CLINICAL STUDY PROTOCOL

Single-Arm, Phase 2 Study of Valemetostat Tosylate Monotherapy in Subjects with Relapsed/Refractory Peripheral T-Cell Lymphoma

(Valemetostat tosylate [DS-3201b], an enhancer of zeste homolog [EZH] 1/2 dual inhibitor, for R/R PTCL)

PROTOCOL NUMBER DS3201-A-U202

IND NUMBER 132312

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VERSION 4.0, 09 Sep 2022

DAIICHI SANKYO, INC.

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INVESTIGATOR AGREEMENT

Single-arm, Phase 2 Study of Valemetostat Tosylate Monotherapy in Subjects with Relapsed/Refractory Peripheral T-Cell Lymphoma

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo, Inc. representative listed below.

PPD	PPD
Print Name	**Signature**
PPD	12 SEP 2022
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (ICH E6[R2]), which has its foundations in the Declaration of Helsinki, and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing.

Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

DOCUMENT HISTORY

Version Number	Version Date
4.0	09 Sep 2022
3.0	20 May 2022
2.0	09 Mar 2021
1.0	12 Oct 2020

SUMMARY OF CHANGES

Please refer to the comparison document for protocol Version 4.0 (dated 09 Sep 2022) versus protocol Version 3.0 (dated 20 May 2022) for actual changes in text. The summary of changes below is a top-line summary of major changes in the current DS3201-A-U202 clinical study protocol (Version 4.0) by section.

Amendment Rationale:

The main purpose of this amendment is to reflect the Sponsor's strategic decision not to pursue the adult T-cell leukemia/lymphoma indication and to therefore close enrollment into Cohort 2. The closure of Cohort 2 was not due to safety, and the safety profile remains consistent with that observed during the ongoing development program. No new safety signals have been observed, and the benefit/risk profile continues to support further clinical development.

CONVENTIONS USED IN THIS SUMMARY OF CHANGES
All locations (section numbers and/or paragraph/bullet numbers) refer to the current protocol version, which incorporates the items specified in this Summary of Changes document.
Minor edits, such as updates to language that does not alter the original meaning, updates to version numbering, formatting, change in font color, corrections of typographical errors, use of abbreviations, moving verbiage within a section or table, changes in style, or changes in case, are not noted in the table below.

Section # and Title	Description of Change	Brief Rationale
Protocol Synopsis (Study Objectives/Outcome Measures and Endpoints) Protocol Synopsis (Statistical Analysis) Section 1.2 (Study Schema) Section 2.2 (Study Rationale) Section 3 (Objectives, Outcome Measures, and Endpoints) Section 4 (Study Design) Section 8.3 (Efficacy Assessments) Section 9 (Statistical Considerations) Section 10.1.5 (Committees)	Updated the efficacy objectives, outcome measures, endpoints, and analyses to align with the Sponsor's strategic decision not to pursue adult T-cell leukemia/lymphoma (ATL) indication and to therefore close enrollment into Cohort 2 . Updated Cohort 2 efficacy endpoints to be assessed by the investigator, not by blinded independent central review, and removed reference to original ATL response criteria.	Sponsor's strategic decision not to pursue ATL.
Protocol Synopsis (Study Design) Section 4 (Study Design)	Updated the time frame for analyses to be based only on meeting the primary efficacy endpoint in Cohort 1.	
Protocol Synopsis (Key Eligibility Criteria) Section 5.1.1 (Inclusion Criteria) Section 8.2 (Enrollment)	Updated eligibility language for both Cohorts	Clarification

Section # and Title	Description of Change	Brief Rationale
Protocol Synopsis (Study Design) Protocol Synopsis (Planned Sample Size) Section 1.2 (Study Schema) Section 4 (Study Design) Section 9.3 (Sample Size Determination)	Updated the sample size for the overall study and Cohort 2 (including statistical rationale).	Enrollment to be stopped for R/R ATL Cohort 2.
Protocol Synopsis (Study Objectives/Outcome Measures and Endpoints) Protocol Synopsis (Study Design) Section 1.2 (Study Schema) Section 3 (Objectives, Outcome Measures, and Endpoints) Section 4.1 (Overall Design) Section 4.1.2 (End of Study) Section 10.6 (Appendix 7 Key Data Analysis Requirements)	Removed the primary completion date for Cohort 2.	Enrollment to be stopped for R/R ATL Cohort 2.
Protocol Synopsis (Statistical Analysis) Protocol Synopsis (Planned Sample Size) Section 4.1 (Overall Design) Section 8.1 (Eligibility Assessment) Section 8.2 (Enrollment) Section 9 (Statistical Considerations)	Removed the central pathology review for Cohort 2.	Enrollment to be stopped for R/R ATL Cohort 2.
Section 1.3 (Schedule of Events) Section 8.4.4 (Other Safety)	Updated the time matching of electrocardiogram (ECG) and pharmacokinetic (PK) assessments.	As it may not always be possible to perform ECG within 15 minutes prior to the PK blood draw, the requirement has been relaxed to allow the sites to perform ECG 30 minutes or more after the PK sample collection for Cycles 2 to 5.
Section 1.3 (Schedule of Events)	Updated footnote b to reflect the update in the visit schedule from Cycle 3 and Beyond.	Operational update based on stopping of R/R ATL cohort enrollment.
Section 8.3 (Efficacy Assessments: Figure 8.1, Figure 8.2, and Table 8.1)	Updated the schedules for efficacy assessments.	Enrollment to be stopped for R/R ATL Cohort 2 and to align with the standard of care for the ATL cohort.
Section 8.3.2 (Bone Marrow Biopsy/Assessment)	Clarified text for local pathology report and bone marrow specimen submission	Clarification

Section # and Title	Description of Change	Brief Rationale
Section 8.3.3 (Cohort 2 Additional Efficacy Assessments)	Skin Lesion Assessment – removed guidance on whole body skin photographs	Central review is no longer required
Section 8.6 (Biomarker Assessments)	Update text for biomarker assessments	Clarification
Section 4.1 (Overall Design) Section 9.7 (Interim Analyses)	Removed the interim analysis for Cohort 2.	Enrollment to be stopped for R/R ATL Cohort 2.
Section 10.1.6 (Study Documentation and Storage)	Added the email address for Sponsor notification regarding records maintenance.	Information update.
Section 10.2 (Appendix 2: Central and/or Local Laboratory)	Updated the list of laboratory tests to be performed.	Enrollment to be stopped for R/R ATL Cohort 2.
Section 10.3.8 (Prespecified Stopping Boundaries)	Updated Tables 10.9 to 10.11 listing prespecified stopping boundaries for Cohort 2.	Enrollment to be stopped for R/R ATL Cohort 2.
Protocol Synopsis (Key Eligibility Criteria) Section 2.1 (Background) Section 5.1.1 (Inclusion Criteria) Section 10.4.4 (mSWAT Score Calculation: Cohort 2) Section 11 (References)	Moved or removed references associated with these changes	Corrections due to updates made to Cohort 2 efficacy endpoints

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1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title
Single-arm, Phase 2 Study of Valemetostat Tosylate Monotherapy in Subjects with Relapsed/Refractory Peripheral T-Cell Lymphoma
Protocol Short Title
Valemetostat tosylate (DS-3201b), an enhancer of zeste homolog (EZH) 1/2 dual inhibitor, for R/R PTCL
Protocol Number
DS3201-A-U202
Sponsor/Collaborators
Daiichi Sankyo, Inc.
Registry Identification(s)
• NCT Number: NCT04703192 • EudraCT Number: 2020-004954-31 • jRCT number: jRCT2071200095
IND Number
IND Number 132312
Study Phase
Phase 2
Planned Geographical Coverage, Study Sites and Location
Global study. Approximately 70 sites in North America, Europe, Asia, and Oceania.
Study Population
The target population of this study is subjects with relapsed/refractory (R/R) peripheral T-cell lymphoma (PTCL), regardless of CD30 positivity. Subjects with anaplastic large cell lymphoma (ALCL) should have been previously treated with brentuximab vedotin. Subjects with adult T-cell leukemia/lymphoma (ATL) will be enrolled in a separate cohort. Throughout the rest of this document, R/R PTCL will be used and refers to subjects who are R/R PTCL excluding ATL.
Study Objectives/Outcome Measures and Endpoints
The table below lists the primary and secondary study objectives and endpoints that have outcome measures.

Objectives	**Outcome Measure**	**Endpoints**	**Category**
Primary			
Cohort 1 Only			
To estimate the objective response rate (ORR) with valemetostat tosylate monotherapy treatment in R/R PTCL	**Title:** Objective response rate **Description:** Percentage of subjects with objective response assessed by blinded	ORR is defined as the proportion of subjects with a best overall response (BOR) of complete response (CR) or partial response (PR), assessed by BICR,	Efficacy

	independent central review (BICR) of PTCL following computed tomography (CT)-based response assessment according to the 2014 Lugano criteria.[1] **Time frame:** At least 10 months after the first dose of valemetostat tosylate of the last subject enrolled into Cohort 1.	among subjects with centrally confirmed PTCL-eligible histology.	
Cohort 2 Only			
To assess the safety and tolerability of valemetostat tosylate monotherapy	**Title:** Number of subjects with treatment-emergent adverse events (TEAEs) during the study **Description:** Total number of Cohort 2 subjects in the Safety Analysis Set with TEAE	All safety assessments, including adverse event (AE) reporting (TEAEs; treatment-emergent adverse events of special interest [TEAESIs]; treatment-emergent serious adverse events [TESAEs]; TEAEs by severity [Common Terminology Criteria for Adverse Events (CTCAE) grading, including Grade 3 and Grade 4]; fatal events; and TEAEs leading to treatment discontinuation, interruption, or reduction), laboratory assessments, vital signs, and electrocardiogram (ECG; including QT interval corrected with Fridericia's formula [QTcF] by central ECG reading)	Safety
Secondary			
All Cohorts			

To evaluate the pharmacokinetics (PK) of valemetostat and major metabolite (CALZ-1809a)	Not applicable	Total and unbound DS-3201a (free form of valemetostat tosylate) and total CALZ-1809a (major metabolite) concentration in plasma	PK
Cohort 1 Only			
To evaluate the duration of response (DoR)	**Title:** Duration of response **Description:** Time from the first documented response (CR or PR) until documented disease progression (progressive or relapsed disease) based on BICR assessments or death from any cause	DoR is defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of disease progression (progressive or relapsed disease) based on BICR assessments or to death due to any cause, whichever occurs first.	Efficacy
To assess the CR rate	**Title:** Complete response rate **Description:** Percentage of subjects with no detectable evidence of PTCL	CR rate is the percentage of subjects achieving CR as the BOR based on BICR assessments.	Efficacy
To evaluate the duration of CR (DoCR)	**Title:** Duration of complete response **Description:** Time from the first documented CR until documented disease progression (progressive or relapsed disease) based on BICR assessments or death from any cause	DoCR is defined as the time from the date of the first documentation of CR to the date of the first documentation of disease progression (progressive or relapsed disease) based on BICR assessments or to death due to any cause, whichever occurs first.	Efficacy
To assess the PR rate	**Title:** Partial response rate **Description:** Percentage of subjects with regression of disease and no detectable evidence of new	PR rate is the percentage of subjects achieving PR as the BOR based on BICR assessment.	Efficacy

	cancer/lesions in other parts of the body		
To assess the safety and tolerability of valemetostat tosylate monotherapy	**Title:** Number of subjects with TEAEs during the study **Description:** Total number of Cohort 1 subjects in the Safety Analysis Set with TEAE	All safety assessments, including AE reporting (TEAEs; TEAESIs; TESAEs; TEAEs by severity CTCAE grading, including Grade 3 and Grade 4; fatal events; and TEAEs leading to treatment discontinuation, interruption, or reduction), laboratory assessments, vital signs, and ECG (including QTcF by central ECG reading)	Safety

Throughout this document, response is used in lieu of remission when discussing CR, and PR for R/R ATL.

Study Design

This is a global, multicenter, open-label, single-arm, 2 cohort, Phase 2 study. The 2 cohorts are:

- Cohort 1: R/R PTCL
- Cohort 2: R/R ATL

Approximately 148 subjects will be enrolled (128 subjects with R/R PTCL and 20 subjects with R/R ATL).

The interventional phase of the study will be divided into 3 periods: Screening, Treatment, and Follow-up (which includes the Long-term Follow-up [LTFU]). The Screening Period will be up to 28 days. Subjects will be enrolled once confirmed eligible and will then enter the Treatment Period. Subjects will undergo disease assessment by radiographic images at regularly scheduled intervals (Table 8.1).

The Follow-up Period begins after the End of Treatment (EOT) Visit, which should occur within 7 days after the last dose of valemetostat tosylate or at the time the decision is made to discontinue valemetostat tosylate (if this is more than 7 days after the last dose of valemetostat tosylate), unless there is a medical condition that prevents subjects from completing the visit within this time, or permanent discontinuation of study drug at any time. In addition, after the EOT visit, a 30-day Safety Follow-up Visit will occur, 30 days (+7 days) after the last dose of valemetostat tosylate. Subsequently, LTFU visits will occur every 3 months. The Survival Follow-up Period is at least 3 years after the first dose of the study drug in the last subject. However, the Sponsor may stop the study at any time.

The primary completion date is based on the initiation of study drug in Cohort 1 by the last subject to meet PTCL eligibility criteria as confirmed by central diagnosis. The primary completion date will be at least 10 months after the first dose of study drug is taken by this subject. All subjects in either cohort who are still on treatment or who discontinued from study drug at the primary completion date will continue to follow the study Schedule of Events (Table 1.1) until the overall End of Study (EOS) is reached, or the subject is lost to follow-up, or the subject withdraws consent, or until death.

Overall EOS will occur when the last subject's last visit has occurred and is defined as the completion of survival follow-up of at least 3 years after the first dose of the last subject either from Cohort 1 or Cohort 2, whichever occurs later.

The subject's EOS is defined as the date of his/her last study visit/contact.

See Figure 1.1 for the study flow diagram.

Study Duration

The study start date is the date when the first subject has signed informed consent. A subject is eligible to be enrolled into the interventional phase of the study when the investigator or designee has obtained written informed consent, has confirmed all eligibility criteria have been met by the subject, and all screening procedures have been completed.

For both Cohort 1 and Cohort 2, the overall duration of enrollment is estimated to be approximately 20 months. The anticipated total duration of the study from the first patient in through the last patient out, which will include survival follow-up is approximately 56 months. The EOS will occur when the last subject's last visit has occurred and is defined as the completion of survival follow-up of at least 3 years after the first dose of the last subject either from Cohort 1 or Cohort 2, whichever occurs later.

It is expected that a subject's total duration of participation in the study will be up to 28 days in the Screening Period, more than 6 months in the Treatment Period, and 30 days (+7 days) in the Follow-up Period after the last study drug administration. The Survival Follow-up Period will be at least 3 years after the first dose of the study drug in the last subject.

Key Eligibility Criteria

Key Inclusion Criteria:

Subjects eligible for inclusion in this study have to meet all inclusion criteria for this study. Below is a list limited to the key inclusion criteria:

- Eastern Cooperative Oncology Group performance status of 0, 1, or 2
- Cohort 1 (R/R PTCL): Diagnosis should be confirmed by the local pathologist; local histological diagnosis will be used for eligibility determination. Subjects with the following subtypes of PTCL are eligible according to 2016 WHO classification prior to the initiation of study drug.[5] Any T-cell lymphoid malignancies not listed below are excluded. Below is the complete list of eligible subtypes:

  - Enteropathy-associated T-cell lymphoma
  - Monomorphic epitheliotropic intestinal T-cell lymphoma
  - Hepatosplenic T-cell lymphoma
  - Primary cutaneous γδ T-cell lymphoma
  - Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
  - PTCL, not otherwise specified
  - Angioimmunoblastic T-cell lymphoma
  - Follicular T-cell lymphoma
  - Nodal PTCL with T-follicular helper (TFH) phenotype
  - ALCL, ALK positive
  - ALCL, ALK negative

- Cohort 2 (R/R ATL): acute, lymphoma, or unfavorable chronic type. R/R ATL should be confirmed by the local pathologist; local diagnosis will be used for eligibility determination. The positivity of anti-human T-cell leukemia virus type 1 (HTLV-1) antibody will be locally determined for eligibility.
- Must have at least one of the following lesions which are measurable in 2 perpendicular dimensions on computed tomography (or magnetic resonance imaging) based on local radiological read:
  - Longest diameter (LDi) ≥2.0 cm for a nodal lesion
  - LDi >1.0 cm for an extranodal lesion
  - For Cohort 2 (ATL), subjects who had disease only in peripheral blood or skin lesions are eligible as defined below.
    - An abnormal lymphocyte count (actual number) is $\geq 1.0 \times 10^9$/L and the abnormal lymphocyte-to-leucocyte ratio is ≥5%.
    - Skin lesion(s) measured by modified severity weighted assessment tool score.[4]
- Documented refractory, relapsed, or progressive disease after at least 1 prior line of systemic therapy.
  - Refractory is defined as
    - Failure to achieve CR (or CRu for ATL) after first-line therapy
    - Failure to reach at least PR following second-line therapy or beyond
- Must have at least 1 prior line of systemic therapy for PTCL or ATL.
  - Subjects must be considered hematopoietic cell transplantation (HCT) ineligible during Screening due to disease status (active disease), comorbidities, or other factors; the reason for HCT ineligibility must be clearly documented.
  - In Cohort 1, subjects with ALCL must have prior brentuximab vedotin treatment.

