where it no longer meets the DLT criteria and satisfies the criteria for starting the next cycle as described in Section 6.1.3, trial treatment will be resumed with the next cycle at a one-level lower dose (30-mg reduction per level). The dose may be reduced down to 60 mg (eg, a maximum reduction equivalent to 3 dose levels is permitted for subjects assigned to 150 mg [dose level 2]), and the dose must not be increased following dose reduction.

In phase 1 (ATLL expansion part) and phase 2, if any AE corresponding to a DLT occurs, trial treatment will be suspended, and if the event fails to improve by 1 or more grades within 3 weeks following the onset of the event, trial treatment will be discontinued. If the event improves to the point where it no longer meets the DLT criteria and satisfies the criteria for starting the next cycle as described in Section 6.1.3, trial treatment will be resumed with the next cycle at a one-level lower dose. The dose may be reduced down to 60 mg, and the dose may be increased up to the RD following dose reduction at the discretion of the investigator or subinvestigator (the dose should be decreased or re-increased cycle by cycle, not within a cycle).

In addition, in phase 1 (ATLL expansion part) and phase 2, trial treatment can be suspended if the investigator or subinvestigator decides that treatment interruption is necessary, but adjustment of the dosing schedule to compensate for missed doses (eg, administering the IMP on Day 16 to compensate a missed dose on Day 8) is prohibited. The dose may be reduced by 1 dose level to 60 mg cycle by cycle with close monitoring for subject's general condition and AEs. Following dose reduction, the dose may be increased up to the RD at the discretion of the investigator or subinvestigator (the dose should be decreased or re-increased cycle by cycle, not within a cycle).

The dose may be reduced down to 60 mg. In the event that an unacceptable adverse reaction occurs after dose reduction to 60 mg, trial treatment will be discontinued.

6.1.3 Criteria for Starting the Next Cycle

The following criteria will be confirmed to be met within 7 days before start of the next cycle.

- AST and ALT ≤ 5 × institutional ULN
- Total bilirubin ≤ 2 × institutional ULN
- Lipase and amylase ≤ 2 × institutional ULN
- Confirmed or suspected cytokine release syndrome, pneumonitis, and interstitial pneumonia: Disappeared

- Nonhematologic toxicities (including skin rash, facial nerve disorder and facial weakness, and left ventricular ejection fraction decreased) other than the above: Grade 2 or less

If the above criteria are not satisfied, the next cycle may be postponed up to Day 50. If the above criteria are still not satisfied on Day 50, then subsequent treatment will be discontinued.

For information regarding the dose regimen and treatment period (including the follow-up period) for each treatment group of the trial, see Section 1.3 and Section 4.1.

6.1.4 Medical Devices

Not applicable.

6.2 Management of Investigational Medicinal Product

For full details on IMP management, please refer to the ASTX660 IB and a separate procedure.

6.2.1 Packaging and Labeling

Investigational medicinal product will be provided by the sponsor or designated agent to the IMP manager. [redacted] will be labeled to clearly disclose the compound ID, trial number, sponsor's name and address, a statement that the product is for trial use, lot number, expiration date, storage method, route of administration, appropriate precautionary statements, and other information required by local regulatory authorities.

6.2.2 Storage

The IMP will be stored in a securely locked cabinet or enclosure. Access will be limited to the IMP manager.

The IMP will be stored according to the conditions indicated on the IMP label.

The trial site staff will maintain a temperature log in the IMP storage area to record the temperature.

6.2.3 Accountability

The IMP manager must maintain an inventory record of IMP received, dispensed, administered, destroyed, and returned. The IMP manager must not provide IMP to any patient not participating in this protocol.

6.2.4 Returns and Destruction

Upon completion or termination of the trial, all used IMP containers, unused IMP, and partially used IMP must be returned to the sponsor or a designated agent. All IMP returned to the sponsor must be accompanied by the appropriate documentation and be clearly identified by protocol number and trial site number on the outermost shipping container. Returned supplies should be in the original containers (eg, subject kits). The assigned trial monitor will facilitate the return of used IMP containers, unused IMP, and partially-used IMP.

6.2.5 Reporting of Product Quality Complaints

A Product Quality Complaint (PQC) is any written, electronic, or oral communication provided by a healthcare professional, consumer, subject, medical representative, competent authority, regulatory agency, partner, affiliate, or other third party that alleges deficiencies or dissatisfaction related to the identity, quality, labeling, packaging, reliability, safety, durability, tampering, counterfeiting, theft, effectiveness, or performance of a medicinal product or medical device after it is released for distribution. Examples include, but are not limited to, communications involving:

- Failure/malfunction of a product to meet any of its specifications
- Incorrect or missing labeling
- Packaging issues (eg, damaged, dirty, crushed, missing product)
- Bottle defects (eg, under-fill, over-fill, no safety seal)
- Vial defects
- Loss or theft of product

6.2.5.1 Eliciting and Reporting Product Quality Complaints

The investigator/subinvestigator or designee must record all PQCs identified through any means from the receipt of the IMP from the sponsor or sponsor's designee, through and including reconciliation and up to destruction, including subject IMP dosing. The investigator/subinvestigator or designee must notify the sponsor or sponsor's designee [redacted] of the information specified in Section 6.2.5.2 by email immediately after becoming aware of the PQC.

Identification of a PQC by the subject should be reported to the site investigator or subinvestigator, who should then follow the reporting mechanism above.

6.2.5.2 Information Required for Reporting Product Quality Complaints

- Description of a PQC

- Reporter identification (eg, subject, investigator or subinvestigator, site, etc)
- Reporter contact information (eg, address, phone number, e-mail address)
- ID of material (product/compound name, kit number)
- Clinical protocol reference (number and/or trial name)
- Dosage form/strength (if known)
- Photos (if available)
- Availability of complaint sample for return

6.2.5.3 Return Process for Product Quality Complaints

Indicate during the report of the PQC if the complaint sample is available for return. The sponsor may provide sample return instructions, when applicable.

It must be documented in the site accountability record that the complaint sample for a dispensed kit has been forwarded to the sponsor for complaint investigation.

6.2.5.4 Assessment/Evaluation

Assessment and evaluation of PQCs of the IMP will be handled by the sponsor.

6.3 Measures to Minimize/Avoid Bias

Not applicable because this is an open-label trial.

6.4 Subject Compliance

Subjects will be under the supervision of the investigator or subinvestigator during the trial. The investigator or subinvestigator will instruct subjects to comply with the following:

- Adhere to the specified dose and regimen when taking the IMP.
- Adhere to the specified schedule during the trial.
- Do not take any prohibited concomitant medications (see Section 6.5.1, Prohibited Medications).
- Do not undergo any prohibited concomitant therapies (see Section 6.5.1, Prohibited Medications).
- Do not communicate to third parties any information obtained through participating in the trial.

6.5 Prior Medications and Concomitant Medications or Therapies

The investigator or subinvestigator will record all regimens or medications used and therapies performed for the primary disease prior to the start of trial treatment in the CRF.

The investigator or subinvestigator will also record all concomitant medications and therapies taken by the subject from the date of signing the ICF through the withdrawal examination in the CRF. The investigator or subinvestigator will also record all medications and therapies taken by the subject for treatment of an AE or which caused an AE up to 30 days after the last dose of IMP or the start date of new therapy, including new exploratory therapy, for the primary disease, whichever is earlier, in the CRF. For concomitant medications, the following will be recorded in the CRF: medication, indication, dose, frequency, route, start date and end date. For concomitant therapy, the following will be recorded in the CRF: therapy, indication, start date and end date.

6.5.1 Prohibited Medications

The following medications or therapies must not be used from informed consent until the withdrawal examination.

- Treatments (including chemotherapy, radiotherapy, hematopoietic stem cell transplantation, ultraviolet therapy, extracorporeal photochemotherapy, and total skin electron beam therapy) for the primary disease
- Commencement of systemic administration of corticosteroids > 10 mg/day prednisone equivalent or dose increase of oral corticosteroids that the subject has been taking at a low dose since before participation in the trial. However, the use of such medications for the treatment of an AE is permitted.
- Live vaccines
- Other IMPs

During the DLT assessment period, the use of G-CSF or other hematopoietic growth factors for a primary preventive purpose is prohibited.

6.5.2 Permitted Supportive and Preventive Therapies

Medications or treatments except for prohibited concomitant medications and therapies may be used. Supportive therapies to ameliorate primary disease-related symptoms, transfusion, and treatments required for management of general conditions may also be used at the discretion of the investigator or subinvestigator. Preventive administration of antibiotics (eg, sulfamethoxazole-trimethoprim [ST]) for bacterial, fungal, viral, and opportunistic infections associated with the primary disease is recommended. All supportive and preventative therapies will be recorded in the CRF.

[redacted]

[redacted] Drugs with the potential to induce torsades de pointes ventricular tachycardia must also be used carefully.