Key Exclusion Criteria:

Subjects meeting any exclusion criteria for this study will be excluded from this study. Below is a list limited to the key exclusion criteria:

- Diagnosis of mycosis fungoides, Sézary syndrome and primary cutaneous ALCL, and systemic dissemination of primary cutaneous ALCL
- Diagnosis of precursor T-cell leukemia and lymphoma (T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma), T-cell prolymphocytic leukemia, or T-cell large granular lymphocytic leukemia
- Prior malignancy active within the previous 2 years except for locally curable cancer that is currently considered as cured, such as cutaneous basal or squamous cell carcinoma, superficial bladder cancer, or cervical carcinoma in situ, or an incidental histological finding of prostate cancer.
- Presence of active central nervous system involvement of lymphoma

- History of autologous HCT within 60 days prior to the first dose of study drug
- History of allogeneic HCT within 90 days prior to the first dose of study drug
- Clinically significant graft-versus-host disease (GVHD) or GVHD requiring systemic immunosuppressive prophylaxis or treatment
- Inadequate washout period from prior lymphoma-directed therapy before enrollment, defined as follows:
  - Prior systemic therapy (eg, chemotherapy, immunomodulatory therapy, or monoclonal antibody therapy) within 3 weeks or 5 half-lives of the drug, whichever is longer, prior to the first dose of study drug
  - Had curative radiation therapy or major surgery within 4 weeks or palliative radiation therapy within 2 weeks prior to the first dose of study drug
- Uncontrolled or significant cardiovascular disease, including:
  - Evidence of prolongation of QT/QTc interval (eg, repeated episodes of QT corrected for heart rate using Fridericia's method >450 ms) (average of triplicate determinations)
  - Diagnosed or suspected long QT syndrome or known family history of long QT syndrome
  - History of clinically relevant ventricular arrhythmias, such as ventricular tachycardia, ventricular fibrillation, or Torsade de Pointes
  - Uncontrolled arrhythmia (subjects with asymptomatic, controllable atrial fibrillation may be enrolled) or asymptomatic persistent ventricular tachycardia
  - Subject has clinically relevant bradycardia of <50 bpm, unless the subject has a pacemaker
  - History of second- or third-degree heart block. Candidates with a history of heart block may be eligible if they currently have pacemakers and have no history of fainting or clinically relevant arrhythmia with pacemakers within 6 months prior to Screening
  - Myocardial infarction within 6 months prior to Screening
  - Angioplasty or stent craft implantation within 6 months prior to Screening
  - Uncontrolled angina pectoris within 6 months prior to Screening
  - New York Heart Association Class 3 or 4 congestive heart failure
  - Coronary/peripheral artery bypass graft within 6 months prior to Screening
  - Uncontrolled hypertension (resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg)
  - Complete left bundle branch block
- History of treatment with other EZH inhibitors
- Current use of moderate or strong cytochrome P450 (CYP)3A inducers (Table 10.4)
- Systemic treatment with corticosteroids (>10 mg daily prednisone equivalents). Note: Short-course systemic corticosteroids (eg, prevention/treatment for transfusion reaction) or use for a non-cancer indication (eg, adrenal replacement) is permissible.
- Known or suspected hypersensitivity to valemetostat tosylate or any of the excipients

Investigational Medicinal Product, Dose, and Mode of Administration

DS-3201b (valemetostat tosylate) tablets 50 mg are white, round-shaped, film-coated tablets, each of which contains 50 mg of DS-3201a as the free form of valemetostat tosylate.

DS-3201b (valemetostat tosylate) tablets 100 mg are grayish-red, oblong-shaped, film-coated tablets, each of which contains 100 mg of DS-3201a as the free form of valemetostat tosylate.

DS-3201b (valemetostat tosylate) will be packed and supplied in a high-density polyethylene plastic bottle with desiccants (with a child-resistant cap).

DS-3201b (valemetostat tosylate) will be administered at a dose of 200 mg once daily.

Subjects are instructed to orally take valemetostat tosylate under fasting conditions (to be taken at least 1 hour before or at least 2 hours after a meal).

Active Ingredient/INN

DS-3201b (valemetostat tosylate). INN: Valemetostat (DS-3201a, the free form of DS-3201b).

Statistical Analysis

Analysis Population

- The Safety Analysis Set will include all subjects who received at least 1 dose of valemetostat tosylate; this set will be the same as the safety population.
- Efficacy population:
  - Cohort 1: Defined as all subjects who received at least 1 dose of valemetostat tosylate and had an eligible PTCL subtype that was confirmed by independent hematopathology central review.
  - Cohort 2: Defined as all subjects who received at least 1 dose of valemetostat tosylate and had an eligible ATL subtype.
- The Pharmacokinetic (PK) Analysis Set will include all the subjects in the Safety Analysis Set who had measurable plasma concentrations of valemetostat.
- The Biomarker Analysis Set will include all subjects who received at least 1 dose of the study drug, who provided specimens for the biomarker study, and whose measurement data obtained for the specimens are usable.

Efficacy Analyses

Analysis will be conducted separately for the PTCL and ATL cohorts.

Primary Efficacy Analysis – Cohort 1 Only

The primary efficacy analysis will be based on the data from the Cohort 1 efficacy population.

- Objective response rate (ORR) (CR + PR) based on CT-based blinded independent central review (BICR) assessment

The primary efficacy analysis will be performed on the ORR in R/R PTCL subjects with centrally confirmed eligible PTCL subtype. The exact 95% confidence intervals (CIs) for the ORR will be calculated using the Clopper-Pearson method. Any response assessment after initiating a subsequent lymphoma therapy or a preparative regimen for a HCT will not be included into the primary efficacy analysis.

Secondary Efficacy Analyses – Cohort 1 Only

- Duration of response (DoR) based on CT-based BICR assessment
- CR rate based on CT-based BICR assessment
- PR rate based on CT-based BICR assessment
- Duration of CR (DoCR) based on CT-based BICR assessment
- ORR, DoR, CR/PR rate, and DoCR based on investigator assessment

Exploratory Efficacy Analyses – Cohort 2 Only

Efficacy for Cohort 2 subjects will be summarized in a descriptive manner.

Safety Analyses

Safety will be measured by the incidence of all clinical and laboratory safety assessments including treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), severe

events (Grades 3 and 4), fatal events, TEAEs associated with treatment discontinuation, interruption, or reduction, and adverse events of special interest (AESIs).

Pharmacokinetics Analyses

Pharmacokinetics analyses will be performed using the PK Analysis Set.

Total and unbound concentrations for valemetostat in plasma and total concentration of CALZ-1809a in plasma will be listed and summarized using descriptive statistics at each time point.

Biomarker Analyses

Peripheral blood and tumor biopsies will be collected at various time points including at baseline, on treatment, and/or at the EOT and/or at the time of relapse in order to characterize associated biomarkers in peripheral blood and tumor biopsies that may predict the effect of valemetostat on safety and efficacy measures.

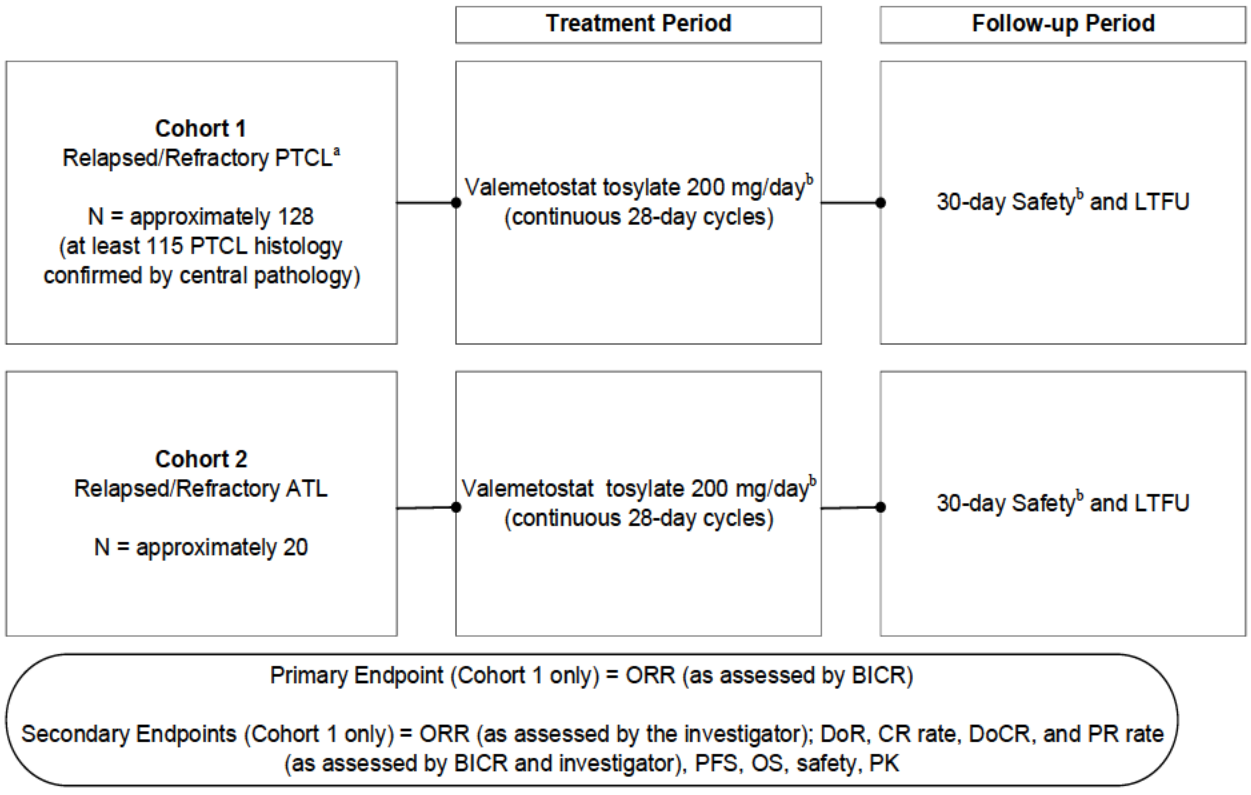
Planned Sample Size

Cohort 1: The total number of Cohort 1 is approximately 128 R/R PTCL subjects. Assuming 90% enrolled R/R PTCL subjects will have PTCL histology confirmed by central pathology, the sample size of 115 R/R PTCL subjects will provide sufficient statistical precision for the inference of the ORR. With a sample size of 115 subjects, the probability of observing the lower bound of the 95% CI >27% (historic ORR rate) is at least 90% if the expected ORR with valemetostat is 42%. The ORR 27% was based on the ORR of 27% from pralatrexate for R/R PTCL.[6]

Cohort 2: A total sample size of approximately 20 R/R ATL subjects is expected at the time of enrollment closing. This sample size is not based on statistical considerations.

1.2. Study Schema

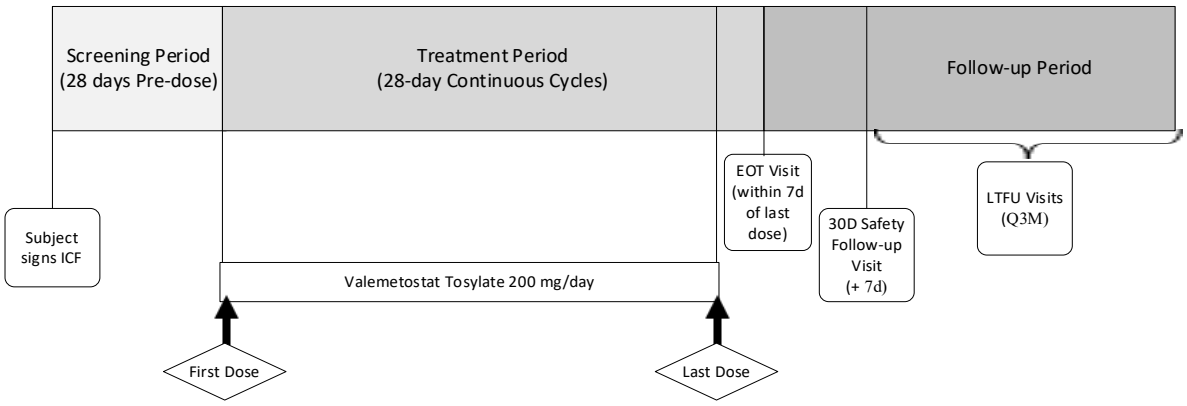
Figure 1.1: Study-level Flow Diagram



ALCL = anaplastic large cell lymphoma; ATL = adult T-cell leukemia/lymphoma; BICR = blinded independent central review; CR = complete response; DoCR = duration of complete response; DoR = duration of response;

LTFU = Long-term Follow-up; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; PTCL = peripheral T-cell lymphoma; QD = once daily; US = United States
[a] Prior brentuximab vedotin treatment is required for the ALCL subtype
[b] The primary completion date is based on the initiation of study drug in Cohort 1 by the last subject to meet PTCL eligibility criteria as confirmed by central diagnosis. The primary completion date will be at least 10 months after the first dose of study drug is taken by this subject.
Note: The overall End of Study is defined as the last subject's last visit.

Figure 1.2: Flow Diagram



EOT = End of Treatment; HCT = hematopoietic cell transplantation; ICF = informed consent form; LTFU = Long-term Follow-up; Q3M = every 3 months
Subjects may discontinue the study drug at any time to undergo HCT. If a subject undergoes HCT, HCT-relevant information and survival status will be collected during the Follow-up Period, starting at the 30-day Safety Follow-up Visit.

1.3. Schedule of Events

Table 1.1: Schedule of Events

Period	Scrn[a]	Treatment Period													Follow-up		Protocol Section	Comments
Cycle (28 days each)		Cycle 1								Cycle 2		Cycle 3 and Beyond[b]		EOT[c]	30D[d]	LTFU		
Day		1					8	15	22	1	15	1	15			Q3M		
Window (days)	-28	±0					±1	±1	±1	±3	±2	±3	±2	+3	+7	±7		
Time after Dosing (hours)		Pre-dose[e]	1	2	4	5	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose					
Procedure																		
Eligibility																		
ICF	X																8.1 10.1.2	Obtain subject's written informed consent prior to performing any study procedures.
Demographics	X																8.1	
Eligibility Assessment	X	X															5.1.1 5.1.2 8.1	Subjects should continue to meet all study protocol eligibility criteria prior to the first dose of study drug, including laboratory results and ECOG PS. Non-clinically significant changes in ECG on C1 D1 would be acceptable.
History																		
Medical	X																8.1	
PTCL/ATL	X																8.1	

Period	Scrn[a]	Treatment Period													Follow-up		Protocol Section	Comments
Cycle (28 days each)		Cycle 1								Cycle 2		Cycle 3 and Beyond[b]		EOT[c]	30D[d]	LTFU		
Day		1					8	15	22	1	15	1	15			Q3M		
Window (days)	-28	±0					±1	±1	±1	±3	±2	±3	±2	+3	+7	±7		
Time after Dosing (hours)		Pre-dose[e]	1	2	4	5	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose					
Procedure																		
Safety																		
Physical Examination	X	X[f]					X	X	X	X	X	X	X	X	X		8.4.4	[f] Must be performed on C1 D1 prior to the first dose.
ECOG PS	X	X[f]								X		X		X	X		8.4.4	[f] Must be performed on C1 D1 prior to the first dose.
Vital Signs	X	X[f]					X	X	X	X	X	X	X	X	X		8.4.4	Measure after ≥5 min resting. [f] Must be performed on C1 D1 prior to the first dose.
Height	X																8.4.4	
12-Lead ECG (Triplicate)[g]	X	X			X		X	X	X	X		X		X	X		8.4.4	[g] All ECGs must be performed within 15 min (Cycle 1 only) or within 30 min (Cycles 2 to 5) prior to the collection of all PK samples collected up to Cycle 5 Day 1. If it is not possible, then ECG should be performed 30 min or more after the PK sample collection. For ECG assessments without time-matched PK samples, ECG should

Period	Scrn[a]	Treatment Period													Follow-up		Protocol Section	Comments
Cycle (28 days each)		Cycle 1								Cycle 2		Cycle 3 and Beyond[b]		EOT[c]	30D[d]	LTFU		
Day		1					8	15	22	1	15	1	15			Q3M		
Window (days)	-28	±0					±1	±1	±1	±3	±2	±3	±2	+3	+7	±7		
Time after Dosing (hours)		Pre-dose[e]	1	2	4	5	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose					
Procedure																		
																		be performed before any blood collection.
Adverse Events																		
Non-serious	←															→	8.4.1 10.5	
Serious	←															→	8.4.1.1 10.5	[h] Only collect SAEs that are considered related to study drug by investigators and secondary malignancies (regardless of seriousness or causality) during this period.
Local Laboratory Assessments																		
Hematology and Blood Chemistry	X	X[i]					X	X	X	X	X	X	X	X	X		8.4.3	[i] Within 48 h before the first dose of the study drug. Screening data may be used for C1 D1 predose assessment, if obtained within 48h prior to the first dose. See Table 10.1 for specific analytes.

Period	Scrn[a]	Treatment Period													Follow-up			
Cycle (28 days each)		Cycle 1								Cycle 2		Cycle 3 and Beyond[b]		EOT[c]	30D[d]	LTFU		
Day		1					8	15	22	1	15	1	15			Q3M		
Window (days)	-28	±0					±1	±1	±1	±3	±2	±3	±2	+3	+7	±7		
Time after Dosing (hours)		Pre-dose[e]	1	2	4	5	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose					
Procedure																	**Protocol Section**	**Comments**
Serology Tests	X	X[i]								X		X		X	X		8.4.3	[i]Within 48 h before the first dose of the study drug. Screening data may be used for C1 D1 predose assessment, if obtained within 48h prior to the first dose. See Table 10.1 for specific analytes.
Coagulation	X																8.4.3	Coagulation at Screening and as clinically indicated. See Table 10.1 for specific analytes.
Lipid Profile	X											X		X			10.2	Lipid profile at Screening, C7 D1, EOT, and as clinically indicated. See Table 10.1 for specific analytes.
Urinalysis	X	X[i]								X		X		X	X		8.4.3	[i]Within 48 h before the first dose of the study drug. Screening data may be used for C1 D1 predose assessment, if obtained within 48h prior to the first dose. See Table 10.1 for specific analytes.