6.5.3 Rescue Medications

Not applicable.

6.6 Intervention After the End of the Trial

Not applicable.

7 Stopping Rules, Withdrawal Criteria, and Procedures

7.1 Entire Trial or Treatment

If the sponsor terminates or suspends the trial for any reason, prompt notification will be given to the heads of the trial sites and regulatory authorities in accordance with regulatory requirements.

7.2 Individual Site

Individual trial site participation may be discontinued by the sponsor, the investigator, or the IRB if judged to be necessary for medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations, and GCP. The head of a trial site will notify the sponsor promptly if the trial is terminated by the investigator or the IRB at the site.

7.3 Individual Subject Discontinuation

7.3.1 Treatment Interruption

See Section 6.1.2, Treatment Interruption Criteria.

7.3.2 Treatment Discontinuation

After trial treatment begins, a subject may stop treatment permanently for a variety of reasons. Treatment discontinuations may be initiated by a subject who is not satisfied with treatment or may become medically necessary due to AEs, required treatment with a disallowed medication or therapy, or other issues, as determined by the investigator or subinvestigator. However, each investigator or subinvestigator must comprehensively review the circumstances and offer the subject options for continued treatment to the degree possible as described in Section 7.3.5, Procedures to Encourage Continued Trial Participation.

7.3.3 Documenting Reasons for Treatment Interruption or Discontinuation

All subjects have the right to discontinue the trial, and the investigator or subinvestigator can discontinue a subject's participation in the trial if medically necessary. In addition, subjects must discontinue the trial if they meet any of the following criteria. Only 1 reason (main reason) for discontinuation will be recorded in the CRF.

- AE
  - A DLT occurred in phase 1 (dose escalation part)
  - An AE corresponding to a DLT occurred in and after Cycle 2 of phase 1 (dose escalation part), or in phase 1 (ATLL expansion part) or phase 2, and the event has not improved based on the DLT criteria despite 3-week treatment interruption, or an adverse reaction occurred after dose reduction to 60 mg
  - The criteria for starting the next cycle are not satisfied even after the next cycle has been postponed to Day 50.
  - Grade > 3 interstitial pneumonia developed
  - Continuing IMP places the subject at undue risk as determined by the investigator or subinvestigator (eg, a safety concern that is possibly, probably, or likely related to IMP)
- Obvious exacerbation or relapse of the primary disease requiring an alternative therapy
- Pregnancy of the subject (see Section 10.3)
- Significant protocol deviation
- The subject's request to discontinue trial treatment for reasons not related to safety or efficacy
- Withdrawal of consent by subject
- Lost to follow-up
- Death
- The investigator decides that trial continuation is not in the best interests of the subject (for reasons other than AEs)
- Other

If the subject discontinues IMP due to an AE, the investigator/subinvestigator, or other trial personnel, will make every effort to follow the event until it has resolved or stabilized. Follow-up procedures in Section 7.3.2, Treatment Discontinuation, must be followed. Subjects who discontinue trial treatment will remain under observation after the withdrawal examination.

7.3.4 Withdrawal of Consent

All subjects have the right to withdraw their consent from further participation in the trial at any time without prejudice. Subjects cannot withdraw consent for use of data already collected as part of the trial but can withdraw consent only for future participation. The investigator or subinvestigator can also discontinue a subject's participation in the trial at any time if medically necessary. Unless the subject provides their written withdrawal of consent or there is other written documentation by the investigator or subinvestigator confirming the subject's verbal intent to completely withdraw from the trial, subjects should be followed for all protocol-specified evaluations and assessments, if possible.

Complete withdrawal of consent requires a subject's refusal of ALL of the following methods of follow-up:

- Participation in all follow-up procedures specified in the protocol (whether in-clinic, by telephone, or by a home visit).
- Participation in a subset of protocol specified follow-up procedures (by a frequency schedule and method, as agreed by subject and trial personnel).
- Contact of the subject by trial personnel, even if only by telephone, to assess current medical condition, and obtain necessary medical or laboratory reports relevant to the trial's objectives.
- Contact of alternative person(s) who have been designated in source records as being available to discuss the subject's medical condition, even if only by telephone, mail, or e-mail (eg, family, spouse, partner, legal representative, friend, neighbor, or physician).
- Access to medical information from alternative sources (eg, hospital/clinic medical records, referring doctor's notes, public records, dialysis, transplantation or vital registries, social media sources).

Withdrawal of consent is a critical trial event and, therefore, should be approached with the same degree of importance and care as is used in initially obtaining informed consent. The reasons for a subject's intended withdrawal need to be completely understood, documented, and managed to protect the rights of the subject and the integrity of the trial. A subject may initially express their desire to discontinue IMP administration, which is not equivalent to a complete withdrawal of consent for further participation (see Section 7.3.1, Treatment Interruption, and Section 7.3.2, Treatment Discontinuation, respectively). A subject may, however, indicate that further trial participation is creating a burden on their work, school, or social schedule. Therefore, the investigator or subinvestigator should follow the procedures outlined in Section 7.3.3, Documenting Reasons for Treatment Interruption or Discontinuation, to determine if the subject can

continue participation in the trial if modifications to his/her treatment and/or schedule of assessments can be accommodated. Only subjects who withdraw their permission for all of the above methods of follow-up are considered to have completely withdrawn their consent to participate in the trial.

[redacted]

7.3.5 Procedures to Encourage Continued Trial Participation

In all cases of impending IMP discontinuation or consent withdrawal, investigators or subinvestigators will be instructed to meet and discuss (without undue coercion) with the subject their options of continuing in the trial, preferably on therapy. The investigator or subinvestigator should ensure understanding and documentation of the reasons for the subject's desire to withdraw consent.

7.4 Definition of Subjects Lost to Follow-up

Subjects who cannot be contacted during or before the investigation of survival status in the treatment period, who do not have a known reason for discontinuation (eg, withdrew consent or AE), and for whom a survival status at the end of the trial cannot be determined will be classified as "lost to follow-up." Survival status can be determined from a variety of sources, either by obtaining acceptable documentation for death (ie, death certificate, medical records, public records, statement by a family member or primary care physician) or acceptable documentation for life (ie, direct contact with the subject, medical records, successful telephone contact with the subject, statement by a family member or primary care physician, or public records).

The site will make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternative similar method, where appropriate, before assigning a "lost to follow-up" status.

If the subject was classified as "lost to follow-up," "Were you able to contact the subject?," "Date of contact/Date of final contact attempt," and "Contact method" will be recorded in the source documents and CRF.

8 Trial Procedures

The assessments to be conducted during the trial are summarized in Section 1.3, Schedule of Assessments.

8.1 Efficacy Assessments

In phase 1 (dose escalation part and ATLL expansion part), ORR as assessed by the investigator or subinvestigator, DOR, PFS, OS, TTR, TTP, and proportion of subjects who proceed to transplantation will be assessed as the secondary endpoints.

In phase 2, ORR as assessed by the Central Efficacy Evaluation Committee based on Lugano response criteria for non-Hodgkin lymphoma (2014)[1] proposed by the IWG will be assessed as the primary endpoint. In addition, DOR, PFS, OS, TTR, TTP, proportion of subjects who proceed to transplantation, and ORR as assessed by the investigator or subinvestigator will be assessed as the secondary endpoints.

8.1.1 Response

8.1.1.1 Peripheral T-cell Lymphoma

8.1.1.1.1 Assessment of Diagnostic Images

Assessment of CT and PET-CT images in phase 1 (dose escalation part) will be performed according to institutional procedures. However, CT scans with contrast will be performed. For phase 2, in order to obtain consistent high-quality imaging data from all trial sites, scanning will be performed under the same conditions throughout the trial period, according to the procedure prepared separately. The date of imaging, and response assessment results for target and nontarget lesions will be recorded in the medical record and CRF.

For phase 2, in order to have the imaging diagnosis assessed by an independent imaging diagnosis institute, all imaging data obtained during this trial will be provided to the sponsor, according to the procedure prepared separately.

8.1.1.1.2 Central Image Review Committee

Phase 2 will include the central image review committee, which is an imaging diagnosis institute independent of the parties involved in the trial (eg, sponsor, medical expert, investigators, and subinvestigators). The central image review committee will assess the imaging data obtained from trial sites, according to the procedure prepared separately. Based on the assessment by the central image review committee, the best overall response will be determined by the Central Efficacy Evaluation Committee.

8.1.1.1.3 Definition of Measurable and Evaluable Lesions

Subjects eligible for this trial should have at least 1 measurable lesion.

Measurable lesions are defined as swollen lymph nodes or extranodal lesions measurable in 2 perpendicular diameters by CT scan with the longest diameter exceeding 1.5 cm

(swollen lymph nodes) or 1.0 cm (extranodal lesions). All other lesions will be considered to be evaluable lesions. Measurement will be performed by imaging diagnosis.

Evaluable lesions are defined as lesions that are difficult to follow quantitatively with imaging, including pleural effusions and ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed with imaging.

From measurable lesions, up to 6 of the largest nodal/extranodal lesions as the product of the perpendicular diameters will be identified as target lesions. Nodal lesions should be from different body regions, where should include, where applicable, mediastinal and retroperitoneal areas. Extranodal lesions include those in solid organs (eg, liver, spleen, kidneys, and lungs), those with gastrointestinal involvement, and skin lesions noted on palpation.

For disease selected as target lesions, from cranial to caudal, the lesion site, examination method, date of examination, long and short diameters (cm) of each lesion, product of both diameters (ie, product of the perpendicular diameters), and sum of the product of the perpendicular diameters for multiple lesions (SPD) will be recorded in the medical record and CRF.

All measurable and evaluable lesions not selected as target lesions will be identified as nontarget lesions, and the lesion site, examination method, and date of examination will be recorded in the medical record and CRF. Nontarget lesions include any measurable nodal and extranodal lesions not selected as target lesions, and those that are measurable but considered abnormal. Bone marrow involvement will be assessed using the result of bone marrow aspiration or biopsy. The date of bone marrow aspiration or biopsy and examination results will be recorded in the medical record and CRF.

8.1.1.1.4 Efficacy Assessment Criteria

Assessment of the efficacy against PTCL will be based on Lugano response criteria for non-Hodgkin lymphoma (2014)[1] by the IWG, and the date of CT/PET-CT imaging and 5-point scale scores and response assessment results for target and nontarget lesions will be recorded in the medical record and CRF. The assessment criteria for each response category are shown below in Table 8.1.1.1.4-1.

Table 8.1.1.1.4-1 Lugano Response Criteria for Non-Hodgkin's Lymphoma (2014) by the IWG		
Response and Site	**PET-CT-Based Response**	**CT-Based Response**
Complete Response (CR)	**Complete Metabolic Response (CMR)**	**Complete Radiologic Response**
Nodal and extranodal lesions	5-PS[a] Score 1, 2, or 3 with or without residual mass[b]	Target lesions must regress to ≤ 1.5 cm in LDi. No extralymphatic sites of disease
Nontarget lesions	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow involvement	No evidence of FDG-avid disease in marrow. If bone marrow involvement positive is confirmed at screening by bone marrow aspiration or biopsy, bone marrow involvement negative should be confirmed by the same method.	Normal by morphology; if indeterminate, flow cytometry or immunohistochemistry negative
Partial Response (PR)	**Partial Metabolic Response (PMR)**	**Partial Remission**
Nodal and extranodal lesions	5-PS[a] Score 4 or 5 with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of target lesions (up to 6 of the largest measurable lesions)[c]
Nontarget lesions	Not applicable	No increase (Absent/normal, or regressed)
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal.
New lesions	None	None
Bone marrow involvement	Residual uptake higher than uptake in normal marrow, but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy is allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy, or an interval PET scan.	Not applicable
No Response or Stable Disease (NR/SD)	**No Metabolic Response**	**Stable Disease**
Target lesions Extranodal lesions	5-PS[a] Score 4 or 5 with no significant change in FDG uptake from baseline at any time during treatment or the end of treatment	< 50% decrease from baseline in SPD of target lesions (up to 6 of the largest measurable lesions); no criteria for progressive disease are met.
Nontarget lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None

Table 8.1.1.1.4-1 Lugano Response Criteria for Non-Hodgkin's Lymphoma (2014) by the IWG

Response and Site	PET-CT-Based Response	CT-Based Response
Bone marrow involvement	No change from baseline	Not applicable
Progressive Disease (PD)	**Progressive Metabolic Disease**	**Progressive Disease**
Individual target lesions Extranodal lesions	5-PS[a] Score 4 or 5 with an increase in intensity of FDG uptake from baseline and/or New FDG-avid foci consistent with lymphoma during treatment or at the end of treatment.	At least 1 of the following is met: PPD progression: ≥ 1 individual nodal lesion is abnormal with all of the following: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and Increase in LDi or SDi from nadir 0.5 cm (for lesion ≤ 2 cm) 1.0 cm (for lesion > 2 cm) In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline. If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly.
Nontarget lesions	None	New nontarget lesions or clear progression of preexisting nontarget lesions
New lesions	New FDG-avid foci consistent with lymphoma. False positives are unlikely. If etiology of new lesions is uncertain, a biopsy or interval PET scan may be considered.	Regrowth of previously resolved lesions. New node > 1.5 cm in any axis. New extranodal site > 1.0 cm in any axis; if < 1.0 cm, it should be unequivocal and attributable to lymphoma. Assessable disease of any size unequivocally attributable to lymphoma.
Bone marrow involvement	New or recurrent FDG-avid foci.	New or recurrent involvement.

5-PS = 5-point scale; FDG = fluorodeoxyglucose; LDi = longest transverse diameter of a lesion; PPD = cross product of the LDi and perpendicular diameter; SDi = shortest axis perpendicular to the LDi; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a]5-PS: 1 = no uptake above background; 2 = uptake ≤ mediastinal blood pool; 3 = uptake > mediastinal blood pool, but ≤ liver; 4 = uptake moderately > liver; 5 = markedly increased uptake at any site involved at baseline compared with liver and/or new lesions estimated to represent lymphoma; X = new areas of uptake unlikely to be related to lymphoma.

[b]It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, as a result of chemotherapy or G-CSF), uptake may be greater than normally seen in the mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than the surrounding normal tissue, even if the tissue has high physiologic uptake.

[c]When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value. When no longer visible, assign 0 × 0 mm. For a node > 5 mm × 5 mm, but smaller than normal, use actual measurements for calculation.

8.1.1.2 Cutaneous T-cell Lymphoma

8.1.1.2.1 Assessment of Skin Lesions

Assessment of CTCL skin lesions will be based on the modified severity weighted assessment tool (mSWAT).[2] From the prespecified percentage total body surface area (%TBSA), as shown in Table 8.1.1.2.1-1, for each region where the whole body is divided into 12, the surface area of each type of skin lesion in each of the 12 body regions will be measured using the surface area of the patient's palm. The area of involvement (%TBSA) will be measured for each region of skin patch, plaque, and tumor. For the measurement, the area of one hand with the thumb bent inward and the other fingers extended can be used as approximately 1%. Subsequently, the total area of involvement for each of patch, plaque, and tumor will be calculated, and then multiplied by a weighting factor (ie, patch = 1, plaque = 2, and tumor = 4), and these products will be summed to calculate the mSWAT skin assessment score.

Patch is defined as skin lesions of any size without significant elevation or induration, and plaque is defined as skin lesions of any size with elevation or induration. Tumor is defined as at least 1 solid or nodal lesion ≥ 1 cm diameter with evidence of deep infiltration in the skin and/or vertical growth.

Table 8.1.1.2.1-1 mSWAT Percentage Total Body Surface Area of Body Regions

Body Region	%TBSA in Body Region	Patch %TBSA (or erythroderma without elevation)	Plaque %TBSA (or erythroderma with elevation/induration)	Tumor %TBSA (or erythroderma with ulceration including fissuring)
Head	7			
Neck	2			
Anterior Trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior Trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal lesion %TBSA				
Weighting factor		×1	×2	×4
Subtotal mSWAT skin assessment score				
Total mSWAT skin assessment score				

8.1.1.2.2 Efficacy Assessment Criteria

Assessment of the efficacy for CTCL skin lesions will be based on the mSWAT, and the date of assessment and %TBSA in each body region and responses for each of patch, plaque, and tumor will be recorded in the medical record and CRF. Responses will be assessed based on the percent change from baseline in the mSWAT skin assessment score. The assessment criteria for overall skin lesions using mSWAT are described in Table 8.1.1.2.2-1.

Table 8.1.1.2.2-1 Assessment of Overall Skin Lesions Using mSWAT

Response	Criteria
Complete response (CR)	No disease evidence: 100% clearance of skin lesions, maintained for at least 4 weeks. No disease subsequently confirmed by CT scan
Partial response (PR)	≥ 50% decrease in the mSWAT skin assessment score from baseline, maintained for at least 4 weeks
Stable disease (SD)	< 50% decrease in the mSWAT skin assessment score from baseline
Progressive disease (PD)	At least a 25% increase in the mSWAT skin assessment score from baseline during the trial treatment period

8.1.1.3 Adult T-cell Leukemia/Lymphoma

8.1.1.3.1 Assessment of Diagnostic Images

Assessment of CT images will be performed according to institutional procedures, and the date of CT and response assessment of target and nontarget lesions will be recorded in the medical record and CRF.