Period	Scrn[a]	Treatment Period													Follow-up			
Cycle (28 days each)		Cycle 1								Cycle 2		Cycle 3 and Beyond[b]		EOT[c]	30D[d]	LTFU		
Day		1					8	15	22	1	15	1	15			Q3M		
Window (days)	-28	±0					±1	±1	±1	±3	±2	±3	±2	+3	+7	±7		
Time after Dosing (hours)		Pre-dose[e]	1	2	4	5	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose					
Procedure																	**Protocol Section**	**Comments**
Pregnancy Test for Women of Childbearing Potential	X[j]	X[k]								X[k]		X[k]		X[k]	X[k]		8.4.2	[j] Serum pregnancy test at Screening (if not performed as a part of routine care within 14 d of C1 D1, must be performed with the results available prior to C1 D1). [k] Serum or urine pregnancy tests may be performed. Screening data may be used for C1 D1 predose assessment, if obtained within 48h prior to the first dose.
Infectious Disease Tests for Screening	X																8.1	Perform HIV antibody test as required by local regulations and hepatitis B and C testing within 28 days prior to the first dose.
Central Laboratory Assessments																		
Markers of Platelet Production		X					X	X	X	X	X	X					8.4.3	Thrombopoietin and IPF will be assessed from C1 D1 to C3 D1. If the platelet count is <75 × 10^9/L, after consultation with the

Period	Scrn[a]	Treatment Period													Follow-up			
Cycle (28 days each)		Cycle 1								Cycle 2		Cycle 3 and Beyond[b]		EOT[c]	30D[d]	LTFU		
Day		1					8	15	22	1	15	1	15			Q3M		
Window (days)	-28	±0					±1	±1	±1	±3	±2	±3	±2	+3	+7	±7		
Time after Dosing (hours)		Pre-dose[e]	1	2	4	5	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose					
Procedure																	**Protocol Section**	**Comments**
																		Sponsor Medical Monitor, the investigator may perform an unscheduled assessment (Table 10.1).
HTLV-1 antibody	X																	Cohort 2 subjects only
CMV Viral Load by Quantitative PCR		X								X		X		X			8.4.3	Tests may be performed at other visits when subjects have any suspicion of CMV infection (Table 10.1).
PK Assessments																		
PK Blood Collection (Valemetostat and CALZ-1809a)		X	X	X	X	X	X	X		X		X (to C5)					8.5	See Table 8.3 for details on postdose times and windows. Additional PK samples will be collected if a strong/moderate CYP3A inhibitor or inducer and/or P-gp inhibitor is coadministered with study drug (see Section 8.5.1 for details of sample timing).
AAG Measurement		X					X	X		X		X (to C5)					8.5.1	AAG will be analyzed in all subjects according to Table 8.3. Additional AAG samples will be collected when a

Period	Scrn[a]	Treatment Period													Follow-up			
Cycle (28 days each)		Cycle 1								Cycle 2		Cycle 3 and Beyond[b]		EOT[c]	30D[d]	LTFU		
Day		1					8	15	22	1	15	1	15			Q3M		
Window (days)	-28	±0					±1	±1	±1	±3	±2	±3	±2	+3	+7	±7		
Time after Dosing (hours)		Pre-dose[e]	1	2	4	5	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose					
Procedure																	Protocol Section	Comments
																		strong/moderate CYP3A inhibitor or inducer and/or P-gp inhibitor is coadministered with study drug (see Section 8.5.1 for details of sample timing).

Period	Scrn[a]	Treatment Period													Follow-up			
Cycle (28 days each)		Cycle 1								Cycle 2		Cycle 3 and Beyond[b]		EOT[c]	30D[d]	LTFU		
Day		1					8	15	22	1	15	1	15			Q3M		
Window (days)	-28	±0					±1	±1	±1	±3	±2	±3	±2	+3	+7	±7		
Time after Dosing (hours)		Pre-dose[e]	1	2	4	5	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose					
Procedure																	Protocol Section	Comments
Biomarker Assessments																		
Tumor Biopsy	X	Tumor biopsies may be performed at unscheduled time points after the first dose, if clinically indicated. In this case, the biopsy samples should be submitted, if possible.															8.1 8.6	Obtain fresh samples after consent but before C1 D1. If not obtainable, it is acceptable to submit previously collected tumor tissue, including biopsy at the initial diagnosis. In Cohort 2, only subjects with ATL disease in peripheral blood can submit circulating malignant cells.
Peripheral blood collection (MRD assessment)		X								X		X[1]					8.6	[1]C5 D1, C13 D1, and every 6 cycles onward starting D1 of C19 (ie, C19 D1, C25 D1, C31 D1, and so on) and at the time of the first CR or, if not obtainable, at the subsequent visit after the first CR when the first CR is determined by investigator per CT-based assessment (for primary efficacy

Period	Scrn[a]	Treatment Period													Follow-up			
Cycle (28 days each)		Cycle 1								Cycle 2		Cycle 3 and Beyond[b]		EOT[c]	30D[d]	LTFU		
Day		1					8	15	22	1	15	1	15			Q3M		
Window (days)	-28	±0					±1	±1	±1	±3	±2	±3	±2	+3	+7	±7		
Time after Dosing (hours)		Pre-dose[e]	1	2	4	5	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose					
Procedure																	**Protocol Section**	**Comments**
																		analysis) or FDG-PET-based assessment (for primary exploratory analysis). Not required at C3 D1.
Peripheral blood collection for flow cytometry assay (Immune cell assessment)		X								X		X[m]					8.6	[m] C3 D1, C5 D1, and C7 D1
Pharmacogenomics Sample		X															8.6.1 8.6.4	Prior to dosing, for subjects who provide consent, collect oral mucosa swabs to be used as reference specimens to identify tumor-specific somatic mutations (Cohort 1 PTCL only) and for optional future pharmacogenetic analysis (both cohorts).
Efficacy Assessments																		
Efficacy Assessment	X											X[n]					8.3	[n] See Table 8.1 for schedule for both cohorts. See Section 8.3 for the requirement of GI

Period	Scrn[a]	Treatment Period													Follow-up		Protocol Section	Comments
Cycle (28 days each)		Cycle 1								Cycle 2		Cycle 3 and Beyond[b]		EOT[c]	30D[d]	LTFU		
Day		1					8	15	22	1	15	1	15			Q3M		
Window (days)	-28	±0					±1	±1	±1	±3	±2	±3	±2	+3	+7	±7		
Time after Dosing (hours)		Pre-dose[e]	1	2	4	5	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose					
Procedure																		
																		endoscopy and colonoscopy (Cohort 2).
CT (or MRI) Scan Neck, Chest, Abdomen, and Pelvis	X[o]											X[p]					8.3	[o] CT/FDG-PET (combined modality) scan can be used if the CT scan is of diagnostic quality. [p] If MRI is used instead of the CT scan, then MRI should be used for all subsequent assessments. May be performed for other lesions (eg, head) if clinically indicated. See Table 8.1 for the schedule.
FDG-PET Scan Base of Skull to Mid-thigh	X											X		X			8.3	See Table 8.2 for the schedules for Cohort 1. Required at Screening (within 28 days prior to the first dose), C5 D1 (±7 d), C13 D1 (±2 w), and EOT (±2 w). FDG-PET scan is optional for Cohort 2.
Bone Marrow Biopsy	X	Bone marrow biopsy is required to confirm normal morphology to declare CR (or CRu for ATL) in the subjects with positive, indeterminate, or unknown lymphoma involvement in bone marrow at baseline															8.3	Required in all subjects except those who underwent bone marrow biopsy within 3 m of the

Period	Scrn[a]	Treatment Period													Follow-up			
Cycle (28 days each)		Cycle 1								Cycle 2		Cycle 3 and Beyond[b]		EOT[c]	30D[d]	LTFU		
Day		1					8	15	22	1	15	1	15			Q3M		
Window (days)	-28	±0					±1	±1	±1	±3	±2	±3	±2	+3	+7	±7		
Time after Dosing (hours)		Pre-dose[e]	1	2	4	5	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose					
Procedure																	Protocol Section	Comments
																		first dose, with documented results.
Cohort 2 (ATL) only Disease Assessment (Peripheral Blood and Skin Lesion[s])	X	X										X[q]					8.3	See Table 8.1 for the schedule. Disease assessment for peripheral blood and skin lesion(s) will be conducted on C1 D1. [q] In Cohort 2 (ATL), efficacy assessment in peripheral blood and skin lesion(s) will be performed at the same timing of tumor assessment by CT (or MRI).
Confirmation of Survival Status															X	X	8.3	

Period	Scrn[a]	Treatment Period													Follow-up		Protocol Section	Comments
Cycle (28 days each)		Cycle 1								Cycle 2		Cycle 3 and Beyond[b]		EOT[c]	30D[d]	LTFU		
Day		1					8	15	22	1	15	1	15			Q3M		
Window (days)	-28	±0					±1	±1	±1	±3	±2	±3	±2	+3	+7	±7		
Time after Dosing (hours)		Pre-dose[e]	1	2	4	5	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose					
Study Drug																		
Administration		Study drug is to be taken at least 1 h before and at least 2 h after a meal.															6.2	
Dispense		X								X		X					6.2	
Assessment of Study Drug Compliance/ Collection of Medication Diary										X		X		X			6.4	
Medications, Non-drug Therapies, and Radiotherapy																		
Prior	X																6.6	Include all prior anti-PTCL and anti-ATL treatments taken.
Concomitant	←													→		X[r]	6.6	Begin recording upon signing of ICF. [r] Include all anti-PTCL and anti-ATL treatments taken since the EOT Visit.

Period	Scrn[a]	Treatment Period													Follow-up		Protocol Section	Comments
Cycle (28 days each)		Cycle 1								Cycle 2		Cycle 3 and Beyond[b]		EOT[c]	30D[d]	LTFU		
Day		1					8	15	22	1	15	1	15			Q3M		
Window (days)	-28	±0					±1	±1	±1	±3	±2	±3	±2	+3	+7	±7		
Time after Dosing (hours)		Pre-dose[e]	1	2	4	5	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose	Pre-dose					
Procedure																		
HCT-related																		
Karnofsky Performance Status														X			8.4.4	Obtain only when subject discontinues study drug due to HCT. Assess prior to the start of the preparative regimen(s).
HCT-Relevant Information															X		8.3.5	Obtain only when subject permanently discontinues study drug and undergoes HCT.

AAG = α-1 acid glycoprotein; ATL = adult T-cell leukemia-lymphoma; C = cycle; CMV = cytomegalovirus; CR = complete response; CRu = uncertified CR; CT = computed tomography; CYP3A = cytochrome P4503A; D or d = day; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; EOT = End of Treatment; FDG-PET = fluorodeoxyglucose-positron emission tomography; GI = gastrointestinal; h = hour; HCT = hematopoietic cell transplantation; HIV = human immunodeficiency virus; ICF = informed consent form; IPF = immature platelet fraction; LTFU = Long-term Follow-up; m = month; min = minute; MRD = minimal residual disease; MRI = magnetic resonance imaging; Q3M = every 3 months; P-gp = P-glycoprotein; PCR = polymerase chain reaction; PK = pharmacokinetics; PTCL = peripheral T-cell lymphoma; SAE = serious adverse event; Scrn = Screening

[a] Subjects may be rescreened as described in Section 5.2.

[b] Every cycle from Cycle 13 and every 3 cycles from Cycle 25.

[c] The EOT Visit should occur within 7 days after the last dose of valemetostat tosylate, for subjects who permanently discontinue study drug or discontinue due to HCT, or at the time the decision is made to discontinue valemetostat tosylate (if this is more than 7 days after the last dose of valemetostat tosylate), unless there is a medical condition that prevents subjects from completing the visit within this time.

[d] 30 days (+7 days) after the last study drug administration. For subjects who go onto HCT, this visit can occur up to 60 days after the last dose of study drug during the Treatment Period. Instead, the data for this visit may be collected via alternative methods, as described in Section 7.1 (Modified Follow-up Options).

[e] Must be performed within 24 hours prior to the first dose unless otherwise specified.

2. INTRODUCTION

2.1. Background

Peripheral T-Cell Lymphomas Background

The term peripheral T-cell lymphoma (PTCL) comprises a heterogenous group of rare lymphoid malignancies, representing 10% to 15% of non-Hodgkin lymphomas (NHLs).[8] The surveillance, epidemiology, and end-result (SEER) cancer registries in the United States (US) identified 20,726 patients with PTCL 15 years or older between 2000 and 2012.[9] Three major subtypes account for approximately 60% to 80% of PTCL: PTCL not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic lymphoma kinase (ALK)-positive- or ALK-negative-systemic anaplastic large cell lymphoma (ALCL). The remaining subtypes are extremely rare and include adult T-cell leukemia/lymphoma (ATL), enteropathy-associated T-cell lymphoma, and others.[5] Subtypes differ by geographic distribution, disease and clinical characteristics, and prognoses[8,10] The incidence of each subtype is influenced by age, gender, and ethnicity.[11,12]

Patients with PTCL have a poor prognosis, with the 5-year overall survival (OS) and 5-year progression-free survival (PFS) being 34.1% and 25.7%, respectively, based on a Swedish registry study (n = 755).[13] First-line standard of care therapy for most PTCL subtypes has not changed for decades. Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP)-based regimens, the current standard treatment for PTCL patients, were initially adopted from the regimen for B-cell NHL (B-NHL) without a strong scientific rationale specific to PTCL.[14,15,16] National Comprehensive Cancer Network guidelines for most PTCL subtypes recommend CHOP as the preferred first-line treatment option.[14] The only exception is the brentuximab vedotin-based regimen, which demonstrated superior PFS and OS in patients with previously untreated CD30-postive PTCL, including ALCL, when compared to CHOP in a Phase 3 study.[17] The benefits from brentuximab vedotin-based regimen is less pronounced in AITL and PTCL-NOS in the subgroup analysis, as the hazard ratio of PFS (95% confidence interval [CI]) was 1.40 (0.64 to 3.07) and 0.75 (0.41 to 1.37) for AITL and PTCL-NOS, respectively, both of which are not statistically significant. Thus, other than ALCL, there have not been recent significant changes to the first-line treatment for PTCL other than ALCL, particularly in CD30-negative PTCL.

Furthermore, approximately 40% to 60% patients achieved a complete response (CR) from first-line therapy for PTCL, whereas the remaining subjects had refractory disease, having failed to attain a CR.[18,19,20,21,22] Additionally, except for the patients with ALK-positive ALCL, the majority of the patients with PTCL treated with first-line therapy who achieved CR experienced a high relapse rate (eg, 43% in PTCL subjects compared to 29% in B-NHL subjects).[22,23,24]. In a Swedish registry study, the median OS after relapse/progression in 211 patients initially responding to primary treatment was 6.0 months, whereas the median OS was only 2.5 months among 143 patients with primary refractory disease.[13] The median OS was reported as 6.5 months for patients who received conventional chemotherapy versus 3.7 months in patients who did not receive chemotherapy.[25] Thus, survival outcome for patients with relapsed/refractory (R/R) PTCL still remains very poor.

For patients with R/R PTCL, the therapeutic options are currently limited. Accelerated approval was granted for belinostat and pralatrexate for R/R PTCL in the US, which demonstrated 25.8% and 27% of objective response rate (ORR), respectively.[6,26,27] No drug is approved for R/R PTCL in the European Union (EU). Forodesine, a purine nucleoside phosphorylase inhibitor, was approved in Japan, with 22.5% of ORR[28]. Brentuximab vedotin, an antibody-drug conjugate against CD30, showed 86% of ORR in ALCL, and is the only drug with full approval for R/R PTCL in the US.[29,30] However, in the US and EU, its indication is limited to ALCL in which CD30 is universally expressed. Although conventional chemotherapy can be used for patients with R/R PTCL, the durability of response is quite short; bendamustine monotherapy resulted in a median duration of response (DoR) of 3.5 months.[31] Patients who are able to achieve a good response (typically CR) can undergo an allogeneic hematopoietic cell transplantation (HCT) for potential cure, but the modality is limited due to the lack of adequate donor and patients' comorbidities. Thus, there remains a compelling unmet need for improved salvage therapy for patients with R/R PTCL.

Adult T-cell Leukemia/Lymphoma Background

ATL, as a subtype of PTCL, is composed of highly atypical lymphocytes, which is caused by human T-cell leukemia virus type 1 (HTLV-1)[2,7,32,33] HTLV-1 infection is endemic in the southwest region of Japan, Central and South America, and other regions.[34]

ATL is sporadically reported in North America.[34] Most of the cases are migrants from endemic areas, particularly in the New York metropolitan area and Florida in the US. In Europe, most cases are reported in France and the United Kingdom.[35] A recent epidemiology study indicated that the incidence of ATL is rising in nonendemic regions of the world.[36]

Whereas favorable chronic and smoldering types are considered as indolent ATL, aggressive ATL consists of acute, lymphoma, and unfavorable chronic types, which usually require immediate systemic therapy. The clinical course for subjects with aggressive ATL is poor. For example, the median survival of newly diagnosed ATL was 6.2, 10.2, and 15 months for acute, lymphoma, and unfavorable chronic types, respectively.[32] Unfortunately, there has been no significant progress in therapy, as the recent report by Katsuya et al indicated that the median survival of newly diagnosed ATL was 8.3 and 10.6 months for acute and lymphoma types, respectively.[37]

The initial treatment for aggressive ATL varies depending on the available therapy by country or region. The 2017 Consensus report recommends prospective clinical studies for all patients with initial diagnosis or R/R ATL.[35] Outside of clinical studies, in Japan, the recommendation of the first-line therapy includes vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP); doxorubicin, ranimustine, and prednisone (AMP); and vindesine, etoposide, carboplatin, and prednisone (VECP) chemotherapy regimens (modified LSG15).[38] However, outside of Japan, the recommended first-line therapy are other chemotherapy regimens (eg, CHOP), because certain components of the modified LSG15 is not available. Regardless, the outcomes from the first line are miserable. For instance, a randomized Phase 3 study showed that the median OS was 12.7 months and 10.9 months from the modified LSG15 regimen (an experimental arm) and from CHOP (a control arm), respectively.[38] The median PFS was 7.0 months and 5.4 months from the modified LSG15 and from CHOP, respectively. Therefore, most of the patients experience refractory or relapsed disease within 1 year from the initial diagnosis.

For refractory or relapsed ATL, no therapy clearly demonstrated survival benefits. In Japan, mogamulizumab and lenalidomide are licensed for use in R/R aggressive ATL based on single-arm Phase 2 studies. Mogamulizumab, an anti-chemokine receptor type 4 (CCR4) was tested in 27 subjects with relapsed CCR4-positive ATL after prior chemotherapy.[39] The ORR was 50% (13/26) (95% CI: 30 to 70); the median PFS and OS were 5.2 months and 13.7 months, respectively. In a Phase 2 study of lenalidomide, for 26 subjects with relapsed or recurrent aggressive ATL, including 11 subjects who were previously treated with mogamulizumab, the ORR was 42% (11/26) (95% CI: 23 to 63); the median PFS and OS were 3.8 months and 20.3 months, respectively.[40] Both studies showed short duration of PFS. Outside Japan, no drug has been approved for relapsed or refractory ATL. Bortezomib showed limited efficacy, with 6.7% of ORR (95% CI 0.17% to 31.95%) in 15 R/R ATL subjects in Japan.[41] The combination of arsenic trioxide and alpha interferon yielded some response in 2 small French and Japanese studies, although the treatment duration was very short.[42,43] A Phase 2 study in the US for previously untreated ATL (n = 9) and R/R ATL (n = 20), alemtuzumab, an anti-CD52 antibody, yielded 15 responders (52% of 29 subjects), but the response was limited predominantly to acute or chronic subtypes; only 1 responder was reported among the 11 subjects with lymphoma-type ATL.[44] Thus, a high unmet need exists for relapsed or refractory ATL patients.

Valemetostat Tosylate

Valemetostat tosylate is a potent and selective dual inhibitor of enhancer of zeste homolog (EZH)1 and EZH2, 2 epigenetic regulators with histone methyltransferase activity at lysine 27 of histone H3 (H3K27).[45, 46] Valemetostat tosylate inhibits EZH1 and EZH2, preventing the tri-methylation of H3K27, and alters gene expression patterns which ultimately attenuate the proliferation of EZH1/2 dependent cancer cells. Whereas selective inhibition of EZH2 caused compensation by EZH1, valemetostat tosylate has been proven to suppress both EZH1 and EZH2 as a dual inhibitor.[47] Valemetostat tosylate is currently the only dual EZH1 and EZH2 inhibitor in clinical development.

2.2. Study Rationale

Recent evidence suggests that PTCL, including ATL, can be driven by epigenetic dysregulation.[48,49] EZH1 and EZH2, catalytic subunits of the polycomb repressive complex 2, specifically methylate H3K27.[50] Hypertrimethylation of H3K27 is considered to silence tumor suppressor genes and has been associated with lymphoma progression, including PTCL and ATL.[49,51,52]

Valemetostat tosylate may modify epigenetic changes, which plays an important role in the pathogenesis of PTCL. In the ongoing open-label Phase 1 study (DS3201-A-J101, 25 Dec 2019 data cut-off), valemetostat tosylate monotherapy demonstrated approximately 62% ORR (34% CR rate) from 21 evaluable R/R PTCL subjects and approximately 50% ORR (20% CR rate) from 10 evaluable R/R ATL subjects; details will be described in Section 2.3.

This Phase 2 study will further characterize the safety and clinical activity of valemetostat tosylate and provide an estimate of the clinical benefit as measured by ORR in subjects with R/R PTCL. Additionally, data from the R/R ATL cohort will be collected to supplement the overall safety and efficacy profile of valemetostat tosylate monotherapy.

Throughout the rest of this document, R/R PTCL will be used and refers to subjects who are R/R PTCL excluding ATL.

2.3. Benefit and Risk Assessment

The current benefit/risk assessment is based on available nonclinical data and clinical data from the Phase 1 studies.

Nonclinical Data

Valemetostat tosylate showed high potency as an inhibitor of the methyltransferase activities of EZH1 and EZH2 both in vitro and high efficacy in an in vivo mouse tumor model. Safety pharmacology studies showed a low possibility for unexpected pharmacology-related adverse events (AEs) with valemetostat tosylate. Completed studies showed no effects on the central nervous system or respiratory systems of rats. In terms of cardiovascular effects, a potential for the prolongation of QT/ corrected QT interval (QTc) was observed both in the 4-week repeated dose toxicity study in dogs (where the QTc was extended in females) and in the dog telemetry study (where QT and QTc were increased). However, there were no effects on QTc in the 13-week dog study. In addition, there were no effects on cardiac pathology in either rat or dog in the 4-week or 13-week repeated dose toxicity studies. Based on the STD10 of 200 mg/kg in rats and the highest nonseverely toxic dose (HNSTD) of 30 mg/kg/day in dogs after 4 weeks of dosing, the first-in-human dose was set at 150 mg. A 3-month toxicology study in rats administered valemetostat tosylate showed the potential risks of developing lymphoid malignancies. A follow-up 3-month toxicity study in older rats (aged 55 weeks old at the time of initiation of dosing) was performed to further understand the pathogenic mechanism of this finding in younger rats showed administration of valemetostat tosylate to aged rats did not induce a lymphoma that had been previously observed with younger rats.

Overall, based on nonclinical data, the potential risks associated with valemetostat tosylate exposure include bone marrow hypocellularity as demonstrated in clinical parameters of reduced platelets, white blood cells, and red blood cells (RBC); QT interval prolongation; and allergic-like reactions due to elevated histamine levels.

Please refer to the current valemetostat tosylate Investigator's Brochure (IB) for additional details of nonclinical data supporting its use in clinical studies.[53]

Clinical Data

As of 18 Jan 2020, valemetostat tosylate has been investigated for malignant lymphoma in 2 clinical studies; a Phase 1 study (DS3201-A-J101) and a Phase 2 study (DS3201-A-J201).

Study DS3201-A-J101 is an ongoing open-label Phase 1 study with dose escalation, dose expansion, and drug-drug interaction (DDI) parts, evaluating the safety, pharmacokinetics (PK), and preliminary efficacy of valemetostat tosylate monotherapy in subjects with R/R NHL, specifically B-NHL, PTCL, and ATL.

Study DS3201-A-J201 is an ongoing Phase 2, multicenter, open-label, single-arm study of valemetostat tosylate, 200 mg/day, in subjects with R/R ATL being conducted in Japan.

As of the data cut-off date of 18 Jan 2020, only 5 subjects have received treatment with valemetostat tosylate, and there is little available data from Study DS3201-A-J201. Therefore, this benefit/risk assessment is based mainly on the data from dose escalation and dose expansion parts from Study DS3201-A-J101.

Preliminary safety data from Study DS3201-A-J101 (data cut-off date: 25 Dec 2019) in 56 subjects (Table 2.1) with R/R NHL, including B-cell NHL (N = 19), PTCL (N = 26), and ATL (N = 11), indicated that valemetostat tosylate appears manageable; 7, 40, 7, and 2 subjects received 150, 200, 250, and 300 mg of valemetostat tosylate once daily, respectively. Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 69.6% of subjects at all doses (150 mg to 300 mg) and in 100% of subjects who were treated at 250 mg or 300 mg.

Table 2.1: Study DS3201-A-J101 Overview of TEAEs, All R/R NHL Subjects, by Dose (Safety Analysis Set)

	Valemetostat Tosylate				
	150 mg/day N = 7 n (%)	**200 mg/day N = 40 n (%)**	**250 mg/day N = 7 n (%)**	**300 mg/day N = 2 n (%)**	**Total N = 56 n (%)**
Subjects with TEAEs, n (%)	7 (100.0)	40 (100.0)	7 (100.0)	2 (100.0)	56 (100.0)
Grade ≥3	4 (57.1)	26 (65.0)	7 (100.0)	2 (100.0)	39 (69.6)
SAE	3 (42.9)	10 (25.0)	0 (0.0)	0 (0.0)	13 (23.2)
Associated with Dose Reduction	0 (0.0)	3 (7.5)	2 (28.6)	1 (50.0)	6 (10.7)
Associated with Dose Interruption	1 (14.3)	17 (42.5)	4 (57.1)	1 (50.0)	23 (41.1)
Associated with Study Drug Discontinuation	1 (14.3)	1 (2.5)	0 (0.0)	0 (0.0)	2 (3.6)
Associated with Fatal Outcome	0 (0.0)	1 (2.5)	0 (0.0)	0 (0.0)	1 (1.8)

SAE = serious adverse event; TEAE = treatment-emergent adverse event
Source: Table 14.3.1.2, data-cut-off date: 25 Dec 2019

Cytopenias (platelet count decreased, anemia, white blood cell count decreased, neutrophil count decreased, and lymphocyte count decreased) were the most common TEAEs (any grade) as well as the most common Grade ≥3 TEAEs. In particular, platelet count decreased was reported as the most frequent TEAE of any grade in 40 (71.4%) subjects, including Grade 3 and Grade 4 platelet count decreased in 6 (10.7%) and 4 (7.1%) subjects, respectively. Additional information regarding thrombocytopenia can be found in Section 8.4.1.4. No R/R NHL subjects discontinued study drug due to thrombocytopenia or platelet count decreased. Opportunistic infections were also reported, including *Pneumocystis jirovecii* pneumonitis (n = 3) and cytomegalovirus (CMV) infection (n = 3). Other common TEAEs included general symptomatology (alopecia, nasopharyngitis, dry skin, rash, fatigue, arthralgia, and pyrexia), gastrointestinal disorders (diarrhea, nausea, and decreased appetite), and central nervous system disorders (dysgeusia),which were primarily Grade 1 or Grade 2 in severity. Electrocardiogram

(ECG) QT prolonged occurred in <10% of all R/R NHL subjects and all events were Grade 1 or Grade 2.

The safety experience was generally similar in R/R PTCL and R/R ATL subjects compared to all R/R NHL subjects. In the R/R PTCL group Grade ≥3 TEAEs occurred in 16 (61.5%) subjects. In R/R PTCL and R/R ATL subjects, platelet count decreased, anemia, white blood cell count decreased, neutrophil count decreased, and lymphocyte count decreased were the most common TEAEs as well as the most common Grade ≥3 TEAEs. As with R/R NHL subjects, the other common TEAEs in these subjects included general symptomatology (alopecia, nasopharyngitis, fatigue, arthralgia, and pyrexia [only reported in R/R PTCL subjects]), gastrointestinal disorders (diarrhea, nausea, and decreased appetite), and central nervous system disorders (dysgeusia), which were primarily Grade 1 or Grade 2 in severity.

In relation to safety data derived from animal studies, no cardiotoxicity, hepatotoxicity, hypersensitivity, or phototoxicity was observed in the Phase 1 clinical study, DS3201-A-J101. Overall, valemetostat tosylate appears manageable.

Preliminary efficacy data from Study DS3201-A-J101 (data cut-off date: 25 Dec 2019) demonstrated that valemetostat tosylate treatment resulted in an objective response of 61.9% (95% CI: 38.4, 81.9) and 50.0 % (95% CI: 18.7, 81.3) in subjects with PTCL and ATL, respectively. The median DoR (estimated using the Kaplan-Meier method) was 44.43 (95% CI: not estimable) weeks in subjects with PTCL but was not calculated for subjects with ATL due to the small number of subjects.

On the basis of the nonclinical and clinical data available to date, the potential benefit from valemetostat tosylate exceeds the risks for a population of patients with late-stage disease with careful dosing and monitoring in clinical studies.

3. OBJECTIVES, OUTCOME MEASURES, AND ENDPOINTS

The objectives, definitions of associated endpoints, as well as applicable outcome measures are described in Table 3.1. Further requirements for the endpoint analyses and censoring rules, where applicable, can be found in Section 9.5.1, Section 9.5.2, and Section 9.5.3.

Table 3.1: Description of Objectives, Outcome Measures, and Endpoints

Objectives	Outcome Measures	Endpoints	Category
Primary			
Cohort 1 Only			
To estimate the ORR with valemetostat tosylate monotherapy treatment in R/R PTCL	**Title:** Objective response rate **Description:** Percentage of subjects with objective response assessed by BICR of PTCL following CT-based response assessment according to 2014 Lugano criteria.[1] **Time frame:** At least 10 months after the first dose of valemetostat tosylate of the last subject enrolled into Cohort 1.	ORR is defined as the proportion of subjects with a BOR of CR or PR, assessed by BICR, among subjects with centrally confirmed PTCL-eligible histology.	Efficacy
Cohort 2 Only			
To assess the safety and tolerability of valemetostat tosylate monotherapy	**Title:** Number of subjects with TEAEs during the study **Description:** Total number of Cohort 2 subjects in the Safety Analysis Set with TEAE	All safety assessments, including AE reporting (TEAEs; TEAESIs; TESAEs; TEAEs by severity [CTCAE grading, including Grade 3 and Grade 4]; fatal events; and TEAEs leading to treatment discontinuation, interruption, or reduction), laboratory assessments, vital signs, and ECG (including QTcF by central ECG reading)	Safety

Objectives	Outcome Measures	Endpoints	Category
Secondary			
All Cohorts			
To evaluate the PK of valemetostat and major metabolite (CALZ-1809a)	Not applicable	Total and unbound DS-3201a (free form of valemetostat tosylate) and total CALZ-1809a (major metabolite) concentration in plasma	PK
Cohort 1 Only			
To evaluate the DoR	**Title:** Duration of response **Description:** Time from the first documented response (CR or PR) until documented disease progression (progressive or relapsed disease) based on BICR assessments or death from any cause	DoR is defined as the time from the date of the first documentation of objective response (CR or PR) to the date of the first documentation of disease progression (progressive or relapsed disease) based on BICR assessments or to death due to any cause, whichever occurs first.	Efficacy
To assess the CR rate	**Title:** Complete response rate **Description:** Percentage of subjects with no detectable evidence of PTCL	CR rate is the percentage of subjects achieving CR as the BOR based on BICR.	Efficacy
To evaluate the DoCR	**Title:** Duration of complete response **Description:** Time from the first documented CR until documented disease progression (progressive or relapsed disease) based on BICR assessments or death from any cause	DoCR is defined as the time from the date of the first documentation of CR to the date of the first documentation of disease progression (progressive or relapsed disease) based on BICR assessments or to death due to any cause, whichever occurs first.	Efficacy

Objectives	Outcome Measures	Endpoints	Category
To assess the PR rate	**Title:** Partial response rate **Description:** Percentage of subjects with regression of disease and no detectable evidence of new cancer/lesions in other parts of the body	PR rate is the percentage of subjects achieving PR as the BOR based on BICR assessment	Efficacy
To assess the safety and tolerability of valemetostat tosylate monotherapy	**Title:** Number of subjects with TEAEs during the study **Description:** Total number of Cohort 1 subjects in the Safety Analysis Set with TEAE	All safety assessments, including AE reporting (TEAEs; TEAESIs; TESAEs; TEAEs by severity CTCAE grading, including Grade 3 and Grade 4; fatal events; and TEAEs leading to treatment discontinuation, interruption, or reduction), laboratory assessments, vital signs, and ECG (including QTcF by central ECG reading)	Safety
To evaluate ORR, CR and PR rates, DoR, and DoCR based on investigator assessments	Not applicable	ORR, CR and PR rates, DoR, and DoCR, as defined above, based on investigator assessments	Efficacy
To evaluate PFS with valemetostat tosylate monotherapy	Not applicable	PFS is defined as the time interval from the date of the first dose of study drug to the date of disease progression (progressive or relapsed disease) or death due to any cause. Disease progression will be evaluated by investigator assessments.	Efficacy

Objectives	Outcome Measures	Endpoints	Category
To evaluate OS with valemetostat tosylate monotherapy	Not applicable	OS is defined as the time interval from the date of the first dose of study drug to the date of death due to any cause.	Efficacy
Exploratory			
All Cohorts			
To analyze EZH1 and EZH2 mutational status and evaluate its impact on the activity of valemetostat tosylate	Not applicable	Efficacy assessments (eg, ORR and DoR) will be analyzed per EZH1 and EZH2 mutational status at baseline.	Efficacy
To characterize associated biomarkers in peripheral blood and tumor biopsies that may help to identify subjects who may receive clinical benefit from valemetostat tosylate treatment	Not applicable	Relationship between biomarker status and clinical efficacy which may include CD markers, changes in H3K27me3 status, immune cell population, gene mutation, and expression profiles. Effects of valemetostat tosylate in peripheral blood and tumor tissue, which may include changes in tumor microenvironment, and immune cell repertoire.	Biomarker
To evaluate the PK and exposure-response relationships for efficacy and safety	Not applicable	Relationship between the exposure to total and unbound valemetostat in plasma and efficacy endpoints. Correlation between the exposure to total and unbound valemetostat in plasma and safety endpoints.	PK

Objectives	Outcome Measures	Endpoints	Category
Cohort 1 Only			
To evaluate the efficacy of valemetostat tosylate monotherapy using PET-CT-based response assessment	Not applicable	Efficacy assessments (eg, ORR and DoR) will be performed using PET-CT-based response assessment in subjects with FDG-avid PET scans at baseline	Efficacy
Cohort 2 Only			
To evaluate the efficacy of valemetostat tosylate monotherapy treatment in R/R ATL based on investigator assessment	Not applicable	ORR, DoR, CR rate (including CRu), PR, DoCR, PFS, and OS	Efficacy

AE = adverse event; ATL = adult T-cell leukemia/lymphoma; BICR = blinded independent central review; BOR = best overall response; CD = cluster of differentiation; CR = complete response; CRu = uncertified complete remission (response); CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; DoCR = duration of CR; DoR = duration of response; ECG = electrocardiogram; EZH = enhancer of zeste homolog; FDG = fluorodeoxyglucose; ORR = objective response rate; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival; PK = pharmacokinetics; PR = partial response; PTCL = peripheral T-cell lymphoma; QTcF = QT interval corrected with Fridericia's formula; R/R = relapsed/refractory; TEAE = treatment-emergent adverse event; TEAESI = treatment-emergent adverse event of special interest; TESAE = treatment-emergent serious adverse event

3.1. Rationale for Selection of Primary and Select Secondary Endpoints for Cohort 1

ORR is generally accepted by oncologists in guiding cancer treatments and is considered as a surrogate endpoint known to reasonably likely to predict clinical benefit.[54] Blinded independent central review (BICR)-assessed ORR was selected as the primary endpoint, which will measure the anti-lymphoma tumor effect of valemetostat tosylate. The BICR will be utilized to provide consistent evaluation of efficacy such as radiographic assessment by central radiologists. The secondary efficacy endpoints include CR or partial response (PR) rates and DoR and CR based on BICR assessments, which may further provide supportive evidence of anti-lymphoma tumor effect.

4. STUDY DESIGN

4.1. Overall Design

This is a global, multicenter, open-label, single-arm, 2-cohort, Phase 2 study designed to evaluate the efficacy and safety of valemetostat tosylate monotherapy in approximately 148 subjects with R/R PTCL (128 subjects) and R/R ATL (20 subjects).

The primary objectives are to evaluate the clinical benefit of valemetostat tosylate monotherapy as measured by BICR-assessed efficacy, that is, ORR in R/R PTCL (Cohort 1) and the safety and tolerability of valemetostat tosylate monotherapy in R/R ATL (Cohort 2). A key secondary objective for the R/R PTCL (Cohort 1) is to evaluate other efficacy measures (eg, DoR) as well as the safety and tolerability of valemetostat tosylate monotherapy.

This study is planned to be conducted in approximately 70 study sites in North America, Europe, Asia, and Oceania. The study population is described in Section 5.

The study start date is the date when the first subject has signed informed consent. A subject is eligible to be enrolled into the interventional phase (divided into 3 periods: Screening, Treatment, and Follow-up) of the study when the investigator or designee has obtained written consent, all screening procedures have been completed, and the investigator has confirmed all eligibility criteria have been met by the subject at both Screening and Cycle 1 Day 1 prior to the first dose of study drug. A subject is considered enrolled once they have taken their first dose of study drug.