8.1.1.3.2 Definition of Measurable and Evaluable Lesions

Measurable lesions are defined as swollen lymph nodes or extranodal lesions measurable in 2 perpendicular diameters by CT scan with the longest diameter exceeding 1.5 cm (swollen lymph nodes) or 1.0 cm (extranodal lesions). All other lesions will be considered to be evaluable lesions. Measurement will be performed by imaging diagnosis.

Evaluable lesions are defined as lesions that are difficult to follow quantitatively followed with imaging, including pleural effusions and ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed with imaging.

From measurable lesions, up to 6 of the largest nodal/extranodal lesions as the product of the perpendicular diameters will be identified as target lesions. Nodal lesions should be from different body regions, where should include, where applicable, mediastinal and retroperitoneal areas. Extranodal lesions include those in solid organs (eg, liver, spleen,

kidneys, and lungs), those with gastrointestinal involvement, and skin lesions noted on palpation.

For disease selected as target lesions, from cranial to caudal, the lesion site, examination method, date of examination, long and short diameters (cm) of each lesion, product of both diameters (ie, product of the perpendicular diameters), and SPD will be recorded in the medical record and CRF.

All measurable and evaluable lesions not selected as target lesions will be identified as nontarget lesions, and the lesion site, examination method, and date of examination will be recorded in the medical record and CRF. Nontarget lesions include any measurable nodal and extranodal lesions not selected as target lesions, and those that are measurable but considered abnormal.

8.1.1.3.3 Efficacy Assessment Criteria

Assessment of the efficacy for ATLL will be based on Japan Clinical Oncology Group (JCOG) Response Criteria for ATLL (2009),[21] and the date of assessment, response assessment results for each variable, and overall response will be recorded in the medical record and CRF. The assessment criteria for each response category are shown below in Table 8.1.1.3.3-1.

Table 8.1.1.3.3-1 JCOG Response Criteria for Adult T-Cell Leukemia-Lymphoma (2009)

Overall Response	Variable								
	Target Lesions		Nontarget Lesions		Bone Marrow Involvement	Peripheral Blood Lesions[d] (Abnormal Lymphocytes)	Skin Lesions	Hepatomegaly, Splenomegaly	New Lesions
	Nodal	Extranodal	Nodal	Extranodal					
Complete response (CR)	Normal	Absent	Normal	Absent	Negative	Normal	Normal	Absent	No
Partial response (PR)	≥ 50% decrease in SPD[a]		Normal or no increase[b]	Absent or no increase[b]	Irrelevant (untested is acceptable)	Normal or decrease	Normal or decrease[c]	Absent or no increase	No
Stable disease (SD)	Fails to attain CR, PR, or PD.								
Progressive disease (PD)	PD is assessed if any one of the following is met.								
	≥ 50% increase[b] in SPD[a] or Nodal target lesion re-enlargement or extranodal target lesion reappearance		Increase[b] or re-enlargement	Increase[b] or re-appearance	Positive conversion	Increase or reappearance	Increase[c]	Increase[e] or reappearance	Yes
Inevaluable (NE)	Any variable is "inevaluable."								

[a]Sum of the product of the perpendicular diameters for multiple lesions.

[b]Increased target/nontarget lesions: ≥ 50% increase from nadir.

[c]Skin lesions: PR, ≥ 50% decrease from baseline; and PD, ≥ 50% increase from baseline.

[d]Peripheral blood lesions: CR, abnormal lymphocytes < 5% AND lymphocyte count < 4000/mm^3; PR, ≥ 50% decrease from baseline; and PD, ≥ 50% increase from nadir AND lymphocyte count ≥ 4000/mm^3.

[e]≥ 50% increase from baseline

8.1.2 Best Overall Response

At trial treatment discontinuation, the best overall response after treatment with ASTX660 for each subject will be recorded in the medical record and CRF.

8.2 Pharmacokinetic Assessments

8.2.1 Pharmacokinetic Plasma Samples

Blood samples (3 mL) will be collected in vacutainers containing ethylenediaminetetraacetic acid (EDTA) and processed into plasma to determine the concentrations of ASTX660. Additional metabolites that are not identified in the protocol may also be analyzed, if needed. In addition, PK samples may be used for the investigation of a bioanalytical method, if needed.

Blood samples for PK analysis will be collected at the time points as shown in Table 1.3-1 (schedule of assessments). Each blood sampling time point has an allowable window as shown in Table 8.2.1-1 and Table 8.2.1-2.

Table 8.2.1-1 Time Points of Blood Sampling for Pharmacokinetics and Allowable Windows (Phase 1 [Dose Escalation Part and ATLL Expansion Part])

Time Point	Allowable Window	Cycle 1				Cycle 2
		Day 1	Day 7	Day 15	Day 21	Day 1
Predose		X[a]	X[b]	X[a]	X[c]	–
0.5 h postdose	± 5 min	X	X	–	–	–
1 h postdose	± 5 min	X	X	–	–	–
2 h postdose	± 10 min	X	X	–	–	–
1 - 2 h postdose	–	–	–	X	X	X
3 h postdose	± 10 min	X	X	–	–	–
4 h postdose	± 20 min	–	–	X	X	–
5 h postdose	± 10 min	X	X	–	–	–
6 h postdose	± 10 min	X	X	–	–	–
8 h postdose	± 20 min	X	X	X	X	–
24 h postdose	± 60 min	X[e] (Day 2)	X (Day 8)	X[f] (Day 16)	X (Day 22)	–
48 h postdose	± 120 min	–	X (Day 9)	–	–	–
72 h postdose	± 120 min	–	X (Day 10	–	–	–

Allowable windows are as follows:

[a]3 h before administration

[b]Predose, AND 24 ± 2 h postdose on Day 6

[c]Predose, AND 24 ± 2 h postdose on Day 20

[e]Predose on Day 2

[f]Predose on Day 16

Table 8.2.1-2 Time Points of Blood Sampling for Pharmacokinetics and Allowable Windows (Phase 2)				
Time Point	**Allowable Window**	**Cycle 1**		
		Day 1	**Day 7**	**Day 21**
Predose		X[a]	X[b]	X[c]
1 - 2 h postdose	–	X	X	X
3 - 4 h postdose	–	X	X	–
4 h postdose	± 20 min	–	–	X
8 h postdose	± 20 min	X	X	X
24 h postdose	± 60 min	–	X (Day 8)	X (Day 22)

Allowable windows are as follows:

[a]3 h before administration

[b]Predose, AND 24 ± 2 h postdose on Day 6

[c]Predose, AND 24 ± 2 h postdose on Day 20

When vital signs or ECGs are scheduled at the same nominal time as PK sample collections, vital signs should be measured and ECGs should be performed before PK samples are collected.

The actual date and time of the PK sample collection will be recorded in the CRF.

After processing into plasma, aliquots will be placed into appropriately labeled tubes and will be placed in a freezer set at −70°C or −20°C, unless otherwise instructed in the Operations.

All plasma samples will be shipped to the bioanalytical laboratory for analysis. Additional information will be provided in the Operations.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.4 Pharmacogenomic Assessments

Not applicable.

8.5 Biomarker Assessments

Not applicable.

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.7 Safety Assessments

Details pertaining to the definitions, collection, reporting, and follow-up of AEs are described in Section 8.8.

8.7.1 Dose Limiting Toxicity

The definition of DLT and details regarding the DLT assessment period are described in Section 4.1, Type/Design of Trial.

8.7.2 Clinical Laboratory Assessments

The clinical laboratory assessments described in Section 10.2 will be performed according to the procedures established by the trial site. Blood and urine samples will be collected, and the date of blood collection, date of urine collection, and test results will be recorded in the CRF. Urine or serum pregnancy test (human chorionic gonadotropin [hCG] test) will be performed for females of childbearing potential (FOCBP).

The level of HBV-DNA will be monitored in subjects who are positive for HBc antibody or HBs antibody at screening, in accordance with the "Guidelines for the prevention of hepatitis B virus reactivation in patients receiving immunosuppressive therapy or chemotherapy.[24]" Virus test (HBV-DNA quantification) and serum chemistry will be performed from Cycle 2 onward, according to Section 1.3, Schedule of Assessments.

8.7.3 Physical Examination

The investigator or subinvestigator will check physical findings by examining each of the following sites: head, ears, eyes, nose, laryngopharynx, chest, abdomen, urogenital system, limbs, nerves, skin, and mucosa. The assessment date and results will be recorded in the CRF. The same investigator or subinvestigator should perform observations, whenever possible. Any clinically significant physical finding that detected after screening examination will be recorded as an AE in the CRF.

8.7.4 Vital Signs

After at least a 3-minute rest, blood pressure (systolic/diastolic), pulse rate, SpO_2, and body temperature will be measured in a sitting position. The date of measurement and measurement results will be recorded in the CRF.

8.7.5 12-Lead Electrocardiogram (Local)

According to the procedures established by the trial site, 12-lead ECGs will be performed using a 12-lead electrocardiograph.