A non-binding futility interim analysis will be conducted for Cohort 1 when the first 46 (40%) subjects with histologically confirmed PTCL, by central pathology review, complete a minimum of 4 months of follow-up from the first dose of valemetostat tosylate. The futility criterion of BICR-assessed ORR is 23.9% or lower, that is, 11 or fewer responders from the first 46 confirmed R/R PTCL subjects observed. This boundary only provides the conditional power of 0.1% if the null hypothesis is true for the future coming patients. If the alternative hypothesis is true for the future coming patients, it provides the conditional power of 40%. This cohort may be terminated based on the totality of the evidence (response rate, safety, and benefit/risk), with consideration of the futility boundaries.

An internal data monitoring committee (DMC) will evaluate the safety and/or efficacy data for these interim analyses, according to statistical procedures defined a priori and for periodic safety reviews and will recommend that the study be terminated early for safety and/or efficacy (futility) or continue as planned (Section 10.1.5). The tasks performed by the DMC will be described in the DMC charter.

The primary completion date is based on the initiation of study drug in Cohort 1 by the last subject to meet PTCL eligibility criteria as confirmed by central diagnosis. The primary completion date will be at least 10 months after the first dose of study drug is taken by this subject.

4.1.1. Design Overview

Approximately 148 subjects will be enrolled (128 subjects with R/R PTCL and 20 subjects with R/R ATL). This study will include 2 cohorts:

- Cohort 1 (R/R PTCL)
  - Prior treatment with brentuximab vedotin is required for ALCL, a subtype of PTCL.
- Cohort 2 (R/R ATL)
  - Subjects with R/R ATL will be enrolled as a separate single-arm cohort because response criteria unique to ATL will be used.

Enrollment into both cohorts will occur independent of each other and will run in parallel.

At the beginning of the Screening Period, prior to undergoing any study procedures, subjects sign the informed consent form (ICF). During the 28-day Screening Period, subjects' eligibility will be confirmed. They will undergo medical history evaluation, physical examination, vital sign determination, and radiographic assessments including computed tomography (CT) (or magnetic resonance imaging [MRI]) scans (neck, chest, abdomen, and pelvis) and fluorodeoxyglucose (FDG)-positron emission tomography (FDG-PET) scan (base of the skull to mid-thigh) (see Section 1.3 for a complete list of assessments). Radiographic assessment for other lesions (eg, head) may be performed if clinically indicated. Bone marrow biopsy is required in all subjects except for subjects who underwent bone marrow biopsy within 3 months of the first dose of study drug and when the bone marrow results are documented. In Cohort 2 subjects, upper gastrointestinal endoscopy is recommended for lesion evaluation during screening; if the presence of a clinical lesion is suspected, colonoscopy may be also performed during screening.

During the Treatment Period, subjects will receive valemetostat tosylate 200 mg/day until disease progression or unacceptable toxicity (Section 7.1). Each cycle will be 28 days in duration.

Subjects may choose to discontinue the study drug at any time, during the Treatment Period, to undergo HCT. Subjects who discontinue study drug for any reason other than disease progression will continue to have radiographic assessments at the intervals described in the Treatment Period until disease progression, start of a new anticancer therapy, lost to follow-up, or withdrawal of study consent.

After study drug is discontinued, subjects will be followed for 30 days for safety (30-day Safety Follow-up). All subjects will then enter Long-term Follow-up for collection of information on subsequent lymphoma treatment, response status, HCT and HCT-relevant information, and survival, including the cause and date of death.

The subject population is described in Section 5. Flow diagrams of study activities are presented in Figure 1.1 and Figure 1.2.

4.1.2. End of Study

The primary completion date is based on the initiation of study drug in Cohort 1 by the last subject to meet PTCL eligibility criteria as confirmed by central diagnosis. The primary completion date will be at least 10 months after the first dose of study drug is taken by this subject.

All subjects in either cohort who are still on treatment or who discontinued from study drug at the primary completion date will continue to follow the study Schedule of Events (Table 1.1) until the **overall End of Study (EOS)** is reached, or the subject is lost to follow-up, or the subject withdraws consent, or until death.

Overall EOS will occur when the last subject's last visit has occurred and is defined as the completion of survival follow-up of at least 3 years after the first dose of the last subject either from Cohort 1 or Cohort 2, whichever occurs later.

The subject's EOS is defined as the date of his/her last study visit/contact.

4.1.3. Dose Regimen

Subjects will be administered oral valemetostat tosylate at a dose of 200 mg once daily starting at Cycle 1 Day 1, until disease progression or unacceptable toxicity, according to the dosage regimens outlined in Table 6.1.

4.1.4. Duration

Study duration will include a Screening Period, a Treatment Period, and a Follow-up Period (which includes a 30-day safety follow-up and long-term survival follow-up), as shown in Figure 1.1.

Duration of Treatment and Subject Participation

After signing the ICF, subjects will be administered valemetostat tosylate at a dose of 200 mg once daily starting at Cycle 1 Day 1, until disease progression or unacceptable toxicity. It is expected that a subject's total duration of participation in the study will be up to 28 days in the Screening Period, more than 6 months in the Treatment Period, and 30 days (+7 days) in the Follow-up Period after the last study drug administration. The Survival Follow-up Period will be at least 3 years after the first dose of the study drug in the last subject.

Overall Study Duration

The overall duration of enrollment for both cohorts is estimated to be approximately 20 months.

The Survival Follow-up Period will be at least 3 years after the first dose of the study drug in the last subject.

The anticipated total duration of the study from the first patient in through last patient out, which will include survival follow-up, will be approximately 56 months. See Section 4.1 and Section 4.1.2 for the definition of study start and for the definition of the overall EOS, respectively.

4.2. Rationale for Study Design

The Phase 2 study is designed assuming that treatment with valemetostat tosylate monotherapy will produce a 95% CI, which would exclude the ORR of 27% in subjects with R/R PTCL (Cohort 1). The ORR 27% was based on the ORR of 25.8, 26.2, and 27% from belinostat, romidepsin, and pralatrexate for R/R PTCL, respectively.[6,26,27]

Conducting a single-arm study is generally acceptable for PTCL due to its rare incidence and the lack of a globally established standard of care for PTCL.

A parallel cohort approach was selected because the response criteria unique to ATL will be used in Cohort 2 for subjects with R/R ATL who may have disease in peripheral blood or skin lesion(s).

4.3. Justification for Dose

The 200-mg dose and once-daily dose regimen were selected based on the results of the ongoing study DS3201-A-J101 (NCT02732275).

As of the data cut-off date (25 Dec 2019), the preliminary clinical data from Study DS3201-A-J101 suggests that 200 mg once daily valemetostat tosylate is expected to provide sufficient efficacy (an objective response of 57.9% and DoR 44.43 [95% CI: 5.86, 56.00] weeks) in PTCL patients while keeping a manageable safety profile.

The exposure-response (E-R) analysis showed that increased exposure did not provide increased efficacy; however, an area under the plasma concentration-time curve (AUC) at steady state can be achieved by most subjects receiving at least 200 mg/day valemetostat tosylate, implying that pharmacologic activity would be sufficient. The E-R relationship for platelet count was also analyzed from Study DS3201-A-J101. Platelet reduction was exposure dependent in the dose range tested (ie, 150 to 300 mg). The frequency of dose reduction and study drug discontinuation at 200 mg/day, in Japan and the US was 7.5% and 2.5%, respectively, indicating that valemetostat tosylate at 200 mg/day was generally well tolerated and demonstrates an acceptable safety profile. Thus, 200 mg/day valemetostat tosylate has been selected as the dose for this study.

In a healthy subject study (Study DS3201-A-J103), food intake (high-fat meal) decreased the valemetostat (DS-3201a) AUC and maximum concentration (Cmax) by approximately 30% and 50%, respectively, relative to a fasted condition. Therefore, valemetostat tosylate tablets will be orally administered once daily to fasting subjects (at least 1 hour before or at least 2 hours after a meal) until additional data for the effect of different meal types become available.

In the DDI study with cytochrome P4503A (CYP3A)/P-glycoprotein (P-gp) inhibitors (DS3201-A-J104), itraconazole (strong CYP3A inhibitor and P-gp inhibitor) increased AUC of valemetostat by 4.2-fold, and fluconazole (moderate CYP3A inhibitor) increased AUC by 1.6-fold. A physiologically based PK model has been developed to elucidate the contribution of CYP3A and P-gp; accordingly, a dosing adjustment guidance has been developed (Table 6.4). To further evaluate the effect of CYP3A/P-gp modulators on the PK of valemetostat to adequately inform DDI dose recommendations, additional PK samples will be collected after the initiation date of a strong/moderate CYP3A inhibitor or inducer, and/or P-gp inhibitor (Section 8.5.1).

5. STUDY POPULATION

Adult subjects (aged ≥18 years or the minimum legal adult age [whichever is greater]) with a diagnosis of R/R PTCL or R/R ATL. Prior brentuximab vedotin treatment is required for the ALCL subtype.

5.1. Treatment Period

5.1.1. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for enrollment into the study:

1. Sign and date the ICF, prior to the start of any study-specific qualification procedures.
2. Subjects ≥18 years of age or the minimum legal adult age (whichever is greater) at the time the ICF is signed.
3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2
4. Cohort 1 (R/R PTCL): Diagnosis should be confirmed by the local pathologist; local histological diagnosis will be used for eligibility determination. Subjects with the following subtypes of PTCL are eligible, according to 2016 World Health Organization classification prior to the initiation of study drug.[5] Any T-cell lymphoid malignancies not listed below are excluded. Below is the complete list of eligible subtypes:
   - Enteropathy-associated T-cell lymphoma
   - Monomorphic epitheliotropic intestinal T-cell lymphoma
   - Hepatosplenic T-cell lymphoma
   - Primary cutaneous γδ T-cell lymphoma
   - Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
   - Peripheral T-cell lymphoma, NOS
   - Angioimmunoblastic T-cell lymphoma
   - Follicular T-cell lymphoma
   - Nodal PTCL with TFH phenotype
   - Anaplastic large cell lymphoma, ALK positive
   - Anaplastic large cell lymphoma, ALK negative
5. Cohort 2 (R/R ATL): Acute, lymphoma, or unfavorable chronic type (Section 10.3.7). R/R ATL should be confirmed by the local pathologist; local diagnosis will be used for eligibility determination. The positivity of anti-HTLV-1 antibody will be locally determined for eligibility (Section 10.3.7).
6. Must have at least 1 of the following lesions which are measurable in 2 perpendicular dimensions on CT (or MRI) based on local radiological read:
   - Longest diameter (LDi) ≥2.0 cm for a nodal lesion

- LDi >1.0 cm for an extranodal lesion

  For Cohort 2 (ATL), subjects who had disease only in peripheral blood or skin lesions are eligible, as defined below.

  - An abnormal lymphocyte count (actual number) is ≥1.0 × 10^9/L and the abnormal lymphocyte-to-leucocyte ratio is ≥5%.
  - Skin lesion(s) measured by modified severity weighted assessment tool (mSWAT) score.[4]

7. Documented refractory, relapsed, or progressive disease after at least 1 prior line of systemic therapy.

   Refractory is defined as

   - Failure to achieve CR (or uncertified CR [CRu] for ATL) after first-line therapy; or
   - Failure to reach at least PR following second-line therapy or beyond.

8. Must have at least 1 prior line of systemic therapy for PTCL or ATL.

   - Subjects must also be considered as HCT-ineligible during Screening due to disease status (active disease), comorbidities, or other factors; the reason for HCT ineligibility must be clearly documented.
   - In Cohort 1, subjects with ALCL must have prior brentuximab vedotin treatment.

9. Local laboratory data must meet the following criteria at both Screening and prior to dosing on the planned Cycle 1 Day 1 Visit to confirm relatively preserved organ function:

   a. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 × upper limit of normal (ULN)
   b. Total bilirubin ≤1.5 × ULN, except for subjects with Gilbert's syndrome (eg, a gene mutation in UGT1A1), who can have total bilirubin <3.0 mg/dL
   c. Absolute neutrophil count (ANC) ≥1.0 × 10^9/L
   d. Hemoglobin ≥8.0 g/dL
   e. Platelet count ≥75 × 10^9/L
   f. Creatinine clearance ≥30 mL/min (measured by the Cockcroft-Gault equation) (Section 10.3.1)

10. Acute non-hematologic toxic effects (as evaluated by National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 5.0) of any prior therapy (except alopecia) resolved as shown below:

    - Peripheral neuropathy: Grade ≤2
    - Fatigue: Grade ≤2
    - All others: Grade ≤1

11. Is willing to provide tumor tissue (obtained during Screening or previously collected as a standard of care). In Cohort 2, subjects with ATL disease should also be willing to submit peripheral blood samples.

12. If the subject is a female of childbearing potential, she must have a negative serum pregnancy test at Screening and must be willing to use highly effective birth control, as detailed in Section 10.3.6, upon enrollment, during the Treatment Period, and for 3 months, following the last dose of study drug. A female is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy) with surgery at least 1 month before the first dose of study drug or confirmed by follicle-stimulating hormone (FSH) test >40 mIU/mL and estradiol <40 pg/mL (<140 pmol/L).
13. If male with partner of childbearing potential, the subject must be surgically sterile or willing to use highly effective birth control (Section 10.3.6) upon enrollment, during the Treatment Period, and for 3 months following the last dose of study drug.
14. Female subjects must not donate, or retrieve for their own use, ova from the time of screening and throughout the study treatment period, and for at least 3 months after the final study drug administration.
15. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and for at least 3 months after the final study drug administration.
16. Is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.
17. Estimated life expectancy >3 months based on investigator's opinion.

5.1.2. Exclusion Criteria

Unless otherwise specified, the below criteria will be evaluated and subjects who meet any of the following criteria will be disqualified from entering the study:

1. Diagnosis of mycosis fungoides, Sézary syndrome, and primary cutaneous ALCL and systemic dissemination of primary cutaneous ALCL
2. Diagnosis of precursor T-cell leukemia and lymphoma (T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma), T-cell prolymphocytic leukemia, or T-cell large granular lymphocytic leukemia
3. Prior malignancy active within the previous 2 years except for locally curable cancer that is currently considered as cured, such as cutaneous basal or squamous cell carcinoma, superficial bladder cancer, or cervical carcinoma in situ, or an incidental histological finding of prostate cancer
4. Presence of active central nervous system (CNS) involvement of lymphoma
5. History of autologous HCT within 60 days prior to first dose of study drug
6. History of allogeneic HCT within 90 days prior to the first dose of study drug
7. Clinically significant graft-versus-host disease (GVHD) or GVHD requiring systemic immunosuppressive prophylaxis or treatment
8. Inadequate washout period from prior lymphoma-directed therapy before enrollment, defined as follows:

- Prior systemic therapy (eg, chemotherapy, immunomodulatory therapy, or monoclonal antibody therapy) within 3 weeks or 5 half-lives of the drug, whichever is longer, prior to the first dose of study drug
- Had curative radiation therapy or major surgery within 4 weeks or palliative radiation therapy within 2 weeks prior to the first dose of study drug

9. Uncontrolled or significant cardiovascular disease, including the following:
   - Evidence of prolongation of QT/QTc interval (eg, repeated episodes of QT corrected for heart rate using Fridericia's method [QTcF] >450 ms) (average of triplicate determinations)
   - Diagnosed or suspected long QT syndrome, or known family history of long QT syndrome
   - History of clinically relevant ventricular arrhythmias, such as ventricular tachycardia, ventricular fibrillation, or Torsade de Pointes
   - Uncontrolled arrhythmia (subjects with asymptomatic, controllable atrial fibrillation may be enrolled), or asymptomatic persistent ventricular tachycardia
   - Subject has clinically relevant bradycardia of <50 bpm unless the subject has a pacemaker
   - History of second- or third-degree heart block. Candidates with a history of heart block may be eligible if they currently have pacemakers, and have no history of fainting or clinically relevant arrhythmia with pacemakers, within 6 months prior to Screening
   - Myocardial infarction within 6 months prior to Screening
   - Angioplasty or stent graft implantation within 6 months prior to Screening
   - Uncontrolled angina pectoris within 6 months prior to Screening
   - New York Heart Association (NYHA) Class 3 or 4 congestive heart failure (see Section 10.3.2)
   - Coronary/peripheral artery bypass graft within 6 months prior to Screening
   - Uncontrolled hypertension (resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg)
   - Complete left bundle branch block
10. History of treatment with other EZH inhibitors
11. Current use of moderate or strong cytochrome P450 (CYP)3A inducers (Table 10.4)
12. Systemic treatment with corticosteroids (>10 mg daily prednisone equivalents). Note: Short-course systemic corticosteroids (eg, prevention/treatment for transfusion reaction) or use for a non-cancer indication (eg, adrenal replacement) is permissible.
13. Female who is pregnant or breast-feeding or intends to become pregnant during the study

14. Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection within 28 days prior to the first dose of study drug (hepatitis B surface antigen positive or have detectable HBV DNA or detectable HCV RNA).
15. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome
16. Evidence of ongoing uncontrolled systemic bacterial, fungal, or viral infection requiring treatment with intravenous antibiotics, antivirals, or antifungals. Note: Subjects with localized fungal infections of skin or nails are eligible.
17. Any active uncontrolled systemic diseases or other medical conditions considered to be poorly controlled by the investigator, including, but not limited to, bleeding diatheses
18. A medical history or complication considered inappropriate for participation in the study, or a serious physical or psychiatric disease, the risk of which may be increased by participation in the study in the investigator's opinion
19. Psychological, social, familial, or geographical factors or substance abuse that would prevent regular follow-up to be compliant with the protocol
20. Known or suspected hypersensitivity to valemetostat tosylate or any of the excipients

5.2. Screening Failures, Rescreening, and Subject Replacement

Retesting of assessments, including laboratory parameters, within any single screening will be permitted. Any new result prior to the first dose of study drug will override the previous result during screening.

Rescreening is permitted in this study. A new subject identification (SID) number should be assigned at the time of rescreening. For any subject who failed to meet the eligibility criteria upon initial screening, the initial screening information and the reason why the subject is ineligible for the initial evaluation will be recorded on the Screening Log.

If the subject successfully repeats the failed initial screening assessment(s) within the Screening Period, the subject may be enrolled. Additionally, if a subject meets all eligibility criteria but cannot begin dosing with study drug within 28 days after signing the ICF, the subject must be rescreened. Any assessments outside of the 28-day window from the first dose should be repeated, and the screening assessment data should be entered into the clinical database under the new SID.

There is no limit on the number of times a subject may be rescreened, but subjects completing screening and enrolled into the study will not be replaced.

6. STUDY TREATMENT

See Figure 1.1 for treatment sequence.

6.1. Study Drug Description

Table 6.1 describes the formulation, dose, regimen, duration, packaging, and labeling of valemetostat tosylate.

Table 6.1: Study Drug Dosing Information

Study Drug Name	DS-3201b tablets 50 mg DS-3201b tablets 100 mg
Dosage Formulation	DS-3201b (valemetostat tosylate) tablets 50 mg are white, round-shaped, film-coated tablets, each of which contains 50 mg of DS-3201a as the free form of valemetostat tosylate. DS-3201b (valemetostat tosylate) tablets 100 mg are grayish-red, oblong-shaped, film-coated tablets, each of which contains 100 mg of DS-3201a as the free form of valemetostat tosylate.
Dosage Level(s)	200 mg
Route of Administration	Oral
Dosing Instructions	200 mg, once daily. Subjects are instructed to orally take valemetostat tosylate under fasting conditions (to be taken at least 1 hour before or at least 2 hours after a meal).
Duration	Until progression or unacceptable toxicity
Packaging	Bottles (32 tablets per bottle) High-density polyethylene plastic bottle with desiccants (with a child-resistant cap) Packaging will clearly display the name of product, storage condition, and other required information as applicable in accordance with local regulations
Labeling	Bottles will be labeled as required per local regulatory requirement

6.2. Preparation, Handling, Storage, and Accountability for Study Drug

Preparation, Handling, and Disposal

The study drug will be supplied as tablets that need no further preparation at the study sites.

The dispensation of study drug will be conducted in accordance with the Pharmacy Manual provided by the Sponsor.

Procedures for proper handling and disposal should be followed in compliance with the standard operating procedures of the site.

Administration

The study drug will be orally administered once daily to fasting subjects (at least 1 hour before or at least 2 hours after a meal). The study drug will be administered over continuous 28-day

cycles and will be continued until disease progression or unacceptable toxicity. There will be no washout period between cycles. When valemetostat tosylate cannot be administered as specified in the protocol, such as overdose or missed doses, then the investigator will promptly evaluate the situation and take the necessary measures. On the following day, the study drug should be taken at least 12 hours after the last dose taken. If a dose is forgotten or missed, the subject should continue to take the study drug at the same dose the next day; a subject should not take the study drug 2 times within a 12-hour period.

If a subject vomits after taking a dose of the study drug, a replacement dose may not be given on the same day.

In the event of overdose, the subject should immediately be examined for any symptoms or signs, and the necessary assessments will be performed, including laboratory tests and 12-lead ECG. Furthermore, the event should be immediately reported to the Sponsor. The Sponsor will give instructions about the dose of valemetostat tosylate on and after the following day.

If a dose is forgotten or missed, or if a subject vomits after taking a dose of study drug, this will be recorded in the patient diary.

Storage

Valemetostat tosylate must be stored in a secure, limited access storage area under the recommended storage conditions noted on the label. If storage conditions are not maintained per specified requirements, then the Sponsor or contract research organization (CRO) should be contacted.

See the Pharmacy Manual for detailed information on storage conditions of study drug and management and collection.

Drug Accountability

When a drug shipment is received, the investigator or designee will check the amount and condition of the drug against the shipping documentation.

The Receipt of Shipment Form should be faxed as instructed on the form, unless receipt is controlled by drug inventory management system (DIMs). The original will be retained at the study site. In Japan, the wet-ink signed “Receipt of Shipment Form” will be returned to the Sponsor, and a photocopy will be kept at the study site.

In addition, the investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

The investigator is responsible for study drug accountability, reconciliation, and record maintenance (ie, Receipt of Shipment Form, dispensation/return record, and certificate of destruction/return receipt).

6.3. Method of Treatment Allocation

This is a non-comparative, open-label, parallel-enrollment, single-arm study with 2 cohorts:

- Cohort 1 (R/R PTCL)

  - Subjects must be considered as HCT-ineligible during Screening due to disease status (active disease), comorbidities or other factors; in case of other factors, the eligibility should be discussed with the study medical monitor, and the reason must be clearly documented.
  - Prior treatment with brentuximab vedotin is required for ALCL, a subtype of PTCL.
- Cohort 2 (R/R ATL)
  - Subjects with R/R ATL will be enrolled as a separate single-arm cohort because response criteria unique to ATL will be used.

6.4. Treatment Compliance

Study drug compliance will be assessed by study staff by collection of the subject medication diary.

6.5. Guidelines for Dose Modification

All dose modifications (interruption, delay, reduction, and/or discontinuation) should be based on the worst preceding toxicity (NCI-CTCAE Version 5.0), as shown in Table 6.2. Dose modification decisions may be based on local laboratory results. For Grade 3 or Grade 4 events, monitoring (including local laboratory tests, when appropriate) should be performed frequently and at an interval no longer than 7 days until the AE is determined to be resolving, as defined in Table 6.2 and Section 8.4.3.

6.5.1. Dose Interruptions and Reductions for Hematological and Nonhematological Toxicity

Table 6.2 details the criteria for dose interruptions/reductions for hematological and nonhematological toxicity.

Table 6.2: Dose Interruptions/Reductions for Hematological and Nonhematological Toxicity

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Valemetostat Tosylate[a]
Hematologic Toxicity	
Neutropenia or febrile neutropenia	Neutropenia: **Grade 4** ($<0.5 \times 10^9$/L) or febrile neutropenia **≥Grade 3** Interrupt the study drug up to 28 days. Resume the study drug at the dose before interruption if lasting ≤7 days or at a reduced dose (by 1 dose level[b]) if lasting >7 days once resolved to ≤Grade 2 (neutrophil count $\geq 1.0 \times 10^9$/L). If a second dose interruption[a] is required, then the study drug should be reduced by 1 dose level[b] for the subsequent cycles.

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Valemetostat Tosylate[a]
Anaemia	**≥Grade 3** (<8.0 g/dL) **requiring transfusion** Interrupt the study drug up to 28 days. Resume the study drug at the dose before interruption once resolved to ≤Grade 2 (hemoglobin ≥8.0 g/dL) at least 7 days since the last transfusion. If a second dose interruption[a] is required, then the study drug should be reduced by 1 dose level[b] for the subsequent cycles.
Thrombocytopenia	**Grade 3** (<50 × 10^9/L) **lasting >7 days** • First occurrence: Interrupt the study drug up to 28 days Resume the study drug at the previous dose once resolved to ≤Grade 2 (platelet count ≥50 × 10^9/L) • Second occurrence: Interrupt the study drug up to 28 days Resume the study drug at a reduced dose (by 1 dose level[b]) once resolved to ≤Grade 2 (platelet count ≥50 × 10^9/L) • Third occurrence: Discontinue subject from the study drug **≥Grade 3** (<50 × 10^9/L) **associated with ≥Grade 2 bleeding** • First occurrence: Interrupt the study drug up to 28 days Resume the study drug at a reduced dose (by 1 dose level[b]) once resolved to ≤Grade 2 (platelet count ≥50 × 10^9/L) • Second occurrence: Discontinue subject from the study drug **Grade 4** (<25 × 10^9/L) Interrupt the study drug up to 28 days. Resume the study drug at a reduced dose (by 1 dose level[b]) once resolved to ≤Grade 2 (platelet count ≥50 × 10^9/L) If a second dose interruption[a] is required due to Grade 4 thrombocytopenia, then the study drug should be reduced by 1 dose level[b] for the subsequent cycles.
Non-hematologic Toxicities	
QTc	**Grade 3** (QTc >500 ms on 2 separate ECGs, or >60 ms change from baseline, as the average from triplicate), regardless of causality Interrupt[a] the study drug immediately. Check and address any potentially attributing factors: Check and correct electrolytes (potassium, calcium, and magnesium). If possible, stop any con concomitant medications that prolong QTc interval.

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Valemetostat Tosylate[a]
	Once resolved to ≤Grade 1 (QTc ≤480 ms, as the average from triplicate), the study drug may be resumed. If causality is attributed to the study drug, reduce dose by 1 dose level[b] in subsequent cycles. If the QTcF increase is assessed to be attributed to a cause other than the study drug, resume the study drug at the dose before interruption or at a reduced dose (by 1 dose level[b]) but the subject must be monitored closely for QT prolongation for the first cycle at the increased dose. If a second dose interruption[a] is required due Grade 3 QTc prolongation, discontinue subject from study drug. **Grade 4** (Torsade de Pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia), regardless of causality Interrupt[a] the study drug immediately. Determine if there are any attributing factors such as electrolytes (potassium, calcium, and magnesium), concomitant medications, or other factors. If causality is attributed to the study drug, discontinue subject from study drug. If causality is not attributed to the study drug, the study drug can resume at a reduced dose (by 1 dose level[b]) once resolved to ≤Grade 1 (QTc ≤480 ms, as the average from triplicate).
Other Non-laboratory Adverse Events	**Drug-related Grade 3 that require treatment** Interrupt the study drug up to 28 days. Resume the study drug at the dose before interruption when resolved to ≤Grade 1 or baseline condition. If a second dose interruption[a] is required due to the same drug-related AE, then the study drug should be reduced by 1 dose level[b] for the subsequent cycles. Exceptions: Fatigue (study drug related), Grade 3, that improves within 72 hours after onset Nausea, vomiting, anorexia, or diarrhea (study drug related), Grade 3, that improves to ≤Grade 2 within 48 hours after onset with appropriate supportive therapy **Grade 4**, regardless of causality Interrupt the study drug up to 28 days. If causality is attributed to the study drug, resume the study drug at a reduced dose (by dose level[b]) for the subsequent cycles once resolved to ≤Grade 1 or baseline condition. If causality is not attributed to the study drug, resume the study drug at the dose before interruption or at a reduced dose (by dose level[b]). If a second dose interruption[a] is required due to the same drug-related AE, discontinue subject from study drug

Criteria	Worst Toxicity NCI-CTCAE Version 5.0 (unless otherwise specified): Dose or Schedule Modification for Valemetostat Tosylate[a]
Other Laboratory Adverse Events	**Drug-related Grade 3 that require treatment** Interrupt the study drug up to 28 days. Resume the study drug at the dose before interruption when resolved to ≤Grade 1 or baseline condition. If a second dose interruption[a] is required, then the study drug should be reduced 1 dose level[b] for the subsequent cycles. Exceptions: Transient laboratory abnormalities (drug-related) that do not involve associated clinical signs or symptoms and that resolve within 72 hours after onset **Drug-related Grade 4** Interrupt the study drug up to 28 days. Resume the study drug at a reduced dose (by 1 dose level[b]) for the subsequent cycles once resolved to ≤Grade 1 or baseline condition. If a second dose interruption[a] is required due to the same drug-related AE, discontinue subject from study drug. Subjects who experience a ≥Grade 3 laboratory AE who are, in the opinion of the investigator, benefiting from treatment may be allowed to continue on study drug.
Other Non-laboratory and Laboratory Adverse Events	**Regardless of causality, any adverse event, laboratory abnormality, or intercurrent illness that presents a substantial clinical risk to the subject with continued dosing per the investigator's opinion** Interrupt the study drug until there is no longer a substantial clinical risk to the subject with continued dosing of the study drug per the investigator's opinion. Resume the study drug at the same dose level.

AE = adverse event; ECG = electrocardiogram; NCI-CTCAE = National Cancer Institute–- Common Terminology Criteria for Adverse Events; QTc = corrected QT interval prolongation

[a] Dose interruptions ≤28 days.

[b] Study drug dose may be reduced up to 2 times to dose level -1 or dose level -2 (see Table 6.3 for details). Once the dose is reduced, the dose should not be increased again.

6.5.2. Dose Reductions for Valemetostat Tosylate

The dose of valemetostat tosylate should be reduced as described in Table 6.3 when a specific AE is observed, as noted in Table 6.2.

Table 6.3: Dose Reductions for Valemetostat Tosylate

Dose Level	Study Drug Dose Administered
1	200 mg/day
-1	150 mg/day
-2	100 mg/day

Once the dose of valemetostat tosylate has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level, unless further dose reduction is required.

During the treatment periods, more than 2 dose reductions because of toxicity are not allowed. If toxicity continues after 2 dose reductions, the subject will be withdrawn from the study drug. The dose reduction of valemetostat tosylate due to concomitant medication use will not be counted toward 2 times (see Section 6.5.4).

6.5.3. Permanent Discontinuation of Study Drug

Discontinue the study drug permanently if

- Study drug interruption >28 days from the previous dose:
  - Except if, in the opinion of the investigator, the resuming of the study drug is considered to continue providing clinical benefits. In such cases, the investigator may resume the study drug after consultation with the Sponsor Medical Monitor.
- Study drug dose has been reduced more than 2 times.

6.5.4. Dose Modifications with Concomitant Strong CYP3A Inhibitors and/or P-gp Inhibitors

When drugs with strong CYP3A inhibitory effect and/or P-gp inhibitory effect are coadministered, the dose of the study drug should be reduced according to Table 6.4. Refer to Table 10.4 for a list of strong CYP3A inhibitors and/or P-gp inhibitors. The dose of the study drug should be returned to the previous dose level that the subject was given (or 200 mg once daily if the dose was reduced from the start of the study) after 3 days from the last dose of the concomitant strong CYP3A inhibitors and/or P-gp inhibitors.

Table 6.4: Dose Reduction for Concomitant Use of Strong CYP3A Inhibitors and/or P-gp Inhibitors

Inhibitor	Study Drug Dose	
	200 mg Once Daily	150 mg or 100 mg Once Daily[a]
Strong CYP3A inhibitors	Reduce the dose of the study drug to 100 mg once daily.	Reduce the dose of the study drug to 50 mg once daily.
P-gp inhibitors	Reduce the dose of the study drug to 100 mg once daily.	Reduce the dose of the study drug to 50 mg once daily.
Drugs having a strong CYP3A inhibitory effect and a P-gp inhibitory effect	Reduce the dose of the study drug to 50 mg once daily.	Interrupt the study drug.

CYP3A = cytochrome P4503A; P-gp = P-glycoprotein

[a] When the dose of study drug is 150 mg or 100 mg once daily, the investigator should consult the Sponsor Medical Monitor before further reduction of the dose due to concomitant use of strong CYP3A or/and P-gp inhibitors.

6.6. Prior and Concomitant Medications

Therapies used within 28 days prior to enrollment until 30 days after the last administration of valemetostat tosylate will be recorded in the electronic case report form (eCRF). COVID-19 vaccination within 12 weeks of the first dose of study drug will be recorded in the eCRF. Prophylactic therapies (including any required premedications), prior therapies, and all concomitant therapies will be recorded in the eCRF.

All therapies received by subjects within 28 days prior to enrollment will be recorded as prior therapies. Concomitant therapies include all prescription, over-the-counter, and herbal remedies.

Prohibited Therapies/Products

The following medications/therapies and products will be prohibited during the Treatment Period:

- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for local disease control, or standard or investigational agents for the treatment of cancer).
- Other investigational therapeutic agents and investigational devices.
- Donor lymphocyte infusion is prohibited after the first dose of valemetostat tosylate. If this is medically essential, investigators should contact the Sponsor Medical Monitor.
- Food products (eg, grapefruit and Seville oranges) that are strong CYP3A inhibitors.
  - Consumption of herbs/fruits that may have an influence on the PK of valemetostat tosylate, such as star fruit, Seville orange or Seville orange-containing foods and beverages, and grapefruit or grapefruit-containing food or beverages, are prohibited from 3 days prior to the first dose of valemetostat tosylate up to the last dose of valemetostat tosylate.
- Strong or moderate CYP3A inducers, including supplements with CYP3A-inducing properties (eg, foods and beverages containing St. John's wort). Refer to Table 10.4 for a list of strong or moderate CYP3A inducers.
  - St. John's wort (hypericin) is not permitted from 14 days prior to the first dose of valemetostat tosylate up to the last dose of valemetostat tosylate.
  - If strong or moderate CYP3A inducers are medically essential to use as supportive care, concomitant use of moderate and strong CYP3A inducers is permissible after the first dose of valemetostat tosylate. In this case, dose interruption of valemetostat tosylate is not needed. Avoid the concomitant use as much as possible because drugs having moderate or strong CYP3A-inducing properties may decrease the plasma concentration of valemetostat (the free form of valemetostat tosylate).

Restricted Therapies/Products

Subjects are permitted to receive the following only when absolutely necessary during the Treatment Period.

Systemic use of corticosteroids is restricted, with the following exceptions:

- Systemic corticosteroid (≤10 mg daily prednisone equivalents)
- Short-course systemic corticosteroids (prevention/treatment for transfusion reaction)
- Use for a non-cancer indication (eg, adrenal replacement)

Topical corticosteroids (including cutaneous, ocular, intranasal, inhalational, or intra-articular use) are allowed. Investigators should contact the Sponsor Medical Monitor when topical corticosteroids are used for cutaneous lesions that are used for response assessment in ATL subjects in Cohort 2.

Avoid the use of sensitive P-gp substrates (digoxin, quinidine, paclitaxel, cyclosporine, sirolimus, tacrolimus, fentanyl, and phenytoin) with a narrow therapeutic index; alternative therapies that are not P-gp substrates should be considered. If concomitant use of valemetostat tosylate and P-gp substrates is unavoidable, separate valemetostat tosylate administration by at least 6 hours before or after the administration of -narrow therapeutic index P-gp substrates to minimize the potential for interactions and monitor closely for adverse reactions, if feasible.

Permitted Therapies/Products

Subjects are permitted to receive prophylactic or supportive treatment (such as granulocyte colony-stimulating factor) as standard of care during the Treatment Period, per the investigator's discretion and institutional guidelines.

Subjects are permitted to receive strong/moderate CYP3A inhibitors or P-gp inhibitors. However, caution should be exercised with concomitant use of these drugs, as valemetostat is a substrate of P-gp and primarily metabolized by CYP3A. Refer to Section 6.5.4 for dose modifications with concomitant use of strong CYP3A inhibitors or P-gp inhibitors. Refer to Table 10.4 for a list of strong/moderate CYP3A inhibitors and/or P-gp inhibitors.

The use of azole antifungal agents is permitted for prophylaxis or treatment for systemic fungal infections but should follow the dose modifications described in Section 6.5.4.

Preventative Treatment

Use of sulfamethoxazole-trimethoprim or drugs with equivalent indications is recommended for the prophylaxis of *Pneumocystis jirovecii* infection.

The risk of tumor lysis syndrome is well described in patients with malignancies, including lymphoma. As a precautionary measure, subjects should be closely monitored and adequately hydrated. Per the institutional standards, additional management (eg, prophylactic use of anti-hyperuricemic agents) should be also considered in subjects with a higher risk of tumor lysis syndrome, including those with high tumor burden.