In phase 1 (dose escalation part), 12-lead ECGs will be performed at screening, predose and 2 hours postdose on Day 15 and Day 21 of Cycle 1, and from Cycle 2 Day 1 onward, predose on Day 1 of each cycle. In phase 1 (ATLL expansion part), 12-lead ECGs will be performed at screening, predose and 2 hours postdose on Day 1, Day 7, Day 15, and Day 21 of Cycle 1, and from Cycle 2 Day 1 onward, predose on Day 1 of each cycle. In phase 2, 12-lead ECGs will be performed at screening, predose and 2 hours postdose on Cycle 1 Day 7, and from Cycle 2 Day 1 onward, predose on Day 1 of each cycle.

The investigator or subinvestigator will check each ECG chart and determine whether the ECG is normal (within the normal range) or abnormal, and date and sign the chart. The date and time of measurement, measured 12-lead ECG data (heart rate, RR interval, PR interval, QRS width, QT interval, and QT corrected for heart rate by Fridericia's formula [QTcF] interval), assessment of normality/abnormality, and abnormal findings (if any) will be recorded in the CRF. The same investigator or subinvestigator should perform assessment, whenever possible.

[redacted]

8.7.7 Other Safety Variables

8.7.7.1 Body Weight

Body weight will be measured according to the procedures established by the trial site, and the date of measurement and measurement result will be recorded in the CRF.

8.7.7.2 Eastern Cooperative Oncology Group Performance Status

The investigator or subinvestigator will assess the subject's PS according to the ECOG criteria (see Table 8.7.7.2-1), and the date of assessment and results will be recorded in the CRF.

Table 8.7.7.2-1 ECOG PS

Score	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: ECOG PS (https://ecog-acrin.org/resources/ecog-performance-status [accessed August 2019])

8.7.7.3 Echocardiogram

Echocardiography or MUGA scan will be performed according to the procedures established by the trial site, and the LVEF will be measured. The date of measurement, measurement method, and measurement result will be recorded in the CRF.

8.7.7.4 Lung Field Assessment by PET-CT or CT Scans

Lung field on CT images by PET-CT or CT scan will be reviewed as part of the safety evaluation, and the date of examination, assessment of normality/abnormality (normal, abnormal), and abnormal findings (if any) will be recorded in the medical record and CRF. Any clinically significant finding will be assessed as an AE.

8.7.7.5 Chest X-Ray

Chest x-ray will be performed according to the procedures established by the trial site, and the date of examination, assessment of normality/abnormality (normal, abnormal), and abnormal findings (if any) will be recorded in the medical record and CRF. Any clinically significant finding will be assessed as an AE. However, if the lung field was assessed on CT images within 7 days, its results can substitute for chest x-ray.

8.8 Adverse Events

8.8.1 Definitions

An AE is defined as any untoward medical occurrence in a patients or clinical trial subject administered an IMP and which does not necessarily have a causal relationship with this treatment. Adverse events would not include information recorded as medical history at screening for pre-planned procedures for which the underlying condition was known and no worsening occurred. An adverse drug reaction is any untoward and unintended response to an IMP related to any dose administered.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the IMP caused the AE.

Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the start of open-label treatment. In more detail, TEAEs are all AEs which started after the start of open-label IMP treatment; or if the event was continuous from baseline and was worsening after the start of open-label IMP treatment. However, AEs will not include worsening of the primary disease in this trial

An SAE includes any event that results in any of the following outcomes:

- Death
- Life-threatening; ie, the subject was, in the opinion of the investigator or subinvestigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Persistent or significant incapacity/disability or substantial disruption of the ability to conduct normal life functions.
- Requires inpatient hospitalization or prolongs hospitalization.
  - Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported.
  - Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs.
  - Prescheduled hospitalization to address a condition that has existed prior to the signing of the ICF should not be considered an SAE.
- Congenital anomaly/birth defect.
- Other medically significant events that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; eg, allergic bronchospasm requiring intensive treatment in an emergency room or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Nonserious AEs are all AEs that do not meet the criteria for a "serious" AE.

Immediately Reportable Event (IRE):

- Any SAE.
- Any DLT.
- Any AE related to occupational exposure.
- Potential serious hepatotoxicity (see Section 8.8.6).
- Pregnancies are also defined as IREs. Although normal pregnancy is not an AE, it will mandate IMP discontinuation and must be reported on an IRE form and the Pregnancy Surveillance Form(s) to the sponsor. Pregnancy will only be documented on the AE CRF if there is an abnormality or complication. This includes pregnancy of the subject or the partner of the subject.

Clinical Laboratory Test Value Changes: It is the investigator/subinvestigator's responsibility to review the results of laboratory tests for each individual subject as they become available. The investigator or subinvestigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. If this laboratory value is considered medically relevant (ie, clinically significant) by the investigator or subinvestigator (subject is symptomatic, requiring corrective treatment or further evaluation), or if the laboratory value leads to discontinuation, and/or fulfills a seriousness criterion, this is considered an AE.

Severity:

Severity of AEs will be graded according to CTCAE version 4.03, on a 5-point scale of Grades 1 through 5 as follows:

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

A Semi-colon indicates 'or' within the description of the grade.

[a]Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b]Self care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

IMP Causality: Assessment of causal relationship of an AE to the use of the IMP is defined as follows:

Related:	There is a reasonable possibility of a temporal and causal relationship between the IMP and the AE.
Not Related:	There is no temporal or causal relationship between the IMP and the AE.

8.8.2 Eliciting and Reporting Adverse Events

The investigator or subinvestigator will regularly assess subjects for the occurrence of AEs. To avoid bias in eliciting AEs, subjects should be asked the nonleading question: "How have you felt since your last visit?" All AEs (serious and nonserious) reported by the subject must be recorded on the source documents and CRF provided by the sponsor. Adverse event collection will begin after a subject signs the ICF.

Medical terminology should be used for AE reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms.

In addition, the sponsor must be notified immediately by e-mail, in principle, of any IREs according to the procedure in Section 8.8.3. Special attention should be paid to recording hospitalization and concomitant medications.

The AE, start date (including start time, in the event vomiting occurs on the scheduled date of blood sampling for PK analysis. At a minimum, the hour should be identified in the event the exact time is unknown), end date, seriousness, severity, relationship to trial treatment (IMP causality), action taken with trial treatment, and outcome will be recorded on the source documents and in the CRF.

8.8.3 Immediately Reportable Events

The investigator or subinvestigator must immediately report (within 24 hours), using an IRE form, etc, after he/she or site personnel become aware of any IRE (SAE, DLT, AE related to occupational exposure, potential serious hepatotoxicity, and confirmed pregnancy), in principle, by e-mail to the sponsor or designee using the contact information on the cover page of this protocol (please note that the IRE form is NOT the AE CRF). The utmost consideration should be given to the protection of subjects' privacy when forwarding IRE forms, etc. If reporting by e-mail is not available, communication by fax may be used.

8.8.4 Medical Device Incidents (Including Malfunctions)

Not applicable.

8.8.5 Adverse Events of Special Interest

Not applicable.

8.8.6 Potential Serious Hepatotoxicity

For a subject who experiences an elevation in AST or ALT that is ≥ 3 times the ULN, a total bilirubin level should also be evaluated. If the total bilirubin is ≥ 2 times the ULN, complete an IRE form, etc, with all values listed and also report as an AE in the CRF.

8.8.7 Procedure for Breaking the Blind

This trial does not use blinding procedures.

8.8.8 Follow-up of Adverse Events

The follow-up period is defined as 30 days after trial treatment discontinuation or the start of new treatment for the primary disease, whichever comes first.

8.8.8.1 Follow-up of Nonserious Adverse Events

Nonserious AEs that are identified at any time from the date on which the subject signs the ICF through the last day of the follow-up period must be recorded on the AE CRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing on the last day of the follow-up period will be recorded as ongoing in the CRF. For any AE having been identified throughout the trial, during analysis, additional relevant medical history information may be requested by the sponsor to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history, and occupation).

8.8.8.2 Follow-up of Immediately Reportable Events

This trial requires that subjects be actively monitored for IREs up to the last day of the follow-up period.

Immediately reportable events that are identified or ongoing on the last day of the follow-up period must be recorded as such on the AE CRF page and the IRE form, etc. If updated information (eg, resolved status) on IRE status becomes available after the last day of the follow-up period for the subject (up to the last day of the follow-up period for the final subject in the entire trial), this must be reported to the sponsor and recorded on the AE CRF page and the IRE form, etc, according to the appropriate reporting procedures described in Section 8.8.3.

It is expected that the investigator or subinvestigator will provide or arrange appropriate supportive care for the subject and will provide prompt updates on the subject's status to the sponsor. The investigator or subinvestigator will follow IREs until the events are:

- Resolved,
- Stabilized,
- The subject is lost to follow-up, or
- Has died.

Resolution means that the subject has returned to the baseline state of health and stabilized means that the investigator or subinvestigator does not expect any further improvement or worsening of the subject's condition. The investigator or subinvestigator will continue to report any significant follow-up information to the sponsor up to the point the event has resolved or stabilized, or the subject is lost to follow-up, or has died.

Refer to Section 10.3 for additional information regarding the follow-up period for subjects that become pregnant or for pregnant partners of male subjects.

8.8.8.3 Follow-up and Reporting of Immediately Reportable Events Occurring After the Last Day of the Follow-up Period

Any new IREs reported to the investigator or subinvestigator which occur after the last day of the follow-up period and are determined by the investigator or subinvestigator to be reasonably associated with the use of the IMP, should be reported to the sponsor according to the procedures outlined in Section 8.8.3. This may include IREs that are captured on follow-up telephone contact or at any other time point after the defined trial period and continue to report any significant follow-up information to the sponsor until the events are resolved or stabilized, or the subject is lost to follow-up or has died.

8.9 Treatment of Overdose

For treatment of overdoses, please refer to the IB Section 6.4 for overdose. If the signs and symptoms due to overdose meet the criteria for an SAE, the actual dose and clinical signs and symptoms associated with an overdose will be recorded on the source document and in the CRF, and the sponsor must be notified within 24 hours by e-mail, according to the procedure in Section 8.8.3, Immediately Reportable Events.

8.10 Subject Assessment Recording

Not applicable.

8.11 Other Assessments

8.11.1 Efficacy and Safety Data Review Committee

The Efficacy and Safety Data Review Committee will consist of individuals who are independent of the parties involved in the trial (eg, sponsor, medical expert, investigators, and subinvestigators) and are not directly involved in the trial. The committee will review the trial-related safety, serious or unexpected AEs, and efficacy from a third party standpoint, and will make recommendations, based on the obtained results of assessment, regarding the conduct and results of the trial, including continuation, modification, or discontinuation of the trial. For phase 1 (dose escalation part), the committee will also make recommendations about DLT assessment, dose, and whether to advance to phase 2. For phase 2, the committee will also serve as the Central Efficacy Evaluation Committee.

8.11.2 Central Pathological Diagnosis Committee

Phase 2 will include the central pathological diagnosis committee, which is a pathological diagnosis institution independent of the parties involved in the trial (eg, sponsor, medical expert, investigators, and subinvestigators). The central pathological diagnosis committee will assess the disease type using pathological samples collected from the trial site, according to the procedure prepared separately.

9 Statistical Considerations

9.1 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),[16]" 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.

9.2 Datasets for Analysis

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

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.

The efficacy analysis set 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.

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.

9.3 Handling of Missing Data for Primary and Secondary Endpoint Analysis

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

9.4 Statistical Analyses

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.

9.4.1 Efficacy Analyses

For the efficacy analysis set, the analysis of efficacy will be summarized as follows.

9.4.1.1 Primary Efficacy Endpoint Analysis

Regarding the ORR 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 CR or PR) over the analysis set. The frequency of the best overall response as assessed by the Central Efficacy Evaluation Committee will be summarized.

9.4.1.2 Key Secondary Efficacy Endpoint Analysis

Regarding the ORR as assessed by the investigator or subinvestigator, the ORR and its two-sided 95% CI (by Clopper-Pearson method) will be calculated. The frequency of the best overall response as assessed by the investigator or subinvestigator will be summarized.

9.4.1.3 Secondary Efficacy Endpoint Analysis

Kaplan-Meier plots will be provided for the DOR, PFS, OS, TTR, and TTP, and the median and 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, date of the start of new treatment for the primary disease, or date of death due to any cause, whichever occurs earlier. Subjects without a documented PD or death date will be censored on the last date of overall response assessment, or responders who undergo transplantation will be censored on the date of transplant.
- 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, date of the start of new treatment for the primary disease, or date of death due to any cause, whichever occurs earlier. Subjects without a documented PD or death date will be censored on the last date of overall response assessment, or responders who undergo transplantation will be censored on the date of transplant.
- 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.
- 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.
- 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 or date of the start of new treatment for the primary disease, whichever occurs earlier. Subjects without a documented PD date will be censored on the last date of overall response assessment, or responders who undergo transplantation will be censored on the date of transplant.

Overall response for the definitions of DOR, PFS, TTR, and TTP will be based on assessment by the investigator or subinvestigator.

In addition, the proportion of subjects who proceed to transplantation (proportion of subjects who undergo transplantation) will be calculated.

9.4.1.4 Control of Experiment-wise Type 1 Error

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.

9.4.1.5 Other Efficacy Endpoint Analysis

Not applicable.

9.4.2 Safety Analysis

For the safety analysis set unless otherwise indicated, the analysis of safety will be summarized as follows.

9.4.2.1 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:

- TEAEs
- TEAEs by CTCAE grade
- TEAEs potentially causally related to the IMP
- TEAEs with an outcome of death
- Serious TEAEs
- TEAEs leading to discontinuation of the IMP

For phase 1 (dose escalation part), the frequencies of DLTs (number and proportion of subjects with DLT) will be summarized in the DLT analysis set.

9.4.2.2 Clinical Laboratory Data

Hematology, serum chemistry, coagulation, and urinalysis (excluding qualitative tests) at each time point will be summarized using the following.

- Descriptive statistics of measured value
- Descriptive statistics of change from baseline
- Shift tables from baseline by CTCAE Grade

Urinalysis (qualitative tests) at each time point will be summarized using the following.

- Shift tables of measured values from baseline

9.4.2.3 Vital Signs Data

Vital signs (blood pressure, pulse rate, SpO_2, and body temperature) at each time point will be summarized using the following.

- Descriptive statistics of measured value
- Descriptive statistics of change from baseline

9.4.2.4 Electrocardiogram Data

Heart rate, RR interval, PR interval, QRS width, QT interval, and QTcF interval at each time point after the start of trial treatment will be summarized using the following.

- Descriptive statistics of measured value
- Descriptive statistics of change from baseline

For QTcF interval, the following will be summarized.

- Number and proportion of subjects who showed a measured value of "> 450 msec," "> 480 msec," and "> 500 msec"
- Number and proportion of subjects who had a change from baseline: > 30 msec and > 60 msec

At each time point, ECG assessment of normality/abnormality will be summarized using the following.

- Shift tables from baseline

9.4.2.5 Other Safety Data

At each time point, ECOG PS will be summarized using the following.

- Shift tables from baseline

Body weight and LVEF at each time point will be summarized using the following.

- Descriptive statistics of measured value
- Descriptive statistics of change from baseline

9.4.3 Other Analyses

9.4.3.1 Analysis of Demographic and Baseline Characteristics

Based on the safety analysis set, for demographic and baseline characteristics, including age, gender, race, ethnicity, height, body weight (screening period), and ECOG PS (screening period), calculation of descriptive statistics or tabulation of frequencies will be performed according to the characteristics of each parameter.

9.4.3.2 Pharmacokinetic Analysis

1) Calculation of Descriptive Statistics

In the PK analysis set, descriptive statistics will be calculated for the parameters for which numerical data were obtained from the majority of subjects.

- Plasma drug concentration: to be summarized for each blood sampling point by period and by dose.
- PK parameters: to be summarized for each parameter by period and by dose.

2) Dose Proportionality

If ASTX660 have been administered at 3 or more dose levels in phase 1 (dose escalation part), the parameters after multiple-dose will 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: parameter (C_{max}, AUC_{24h})

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

9.4.3.3 Pharmacodynamic Analysis

See Section 9.4.3.6.

9.4.3.4 Pharmacokinetic/Pharmacodynamic Analysis

No PK/PD analysis is planned.

9.4.3.5 Pharmacogenomic Analysis

No pharmacogenomic analysis is planned.

[redacted]

9.5 Interim Analysis

No interim analysis is applicable.

9.5.1 Data Monitoring Committee

Not applicable.

10 Supporting Documentation and Operational Considerations

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Ethics and Responsibility

This trial must be conducted in compliance with the protocol, ICH-GCP Guideline (E6) [25], international ethical principles derived from the Declaration of Helsinki and Council for International Organizations of Medical Science (CIOMS) guidelines, and applicable local laws and regulations. Each trial site will seek approval by an IRB according to regional requirements, and the trial site will provide that documentation to the sponsor. The IRB will evaluate the ethical, scientific, and medical appropriateness of the trial. Further, in preparing and handling the CRF, IRE and any safety information, the investigator, subinvestigator, and their staff will take measures to ensure adequate care in protecting subject privacy. To this end, a subject ID will be used to identify each subject.

Financial aspects, subject insurance, and the publication policy for the trial will be documented in the agreement between the sponsor and the trial site.