7. STUDY DRUG DISCONTINUATION AND DISCONTINUATION FROM THE STUDY

7.1. Discontinuation of Study Drug

The primary reason for the permanent discontinuation of valemetostat tosylate treatment administration must be recorded. Reasons for treatment discontinuation include the following:

- Death
- Adverse event
- Progressive or relapsed disease meeting the 2014 Lugano criteria for Cohort 1 (Section 10.4.2) or meeting the modified 2009 ATL criteria for Cohort 2 (Section 10.4.3)
- Clinical progression
- Withdrawal by Subject (**to discontinue study drug**). NOTE: in this section this is only withdrawal for treatment with study drug and is NOT the same thing as a complete withdrawal from the study. Discuss with the subject that he/she will remain in the study (ie, continue with study visits and assessments, including survival follow-up).
- Lost to follow-up (see Section 7.3 for details on when a subject is considered lost to follow-up)
- HCT
- Pregnancy
- Protocol deviation
- Study termination by Sponsor
- Other

After study drug is permanently discontinued for any reason other than death or lost to follow-up, the subject will be treated as clinically indicated by the investigator or referring physician.

Progressive or relapsed disease or clinical progression is considered a sufficient reason to discontinue the study drug; however, the investigator may continue the study drug until the investigator has alternative lymphoma therapies and considers the study drug to be no longer beneficial to the subject. The decision to discontinue a subject from study drug remains the responsibility of the investigator.

The investigator must discuss with the subject that his/her decision to permanently discontinue the study drug means the subject still agrees to continue into the Follow-up Period for onsite or modified follow-up visits. Subjects will be followed for disease progression, if applicable, and survival at regularly scheduled intervals (see Table 1.1).

Procedures for Discontinuation from Study Drug

The subject should be instructed to contact the investigator or study site staff before or at the time study drug is discontinued.

If a subject is discontinued from the study drug

- The reason(s) for discontinuation and the last dose date should be documented in the subject's medical record and eCRF.
- Due to an AE, the investigator will follow the subject until the AE has resolved or stabilized.
- An End of Treatment (EOT) evaluation should be performed as described in the Schedule of Events (SoE) (Table 1.1).
- A safety follow-up evaluation should be performed 30 days (+7 days) after the last dose of study drug as described in the SoE (Table 1.1).
- If subject has not discontinued for "progressive or relapsed disease," continue efficacy and survival assessments until disease progression or start of subsequent lymphoma therapy, if applicable, as described in the SoE (Table 1.1).
- If subjects permanently discontinue the study drug with the intent to undergo HCT, valemetostat tosylate should be discontinued at least 7 days before starting preparative regimens. After HCT, data collection of HCT-relevant information will be required (see details in Section 8.3.5).
- Long-term Follow-up evaluations will be performed to assess survival, as described in the SoE (Table 1.1).

The investigator will complete and report the observations as thoroughly as possible up to the date of discontinuation, including the date of the last dose. All procedures and tumor assessments specified for the EOT Visit will be conducted. See Table 1.1 for specific EOT procedures.

If a subject does not agree to continue to come to the study site or is unable to come to the study site, then a modified follow-up must be arranged to ensure the continued collection of endpoints and safety information. Options for modified follow-up are noted below.

Modified Follow-up Options

The following modified follow-up options can be offered to a subject who does not agree to study visits at the study site or is unable to come to the study site.

- Study personnel contacting the subject by telephone (may be quarterly, bi-annually, annually, or only at the end of the study)
- Study personnel contacting an alternative person (eg, family member, spouse, partner, legal representative, physician, or other healthcare provider)
- Study personnel accessing and reviewing the subject's medical information from alternative sources (eg, doctor's notes and hospital records), including records from the transplant unit for subjects who have undergone HCT.

Dates of the modified follow-up contact(s) should be recorded. See Section 7.2 for the definition of withdrawal by subject from the study (ie, withdrawal of consent).

7.2. Subject Withdrawal/Discontinuation from the Study

Subjects may discontinue from the study for any of the following reasons:

- Death
- Withdrawal by subject (**from the study**). NOTE: this indicates that the subject withdraws consent and refuses to undergo any further study procedures or be followed for long-term survival
- Lost to follow-up (see Section 7.3 for details on when a subject is considered lost to follow-up)
- Study termination by the Sponsor
- Other

If the reason for study discontinuation is the death of the subject, the options for categorizing the primary cause of death are progressive disease or adverse event. If reason of death is unknown every effort should be made to obtain the primary cause of death. Only one AE will be recognized as the primary cause of death.

Only subjects who refuse all of the following methods of follow-up will be considered to have withdrawn consent from study participation (ie, from the interventional portion and follow-up):

- Attendance at study visits per protocol
- Study personnel contacting the subject by telephone
- Study personnel contacting an alternative person
- Study personnel accessing and reviewing the subject's medical information from alternative sources

If the subject refuses all of the above methods of follow-up, the investigator should personally speak to the subject to ensure the subject understands all of the potential methods of follow-up. If the subject continues to refuse all potential methods of follow-up, the investigator will document this as a withdrawal of consent (from the interventional portion and follow-up).

Withdrawal Procedures

If a subject is withdrawn from both the interventional and follow-up portions of the study:

- The investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last dose, date of last contact, and the reason for withdrawal
- When disclosure of future information is also withdrawn, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent
- The subject may request destruction of any samples taken and not tested, and the investigator must document this in the site study records

- Study site personnel may use local, regional, and national public records (in accordance with local law) to monitor vital status.

See SoE (Table 1.1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-up

Subjects will be considered lost to follow-up if he/she fails to return for scheduled visits and is unable to be contacted by the study site staff. Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, telephone calls, texts, emails, and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented.

If direct contact with the subject is not possible, the site must make every effort to collect survival status from public records (eg, obituaries, death certificates, etc) in accordance with local laws.

8. STUDY PROCEDURES

See the SoE, Table 1.1, for Screening, Treatment, EOT, and Follow-up study procedures.

8.1. Eligibility Assessment

The subject's demographics, medical and target disease history, vital signs, CT (or MRI) and FDG-PET scans, and results of tests done (eg, physical examination, ECG, ECOG PS, and laboratory assessments) should be reviewed and compared against the eligibility criteria (Section 5.1.1 and Section 5.1.2). Retesting of laboratory parameters and/or other assessments within any single screening will be permitted. A unique SID will be assigned after the subject has signed the ICF. Any new result prior to the first dose of study drug during a single screening will override the previous result. Subjects should continue to meet all study protocol eligibility criteria prior to the first dose of study drug, including laboratory results and ECOG PS. Non-clinically significant changes in ECG on Cycle 1 Day 1 Visit would be acceptable. For rescreening information, refer to Section 5.2.

Informed Consent

Before a subject's participation in the study, it is the investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive responses to their inquiries and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population. See Section 10.1.2 for additional details.

Demographics

Review the subject's demographics against the eligibility criteria. Demographics include birth date, age at screening, sex, race, and ethnicity.

General Medical History and Baseline Conditions

Subject's medical history will be obtained by the investigator or a qualified designee.

Untoward medical occurrence (including clinically relevant laboratory values that are not symptoms of the primary disease/vital signs that are out of range) that were diagnosed or known to exist prior to the signing the ICF will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF. Record the start date of any medical occurrence that started before the ICF was signed and is ongoing at the time of the first dose of valemetostat tosylate on the General Medical History and Baseline Conditions eCRF.

R/R PTCL or R/R ATL History

Subject's R/R PTCL or R/R ATL history will be obtained by the investigator or a qualified designee.

Qualifying Tumor Tissue Specimen

- A fresh sample at baseline is mandatory for all subjects.
  - If a fresh sample is not obtainable during screening, it is acceptable to submit previously collected tumor tissue, including the samples at the initial diagnosis of lymphoma.
  - Along with the fresh sample, submission of previous tumor tissue samples from the initial diagnosis of lymphoma, if available, is strongly encouraged but is optional.
- Samples should be from an excisional, incisional, or core needle biopsy.
- Additional information on tumor tissue collection, processing, and immediate shipping procedures is included in the Study Laboratory Manual.
- Specimens must be submitted to the central laboratory as soon as possible.
- Central Pathology Review
  - After all eligibility criteria have been met, the central pathologist(s) will review tumor tissue (slides) to confirm PTCL. Central pathologist(s)' responsibilities and procedures of central review will be specified in the Central Pathology Review charter.

Human Immunodeficiency Virus Antibody Test

An HIV antibody test should be performed within 28 days prior to the first dose or as required by local regulations or independent institutional review boards (IRBs)/ethics committees (ECs). For subjects enrolled in Japan and Germany, an HIV antibody test must be performed.

Hepatitis Screening

Hepatitis B and C testing should be performed during Screening (within 28 days prior to the first dose), which should include hepatitis B surface antigen, hepatitis B core antibody (anti-HBc), hepatitis B surface antibody, and hepatitis C antibody tests. Hepatitis B virus DNA level or hepatitis C virus RNA testing may be performed if necessary.

8.2. Enrollment

Cohort 1 (R/R PTCL): Diagnosis should be confirmed by the local pathologist and shared with the investigators; local histological diagnosis will be used for eligibility determination. After all eligibility criteria have been met, histology will be centrally confirmed. Copies of de-identified local report for histological diagnosis and additional clinical information may be collected for central histology review. Eligible T-cell lymphoma subtypes are provided in the inclusion criteria (Section 5).

Cohort 2 (R/R ATL): Acute, lymphoma, or unfavorable chronic type. R/R ATL should be confirmed by the local pathologist and shared with the investigators; local diagnosis will be used for eligibility determination. The positivity of anti-HTLV-1 antibody will be locally confirmed for eligibility determination.

After all screening procedures are performed, results of screening tests are available (ie, between the Screening Visit and the Cycle 1 Day 1 Visit, as required in Section 5 and Section 5.1.2), and subjects are confirmed to continue to meet all eligibility criteria at the Cycle 1 Day 1 Visit, eligible subjects will be enrolled in study to receive valemetostat tosylate.

8.3. Efficacy Assessments

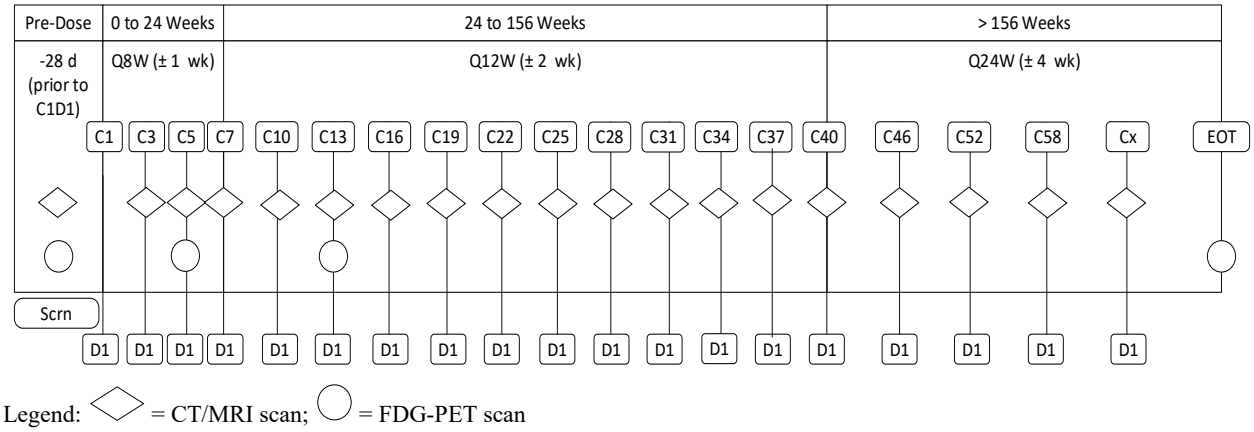
Efficacy assessments (radiographic assessments for all subjects and peripheral blood and skin lesion[s] assessments for Cohort 2 subjects) will be performed according to the schedule in Table 8.1, Figure 8.1, and Figure 8.2. Radiological assessments performed for the evaluation of disease progression on the prior therapy will be acceptable as baseline if performed within 28 days of the Cycle 1 Day 1 Visit.

Efficacy assessment will be performed independently by BICR (Cohort 1) and investigators (Cohorts 1 and 2) using the following response criteria:

- Cohort 1: CT-based response assessment per the 2014 Lugano criteria (Section 10.4.2).
  - The BICR and investigators will perform ancillary response evaluation based on PET-CT-based response assessment using 5-PS scores per the 2014 Lugano criteria in subjects with FDG-avid PET scans (5-PS score of 4 or 5 at baseline)
- Cohort 2: Modified 2009 ATL criteria (Section 10.4.3), based on the response criteria from an International Consensus Meeting.[2] The modification was made such that there is no requirement for each criterion to be present for a period of at least 4 weeks.
  - mSWAT score will be used to evaluate skin lesions (Section 10.4.4).
  - Subjects' body surface area (BSA) will be calculated using Table 10.19.

All CT (or MRI) and FDG-PET scans that are performed until disease progression or prior to the initiation of a subsequent lymphoma therapy, whichever occurs earlier, should be submitted to the BICR.

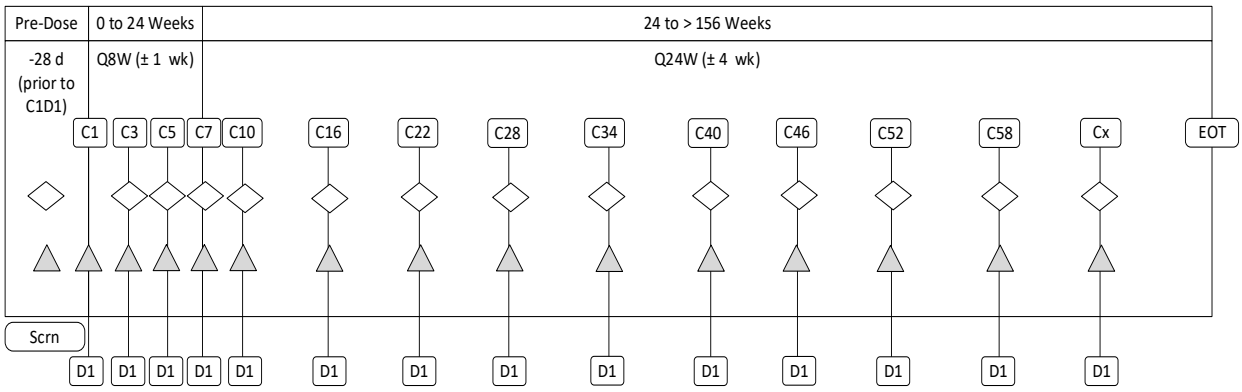
Figure 8.1: Cohort 1 Efficacy Assessment Schedule



Legend: ◇ = CT/MRI scan; ○ = FDG-PET scan

5-PS = 5-point scale; C = cycle; CT = computed tomography; D = day; EOT = End of Treatment;
FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; PET = positron emission tomography;
QxW = every x weeks; Scrn = Screening; wk = week
Note: Post-baseline FDG-PET scan will be required only for the subjects who had FDG-avid tumor (4 or 5 on the 5-PS score), per the investigator's assessment at baseline. If a FDG-PET scan was performed within 28 days prior to C5 D1, C13 D1 or EOT, then the FDG-PET scans on C5 D1, C13 D1, or EOT, respectively, do not need to be done. Investigators can perform an FDG-PET scan at any time point during the study.

Figure 8.2: Cohort 2 Efficacy Assessment Schedule



Legend: ◇ = CT/MRI scan; △ = peripheral blood and skin lesion(s) assessment

C = cycle; CT = computed tomography; D = day; EOT = End of Treatment; MRI = magnetic resonance imaging; QxW = every x weeks; Scrn = Screening; wk = week

8.3.1. Radiographic Assessments (CT/MRI and FDG-PET Scans)

CT/MRI Scan

A CT for neck, chest, abdomen, and pelvis and a FDG-PET scan from the base of the skull to the mid-thigh will be required at baseline and at the time points described in Table 8.1 and Table 8.2.

- During the Treatment Period, CT, MRI, or FDG-PET scans should be performed with the same imaging parameters as those at Screening.
- Radiographic assessments should be performed until disease progression (ie, progressive or relapsed disease) or until the subject initiates a subsequent lymphoma therapy, whichever occurs earlier. If there is clinical suspicion of disease progression, a physical examination and radiographic assessment should be performed promptly, if feasible, rather than waiting for the next scheduled radiological assessment.

CT scans of the neck to pelvis will be performed with a slice thickness of ≤5 mm for evaluation. Contrast media will be used for CT scans except for contraindications such as renal impairment or allergies to contrast media. CT (or MRI) for other lesions (eg, head) may be performed if clinically indicated.

- Combined hybrid PET-CT scanners may be used to acquire the CT images if CT images produced by the scanner are of diagnostic quality with intravenous contrast (if medically not contraindicated).

- An MRI can be used as an alternative to CT. However, if used instead of a CT scan, then it should be used for all subsequent assessments.
- Up to 6 target nodal or extranodal lesions will be selected at Screening. See Section 10.4.1.

Radiographic evaluations will be performed according to the schedule in Table 8.1.

For Cohort 1 only, all CT (or MRI) scan images, including those at unscheduled visits, should be submitted to the BICR.

Table 8.1: Schedule for Efficacy Assessment by CT (or MRI) Scan

Time on Study	Assessment Frequency	Assessment Visit	Assessment Window
Predose	Once	Screening	Within 28 days prior to the first dose
Cohort 1 Only			
For the first 24 weeks	Every 8 weeks	Day 1 of Cycles 3, 5, and 7	±1 week
After the first 24 weeks and up to the first 156 weeks	Every 12 weeks	Day 1 of Cycles 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, and 40	±2 weeks
After the first 156 weeks and onward during the study	Every 24 weeks	Day 1 of Cycles 46, 52, 58, and so on	±4 weeks
Cohort 2 Only			
For the first 24 weeks	Every 8 weeks	Day 1 of Cycles 3, 5, and 7	±1 week
After the first 24 weeks and onward during the study	Every 24 weeks	Day 1 of Cycles 10, 16, 22, 28, 34, 40, 46, 52, 58, and so on	±4 weeks

ATL = adult T-cell leukemia/lymphoma; CT = computed tomography; MRI = magnetic resonance imaging
Note: In Cohort 2 (ATL), efficacy assessment in peripheral blood and skin lesion(s) will be performed at the same time as tumor assessment by CT (or MRI).

FDG-PET Scans

An FDG-PET scan from the base of the skull to mid-thigh will be performed for Cohort 1 (PTCL) according to the schedule in Table 8.2.