10.1.2 Informed Consent

Informed consent will be freely obtained from all subjects (or their guardian or legally acceptable representative, as applicable for local laws). The ICF will be approved by the same IRB that approves this protocol.

Each ICF will comply with the ICH-GCP Guidelines (E6),[25] and local regulatory requirements. In support of the site's standard process for administering informed consent, this trial will also allow for eICF as a tool within applicable regions and trial sites. The eICF utilizes the IRB approved site-specific ICF to offer subjects an enhanced platform to review and understand their rights as a research subject as well as required trial procedures. When possible, trial sites will have subjects review and sign the eICF prior to starting any trial procedures; however, if local regulations do not allow for use of the electronic format, subjects may continue in the trial utilizing the standard paper and wet ink signature process.

Investigators or subinvestigators may discuss trial availability and the possibility for entry with a potential subject without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this trial, including withdrawal from current medication(s).

Potential subjects are free to refuse entry into the trial, or withdraw from the trial at any time, without justification, and there will be no consequences to their further care.

Once appropriate essential information has been provided and fully explained in layman's language to the subject by the investigator or subinvestigator (or a qualified designee), and it has been documented that the subject has had the opportunity to ask questions and have those questions answered, the IRB-approved ICF will be signed and dated by both the subject and the person obtaining consent (investigator/subinvestigator or designee), as well as by any other parties required by the IRB. The subject will receive a copy of the signed ICF; the original shall be kept on file by the investigator or subinvestigator. Subjects may be asked to sign additional ICFs if the protocol is amended and the changes to the protocol result in additional information that needs to be provided to the subjects, so that they can make a knowledgeable and voluntary decision on continued trial participation. Female partners of male subjects who become pregnant during the course of the trial may be asked to sign additional ICFs in order to collect additional information regarding the nonsubject partner and fetus.

[redacted]

10.1.3 Confidentiality

All information generated in this trial will be considered confidential and will not be disclosed to anyone not directly concerned with the trial without the sponsor's prior written permission. Subject confidentiality requirements of the region(s) where the trial is conducted will be met. However, authorized regulatory officials and sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All IMPs, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the sponsor.

Subjects will be identified only by unique subject ID in the CRF. If further subject identification is required, subjects' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

10.1.4 Quality Control and Quality Assurance

The sponsor will implement the quality management activities for this trial according to ICH-GCP guidance and standard operating procedures.

Details of the quality management activities will be separately provided in the quality management plan.

10.1.4.1 Monitoring

The sponsor has ethical, legal, and scientific obligations to follow this trial in accordance with established research principles, ICH-GCP Guideline (E6)[25], and applicable regulatory requirements and local laws. As part of a concerted effort to fulfill these obligations (maintain current personal knowledge of the progress of the trial), the sponsor's monitors will visit the site during the trial, as well as communicate frequently via telephone, e-mail, and written communications. In addition, all investigators or subinvestigators and trial site personnel will undergo initial and ongoing training for this particular trial, and this training will be clearly documented.

10.1.4.2 Auditing

The sponsor's Quality Assurance Unit (or representative) may conduct trial site audits. Audits will include, but are not limited to, IMP supply, presence of required documents, the informed consent process, and a review of the CRF with source documents, as applicable. The investigator will cooperate with audits.

Regulatory authorities may inspect the trial site during or after the trial. The investigator will cooperate with such inspections and will contact the sponsor immediately if such an inspection occurs.

10.1.5 Protocol Deviations

In the event of a significant deviation from the protocol due to an emergency, accident, or mistake (eg, violation of informed consent process, IMP dispensing or subject dosing error, treatment assignment error, subject enrolled in violation of eligibility criteria or concomitant medication criteria), the investigator/subinvestigator or designee will contact the sponsor or designee at the earliest possible time by telephone or via e-mail. The investigator/subinvestigator and sponsor (or designee) will come as quickly as possible to a joint decision regarding the subject's continuation in the trial. This decision will be documented by the investigator/subinvestigator and the sponsor (or designee) and reviewed by the site monitor.

Any major protocol deviation will be recorded in the CRF along with the start date and details of the deviation.

10.1.6 Records Management

10.1.6.1 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this trial will be maintained by the trial site and made available for direct inspection by authorized persons.

Investigator(s)/trial site(s) will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. Documents (eg, original copies of reports and measurement data) for drug concentration measurement, [redacted] will be stored by the bioanalytical laboratory, [redacted] respectively. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

10.1.6.2 Data Collection

During each subject's visit to the site, an investigator/subinvestigator or their designee participating in the trial will record information to document all significant observations. At a minimum, these notes will contain:

- Documentation of the informed consent process, including any revised consents;
- Documentation of the investigator/subinvestigator's decision to enroll the subject into the trial, the review of all inclusion/exclusion criteria prior to IMP administration, and confirmation of the subject's actual participation in the trial;
- The date of the visit and the corresponding Visit or Day in the trial schedule;
- General subject status remarks, including any *significant* medical findings. The severity, frequency, duration, action taken, and outcome of any AEs and the investigator/subinvestigator's assessment of relationship to IMP must also be recorded;
- Any changes in concomitant medications or dosages;
- Date and time of taking IMP;
- A general reference to the procedures completed
- The signature (or initials) and date of the investigator or subinvestigator (or designee) who made an entry in the medical record.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Any changes to information in medical records and other source documents will be initialed and dated on the day the change is made by a trial site staff member authorized to make the change. Changes will be made by striking a single line through erroneous data (so as not to obliterate the original data), and clearly entering the correct data (eg, ~~wrong data~~ right data). If the reason for the change is not apparent, a brief explanation for the change will be written in the source documentation by the investigator/subinvestigator or their designee.

Information from medical records and other source documents will be entered by trial site personnel onto eCRFs in the sponsor's electronic data capture (EDC) system that is 21 CRF Part 11 compliant. Changes to the data will be captured by an automatic audit trail in the EDC system.

[redacted]

10.1.6.3 File Management at the Trial Site

The head of the trial site will ensure that the trial site file is maintained in accordance with the ICH-GCP Guideline (E6) Chapter 8 and as required by applicable local regulations. The trial site will take measures to prevent accidental or premature destruction of these documents.

10.1.6.4 Records Retention at the Trial Site

The trial site will maintain all materials and records relevant to this trial for the longest of the following 3 periods. If the sponsor needs a longer retention, however, the trial site will discuss the period and method of retention with the sponsor.

- A period of at least 2 years after the date on which approval to market the drug is obtained; however, if the sponsor notifies the trial site that the drug development is terminated or the results of the trial are not included in the new drug application form, a period of at least 3 years after the notification.
- A period of at least 3 years after the trial is discontinued or completed.
- [redacted]

The trial site must not dispose of any records relevant to this trial without either (1) written permission from the sponsor or (2) provision of an opportunity for the sponsor to

collect such records. The trial site will be responsible to maintain adequate and accurate electronic or hard copy source documents of all observations and data generated during this trial including any data clarification forms received from the sponsor. Such documentation is subject to inspection by the sponsor and relevant regulatory authorities.

10.1.6.5 Publication Authorship Requirements

Authorship for any Otsuka-sponsored publications resulting from the conduct of this trial will be based on International Committee of Medical Journal Editors (ICMJE) authorship criteria (http://www.icmje.org/recommendations). According to ICMJE guidelines, one may be considered an author only if the following criteria are met:

1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

Investigators or other trial subjects who do not qualify for authorship may be acknowledged in publications resulting from the trial. By agreeing to participate in the trial, investigators or other trial subjects consent to such acknowledgement in any publications resulting from its conduct.

10.2 Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 10.2-1 will be performed.

Table 10.2-1 Clinical Laboratory Assessments

Hematology	Serum Chemistry	Urinalysis
• Complete blood count (CBC) - Hemoglobin - Hematocrit - Red blood cell count - White blood cell (WBC) count - Platelet count • WBC differential - Neutrophils - Eosinophils - Basophils - Lymphocytes - Monocytes - Abnormal lymphocytes	• Albumin • Alkaline phosphatase (ALP) • Alanine aminotransferase (ALT) • Aspartate aminotransferase (AST) • Blood urea nitrogen (BUN) • Total bilirubin • Direct bilirubin • Creatinine • γ-Glutamyl transpeptidase (γ-GTP) • Glucose (fasting) • Lactate dehydrogenase (LDH) • Calcium • Chloride • Inorganic phosphorus • Potassium • Sodium • Total protein • Uric acid • Amylase • Amylase isozymes • Lipase • Hemoglobin A1c • C-reactive protein (CRP) • KL-6 • [redacted] • [redacted]	• Occult blood • Glucose • Ketones • pH • Protein
Coagulation	Virus tests	Pregnancy test
• Prothrombin time/international normalized ratio (PT-INR) • Activated partial thromboplastin time (APTT)	• HIV antibody • HBc antibody • HBs antibody • HBV-DNA • HCV antibody	• Urine [or serum] pregnancy for FOCBP

[redacted]

10.3 Appendix 3: Contraceptive Guidance and Collection of Pregnancy Information

Females of childbearing potential are females whose menstruation has started and who are not documented as sterile (eg, have had a bilateral oophorectomy, or hysterectomy, or who have been postmenopausal for at least 12 months, except for cases where menopause could be due to the effect of antineoplastic treatment).

For males and FOCBP who are sexually active, there must be a documented agreement that the subject and their partner will take effective measures (ie, 2 different approved methods of birth control) to prevent pregnancy during the course of the trial and for 3 months after the last dose of IMP. Unless the subject or their partner is sterile (ie, females who have had a bilateral oophorectomy, have had a hysterectomy, or have been postmenopausal for at least 12 consecutive months except for cases where menopause could be due to the effect of antineoplastic treatment; or males who have had a bilateral orchiectomy), 2 of the following approved methods of birth control must be used: vasectomy, tubal ligation, intrauterine device, birth control pill, or condom (all of these methods are approved or certified in Japan). Abstinence is not an acceptable method of birth control. Any single method of birth control, including vasectomy and tubal ligation, may fail, leading to pregnancy. Male subjects must also agree not to donate sperm from trial screening through 3 months after the last dose of IMP.

Before enrolling males and females in this clinical trial, investigators or subinvestigators must review the below information about trial participation as part of the ICF process. The topics should generally include:

- General information
- Informed consent form
- Pregnancy prevention information
- Drug interactions with hormonal contraceptives
- Contraceptives in current use
- Follow-up of a reported pregnancy

Before trial enrollment, males and FOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. Subjects must sign the ICF confirming that the above-mentioned risk factors and the consequences were discussed.

A urine or serum pregnancy test for hCG will be performed at screening on all FOCBP. If a urine test is performed and is positive, the investigator or subinvestigator will follow-up with a confirmatory serum test.

During the trial, all FOCBP should be instructed to contact the investigator or subinvestigator immediately if they suspect they might be pregnant (eg, missed or late menstrual cycle). Male subjects must be instructed to contact the investigator immediately, during the trial, if their partner suspects that they might be pregnant (eg, missed or late menstrual cycle).

If a subject is suspected to be pregnant before she receives IMP, the IMP administration must be withheld until the results of serum pregnancy tests are available. If the pregnancy is confirmed, the subject must not receive the IMP and must not be enrolled in the trial. If pregnancy is suspected while the subject is taking IMP, the IMP must be withheld immediately (if reasonable, taking into consideration any potential withdrawal risks) until the result of the pregnancy test is known. If pregnancy is confirmed, the IMP will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety) and the subject will be withdrawn from the trial. Exceptions to trial discontinuation may be considered for life-threatening conditions only after consultations with the IRE contact (see the title page of this protocol for contact information).

The investigator or subinvestigator must immediately notify the sponsor (within 24 hours) of any pregnancy associated with IMP exposure during the trial and for at least 30 days after the last dose of IMP, and record the event on the IRE form, etc, and forward it to the sponsor. The sponsor will forward the Pregnancy Surveillance Form(s) to the investigator or subinvestigator for monitoring the outcome of the pregnancy.

Protocol required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator or subinvestigator must report to the sponsor, on the Pregnancy Surveillance Form(s), follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants will be followed for a minimum of 6 months from the date of birth.

10.4 Appendix 4: Abbreviations

Abbreviation	Definition
%TBSA	Percentage total body surface area
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
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 $[(AUC_\infty - AUC_t) / AUC_\infty \times 100]$
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_∞/D	AUC_∞ normalized by dose
AUC_τ	Area under the concentration time curve during a dosing interval (τ) at steady state
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
BUN	Blood urea nitrogen
CAR-T	Chimeric antigen receptor T cell
CFR	Code of Federal Regulations
cIAP	Cellular inhibitor of apoptosis protein
CIOMS	Council for International Organizations of Medical Science
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
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
[redacted]	[redacted]
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid

Abbreviation	Definition
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FDG	Fluorodeoxyglucose
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
γ-GTP	γ-Glutamyl transpeptidase
HBc	Hepatitis B core
HBs	Hepatitis B surface
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HTLV-1	Human T-cell leukemia virus type 1
IAP	Inhibitor of apoptosis protein
IB	Investigator's brochure
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
INR	International normalized ratio
IPI	International prognostic index
IRE	Immediately reportable event
IWG	International working group
JCOG	Japan Clinical Oncology Group
λ_z	Apparent terminal-phase disposition rate constant (first-order)
LDH	Lactate (lactic acid) dehydrogenase
LDi	Longest transverse diameter of a lesion
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mSWAT	Modified severity weighted assessment tool
MTD	Maximum tolerated dose
MUGA	Multiple gated acquisition
NK	Natural killer
NYHA	New York Heart Association
ORR	Overall response rate
OS	Overall survival
[redacted]	[redacted]
PD	Pharmacodynamic
PET-CT	Positron emission tomography-computed tomography
PFS	Progression free survival
PQC	Product quality complaint
PR	Partial response
PS	Performance status
PTCL	Peripheral T-cell lymphoma

Abbreviation	Definition
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
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
SD	Stable disease
SPD	Sum of the product of the perpendicular diameters for multiple lesions
SpO_2	Percutaneous oxygen saturation
ST	Trimethoprim-sulfamethoxazole
$t_{1/2,z}$	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
TRAF2	TNF receptor associated factor 2
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
WHO	World Health Organization
XIAP	X-linked inhibitor of apoptosis protein

10.5 Appendix 5: Protocol Amendments

The investigator or subinvestigator will not make any changes to this protocol without the sponsor's prior written consent and subsequent approval/favorable opinion by the IRB. Any permanent change to the protocol, whether an overall change or a change for specific trial site(s), must be handled as a protocol amendment. Any amendment will be written by the sponsor. Each amendment will be submitted to the IRB, as required by local regulations. Except for "administrative" or "nonsubstantial" amendments, investigators or subinvestigators will wait for IRB approval/favorable opinion of the amended protocol before implementing the change(s). Administrative amendments are defined as having no effect on the safety of subjects, conduct or management of the trial, trial design, or the quality or safety of IMP(s) used in the trial. A protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, followed by IRB notification within local applicable timelines. If necessary, the sponsor will submit protocol amendments to the applicable regulatory agencies within local applicable timelines.

When the IRB, investigators, and/or the sponsor conclude that the protocol amendment substantially alters the trial design and/or increases the potential risk to the subject, the currently approved written ICF will require similar modification. In such cases, after approval/favorable opinion of the new ICF by the IRB, repeat written informed consent will be obtained from subjects enrolled in the trial before expecting continued participation and before the amendment-specified changes in the trial are implemented.

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Agreement

I, the undersigned principal investigator, have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal, and scientific information necessary to conduct this trial in accordance with the principles of Good Clinical Practices and as described herein and in the sponsor's (or designee's) Clinical Trial Agreement.

I will provide copies of the protocol to all physicians, nurses, and other professional personnel to whom I delegate trial responsibilities. I will discuss the protocol with them to ensure that they are sufficiently informed regarding the investigational new drug, ASTX660, the concurrent medications, the efficacy and safety parameters and the conduct of the trial in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) responsible for such matters in the clinical trial facility where ASTX660 will be tested prior to commencement of this trial. I agree to adhere strictly to the attached protocol (unless amended in the manner set forth in the sponsor's Clinical Trial Agreement, at which time I agree to adhere strictly to the protocol as amended).

I understand that this IRB-approved protocol will be submitted to the appropriate regulatory authority/ies by the sponsor. I agree that clinical data entered on eCRF by me and my staff will be utilized by the sponsor in various ways, such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow sponsor and designee monitors and auditors full access to all medical records at the research facility for subjects screened or enrolled in the trial.

I agree to await IRB approval before implementation of any substantial amendments to this protocol. If, however, there is an immediate hazard to subjects, I will implement the amendment immediately, and provide the information to the IRB within the required local applicable timelines. Administrative changes to the protocol will be transmitted to the IRB for informational purposes only, if required by local regulations.

I agree to provide all subjects with informed consent forms, as required by the applicable regulations and by ICH guidelines. I agree to report to the sponsor any adverse experiences in accordance with the terms of the sponsor's Clinical Trial Agreement and the relevant regional regulation(s) and guideline(s). I further agree to provide all required information regarding financial certification or disclosure to the sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s). I understand that participation in the protocol involves a commitment to publish the data from this trial in a cooperative publication before publication of efficacy and safety results on an individual basis may occur, and I consent to be acknowledged in any such cooperative publications that result.

_____	_____
Principal Investigator Print Name	Trial Site Name
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Signature	Date

This agreement is electronically signed by the sponsor. The sponsor signature page is attached to this document.