- Subjects who had FDG-avid tumor, per the investigator's assessment (4 or 5 on the 5-PS score) at baseline will have an FDG-PET scan at the time points noted in Table 8.2.
- Subjects who had FDG non-avid tumor per the investigator's assessment (1, 2, or 3 on the 5-PS score) at baseline do not need an FDG-PET scan after Cycle 1 Day 1.

For Cohort 1 only, all FDG-PET scan images, including those at unscheduled visits, should be submitted to the BICR.

An FDG-PET scan is optional for Cohort 2 (ATL).

Table 8.2: Schedule for FDG-PET Scans

Time on Study	Assessment Frequency	Assessment Visit	Assessment Window
Predose	Once	Screening	Within 28 days prior to the first dose
After the first dose Only for subjects who had FDG-avid tumor per the investigator's assessment (4 or 5 on the 5-PS score) at baseline	Once	Cycle 5 Day 1[a]	± 1 week
	Once	Cycle 13 Day 1[a]	± 2 weeks
	Once	EOT[b]	± 2 weeks
	As needed	In addition, investigators can perform an FDG-PET scan at any time point during the study	

5-PS = 5-point scale; EOT = End of Treatment; FDG = fluorodeoxyglucose; HCT = hematopoietic cell transplantation; PET = positron emission tomography

[a] FDG-PET scans on Cycle 5 Day 1 or Cycle 13 Day 1 are not mandated in subjects who underwent an FDG-PET scan within 28 days prior to Cycle 5 Day 1 or Cycle 13 Day 1.

[b] This is unnecessary if a previous FDG-PET scan was performed within 28 days from the EOT.

Note: Subjects who had FDG non-avid tumor per the investigator's assessment (1, 2, or 3 on the 5-PS score) at baseline do not need an FDG-PET scan after Cycle 1 Day 1.

8.3.2. Bone Marrow Biopsy/Assessment

- Baseline bone marrow biopsy during the Screening Period is required in all subjects, except those who underwent bone marrow biopsy within 3 months of the first dose, with documented results.
  - The bone marrow sample will be sent to the local laboratory for assessment.
- During treatment, bone marrow biopsy is required to confirm normal morphology to declare CR (or CRu for ATL) per CT-based response assessment in subjects with positive, indeterminate, or unknown lymphoma involvement in bone marrow at baseline. Investigators may also perform bone marrow biopsy when an FDG-PET scan shows CR (or CRu for ATL) in subjects with positive, indeterminate, or unknown lymphoma involvement in bone marrow at baseline.
  - Bone marrow assessment will be performed by the local laboratory.
  - All results of bone marrow assessment until disease progression, until clinical progression, or prior to the initiation of a subsequent lymphoma therapy, whichever occurs earlier, should be reported.
- A deidentified local pathology report should be collected and submitted to the Sponsor (for submission to the BICR upon request for Cohort 1 only).

- Submission of bone marrow specimen to the central laboratory at any time point (including baseline) is not required.

8.3.3. Cohort 2 Additional Efficacy Assessments

Assessment for disease in peripheral blood and skin lesion(s) will be performed at the same timing of tumor assessment by CT (or MRI) according to the schedule in Table 8.1.

Disease assessment for peripheral blood and skin lesion(s) will be conducted during Screening and on Cycle 1 Day 1; whichever was assessed later prior to initiating the study drug will serve as the baseline values.

Note that tumor assessment by CT (or MRI) and FDG-PET scan will be performed according to the schedule in Table 8.1, even for subjects who had disease only in peripheral blood, only in skin, or only in peripheral blood and in skin at baseline.

Skin Lesion Assessment

Disease in cutaneous lesions is evaluated by visual inspection based on the mSWAT score (Section 10.4.4).

- In principle, the same physician should consistently assess cutaneous lesions in the same subject during the entire study to avoid inter-evaluator variability.
- If it is difficult to determine whether it is an ATL lesion or not by visual inspection, a biopsy should be performed to make a histopathological diagnosis.

Peripheral Blood Assessment

Disease in peripheral blood, using the sample collected for the local hematology, will be evaluated based on white blood cell count, absolute lymphocyte count, and abnormal lymphocyte count (absolute count and abnormal lymphocyte-to-leukocyte percentage).

- Peripheral blood must be assessed at every timepoint that a radiographic assessment is done (Table 8.1, Table 1.1, and Figure 8.2).
- If there is clinical suspicion of disease progression, a physical examination and a peripheral blood assessment should be performed promptly, if feasible, rather than waiting for the next scheduled peripheral blood assessment.

Evaluation of Gastrointestinal Lesions

For subjects in Cohort 2, upper gastrointestinal endoscopy is recommended for lesion evaluation during screening. If the presence of a clinical lesion is suspected, colonoscopy may also be performed during screening. If the subject had gastrointestinal ATL lesions at baseline, an upper gastrointestinal endoscopy or/and colonoscopy will be performed when CR or CRu is declared. It is desirable to perform a biopsy for subjects when gastrointestinal endoscopy and/or colonoscopy is performed.

8.3.4. Subsequent Anti-Lymphoma Treatments

Subsequent anti-lymphoma treatments taken after the last dose of the study drug and their outcomes must be monitored and recorded in the eCRF. Monitoring will continue until death, withdrawal of consent, lost to follow-up, or study closure.

8.3.5. Subsequent Hematopoietic Cell Transplantation

HCT-relevant information will be reported from the subjects who underwent a subsequent HCT after permanent discontinuation of the study drug. Subjects should complete the EOT, a 30-day Safety Follow-up Visit, and Long-term Follow-up. Additionally, HCT-related toxicities (eg, GVHD after a subsequent allogeneic HCT; Section 10.3.9) as of Day 100, 6 months from the date of HCT, and every 6 months thereafter will be collected and reported from these subjects.

Submission of radiographic images to BICR will not be required after a subsequent HCT. Instead, the investigator will report disease status according to 2014 Lugano criteria (CT and/or PET-CT-based response assessment, if applicable) for subjects in Cohort 1 and to the modified 2009 ATL criteria (CT-based response assessment) for subjects in Cohort 2, as follows:

- The disease status (CR or non-CR) as of Day 100, 6 months from the date of HCT, and every 6 months thereafter will be collected and reported
- The date of the first relapse/disease progression after HCT

Alternatively, with the subject's permission the investigator may make telephone contact with the subject's referring hematologist, oncologist, and/or transplant physician to obtain and document this information if the subject is being followed by another physician.

8.3.6. Survival Follow-up

All subjects should be followed for survival at least every 3 months after discontinuing study drug. Survival monitoring will continue until death, withdrawal of consent, lost to follow-up, or study closure.

8.4. Safety Assessments

8.4.1. Adverse Event

Method to Detect Adverse Events

The definitions of an AE or SAE can be found in Section 10.5. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative) at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality. The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue valemetostat tosylate.

All clinical laboratory results, vital signs, and ECG results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal laboratory results, vital sign findings, or ECG findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, lead to dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

Time Period for Collecting Adverse Events, Including Adverse Events of Special Interest and Serious Adverse Events

All AEs, including SAEs, occurring after the subject signs the ICF and up to 30 days after the last dose of study drug (ie, the Follow-up Period), whether observed by the investigator or reported by the subject, will be recorded on the Adverse Event eCRF. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up. After 30 days from the last dose of study drug, only SAEs considered to be related to study drug by the investigators and secondary malignancies (regardless of seriousness or causality) should be reported.

All non-serious AEs occurring after the subject signs the ICF until 30 days after the last dose of study drug will be recorded on the Adverse Event eCRF.

Exacerbation of a pre-existing medical condition and symptom after the subject signs the ICF including increase in severity of the symptom will be recorded as an AE on the Adverse Event eCRF, unless it is a condition of PTCL/ATL.

Reporting Procedure for Investigators

All AEs (including AEs of special interest [AESIs] and SAEs) will be reported in the Adverse Event eCRF. Procedure-related events must be reported as a non-serious or serious AEs. All AEs (serious and non-serious) must be reported with the investigator's assessment of seriousness, severity, and causality to valemetostat tosylate. Additionally, the action taken with regard to the study drug and for the event must be reported. See Section 10.5 for additional details.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

Disease-Specific AEs and SAEs

Disease progression/worsening of R/R PTCL or R/R ATL will **not** be recorded as an AE on the Adverse Event eCRF. However, events associated with disease progression, such as intestinal perforation of malignant lymphoma, may be recorded as AEs. As an exception, if no other immediate cause of death is identified, then Grade 5 disease progression should be reported as an SAE.

Death due to disease progression should be recorded on the Death eCRF; in this case, disease progression should be reported as the primary cause of death. If a subject died due to disease progression as the primary cause of death within 30 days from the last dose of study drug, the

Grade 5 AE, which was the underlying or immediate cause of death should be also reported as an SAE.

Example

If a subject died due to intestinal perforation of malignant lymphoma, disease progression should be reported as the primary cause of death. Additionally, if death occurred within 30 days from the last dose of study drug, intestinal perforation of malignant lymphoma should be reported as a Grade 5 SAE.

8.4.1.1. Serious Adverse Events Reporting

The following types of events should be reported by the investigator in the electronic data capture (EDC) within 24 hours of awareness:

If death is due to progressive disease, it should be reported within 24 hours even though it is **NOT** an SAE.

- SAEs (Section 10.5.2)
- Hepatic events (both serious and non-serious) meeting the laboratory criteria of a potential Hy's Law criteria (as defined in Section 8.4.1.4).
- Overdose (as defined in Section 8.4.1.2)
- Secondary malignancy (both serious and non-serious, Section 8.4.1.4)
- Pregnancy (as defined in Section 8.4.2)

Details summarizing the course of the SAE, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of AE onset, treatment, and resolution should be included. Medical history, concomitant medications, and laboratory data that are relevant to the event should also be summarized in the SAE report. For fatal events, the SAE report should state whether an autopsy was or will be performed and should include the results if available. Source documents (including medical reports) will be retained at the study site and should not be submitted to the Sponsor for SAE reporting purposes.

If using EDC for SAE reporting: Complete the eCRF within 24 hours of awareness. In the event that the eCRF is unavailable, report SAEs by faxing or emailing the SAVER (Serious Adverse Event Report) form to the CRO using the provided fax transmittal form and the appropriate fax number provided for your country or email address. Once EDC becomes available, please enter SAEs reported on the SAVER form into the eCRF as soon as possible. Please refer to the eCRF Completion Guide for additional instructions.

See Section 8.4.1 for details on the time period for collecting SAEs.

Reporting Requirement to Sites and Regulatory Authorities

The Sponsor/CRO will inform investigators and regulatory authorities of any suspected unexpected serious adverse reactions (SUSARs) occurring in study sites or other studies of the study drug, as appropriate per institutional and/or local reporting requirements.

Sponsor and/or CRO will comply with any additional local safety reporting requirements. The investigator will assess if an AE is to be considered "unexpected" based on the "Reference Safety Information" section in the current IB.[53]

Follow-up for AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.

Urgent safety queries and follow-up information such as those upgraded to fatal/life-threatening cases must be followed up and addressed promptly. The investigator will submit any updated SAE data to the CRO/Sponsor within 24 hours of receipt of the information. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up report.

8.4.1.2. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose (regardless of whether an AE occurs) must be reported to (CRO or Sponsor) within 24 hours of awareness. Overdose will be reported via eCRF. The Sponsor will give instructions about the dose of valemetostat tosylate on and after the following day.

In the event of overdose, the subject should immediately be examined for any symptoms or signs, and the necessary assessments will be performed, including laboratory tests and 12-lead ECG. It is advised to frequently monitor complete blood count for thrombocytopenia for the subsequent 3 weeks after the overdose incident. Supportive care should be provided per the local standard of care that is in the best interest of the subject.

An "excessive and medically important" overdose includes any overdose in which either an SAE, a non-serious AE, or no AE occurs and is considered by the investigator as clinically relevant, ie, poses an actual or potential risk to the subject.

Occupational exposures must be reported via the SAVER form.

8.4.1.3. Medication Error, Misuse, and Abuse

Medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product, shall be subject to the same reporting obligations as AEs.

- **Medication error**: This is an unintended failure in the drug treatment process that leads to, or has the potential to lead to harm to the subject
- **Misuse**: This refers to situations in which the medicinal product is intentionally and inappropriately used in a manner inconsistent with the protocol or the product labeling

- **Abuse**: This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects to the user

8.4.1.4. Adverse Events of Special Interest

An AESI will include hepatic events that meet the potential Hy's Law criteria (defined as an elevated ALT and/or AST ≥3 × ULN and an elevated TBL >2 × ULN, regardless if it is due to disease progression per investigator assessment, which may occur at different time points during the study conduct), thrombocytopenia, and secondary malignancy, including lymphoid malignancy.

Combined Elevations of Aminotransferases and Bilirubin

Hepatic events (both serious and non-serious) that meet the potential Hy's Law criteria defined as an elevated (ALT and/or AST) ≥3 × ULN and an elevated TBL >2 × ULN, regardless if it is due to disease progression per investigator assessment, that may occur at different time points during the study conduct, should always be reported to the Sponsor.[76] These events must be reported by eCRF, with the investigator's assessment of seriousness, severity, causality, and a detailed narrative. These events should be reported within 24 hours of investigator's awareness of the event regardless of seriousness. A targeted questionnaire will be available as an eCRF to collect relevant additional information for these potential cases.

If the subject discontinues study drug due to liver enzyme abnormalities, the subject will have additional clinical and laboratory evaluations as described in Section 10.2 in order to determine the nature and severity of the potential liver injury.

Secondary Malignancy

A 3-month nonclinical toxicology study in rats administered valemetostat tosylate showed the potential risks of developing lymphoid malignancies. A follow-up 3-month study in older rats performed to further understand the pathogenic mechanisms of this above finding in younger rats showed administration of valemetostat tosylate to aged rats did not induce a lymphoma that had been previously observed with younger rats. In addition, no similar findings were noted in other 3-month animal toxicity studies of valemetostat tosylate (see Section 2.3 for details). In the ongoing clinical program, cases of secondary malignancies have been reported (see current valemetostat IB for additional details).

The treatment of subjects with an EZH2 inhibitor may increase the risk of developing a secondary T-cell malignancy. T-cell lymphomas have been observed in animals treated with valemetostat tosylate and other agents that inhibit EZH2 in repeat-dose toxicology studies. A pediatric patient treated with an EZH2 inhibitor (tazemetostat) developed a secondary T-cell lymphoblastic lymphoma after approximately 15 months of therapy. A dose or duration of therapy at which agents that inhibit EZH2 would not increase the risk of a secondary T-cell malignancy is currently unknown.

Subjects receiving valemetostat tosylate should further be monitored for signs and symptoms of toxicities suggestive of secondary malignancy. Any confirmed new diagnosis of secondary malignancy should be reported as AESIs and reported to the Sponsor in an expedited manner.

Generally, these events should be reported as SAEs (Section 8.4.1.1) (with at least a seriousness criterion of important medical event, unless other criteria are met); however, if the events do not meet the seriousness criteria, the events should be reported as non-serious AESIs. These events should be reported within 24 hours of investigator's awareness of the event regardless of seriousness.

Thrombocytopenia

A nonclinical toxicology study in rats and dogs showed the potential risks of hematopoietic changes (including changes in RBC parameters and platelets). Clinical data from the ongoing Phase 1 study (DS3201-A-J101) in R/R NHL, including R/R PTCL subjects support this. The most commonly reported TEAE overall was platelet count decreased, occurring in 40 (71.4%) R/R NHL subjects and 15 (57.7%) R/R PTCL subjects, as of the data cut-off date of 25 Dec 2019.

Based on laboratory data in R/R NHL subjects, among 56 subjects who had a baseline and post-baseline platelet count recorded, 29 (51.8%) subjects had a platelet count decrease of maximum Grade ≤1, 12 (21.4%) subjects had Grade 2, and 13 (23.2%) subjects had Grade 3 or Grade 4 across all dose levels.

In Study DS3201-A-J101, there were 13 subjects who experienced ≥Grade 3 thrombocytopenia based on laboratory data. The overall median time to onset was 50.0 days (range: 10 days to 457 days) across all dose cohorts. Among these 13 subjects, 10 subjects had platelet recovery to $\geq 50 \times 10^9$/L. The overall median time to onset of recovery of platelet count (defined as the first date of platelet increase $\geq 50 \times 10^9$/L from the first date of platelet reduction $< 50 \times 10^9$/L) was 13.8 days (range: 2 days to 31 days).

Subjects should be monitored for signs and symptoms of platelet count decreased (see Table 6.2 for dose modifications guidelines to be followed for thrombocytopenia). The usual AE/SAE reporting conventions should be applied.

8.4.2. Pregnancy

Sponsor must be notified of any female subject or partner of a male subject who becomes pregnant while receiving or within 90 days of discontinuing valemetostat tosylate.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

This information is important for both drug safety and public health concerns. It is the responsibility of the investigator, or designee, to report any pregnancy in a female subject or partner of a male subject using the Exposure In Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU Reporting form upon learning of a pregnancy. The investigator should make every effort to follow the female subject or partner of a male subject (upon obtaining written consent from partner) until completion of the pregnancy and complete the EIU Reporting form with complete pregnancy outcome information, including normal delivery and induced abortion. Any adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, post-partum complications, spontaneous or induced

abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs.

Pregnancy Test

For women of childbearing potential (as defined in Section 5), document the results of a negative serum pregnancy test at Screening. For eligibility, if not performed as a part of routine care within 14 days of Cycle 1 Day 1, a serum pregnancy test must be performed, with the results available prior to Cycle 1 Day 1. A serum or urine pregnancy should also be performed per the SoE (Table 1.1).

8.4.3. Clinical Laboratory Evaluations

The clinical laboratory tests, including hematology, coagulation, serology, blood chemistry, lipid profile, and urinalysis, will be locally performed. Refer to Section 10.2 for the complete list of laboratory parameters.

Abnormal laboratory values (NCI-CTCAE Grade 3 or Grade 4) occurring during the clinical study will be followed until repeat test results return to normal (or baseline), stabilize, or are no longer clinically relevant. Routine scheduled local laboratory tests and relevant unscheduled local laboratory test results should be recorded into the Lab eCRF. New or worsened clinically relevant abnormalities should be recorded as AEs on the Adverse Event eCRF.

As described in Section 2.3, platelet count decreased was reported as the most frequent TEAE of any grade from the ongoing, open-label, Phase 1 study (DS3201-A-J101, 25 Dec 2019 data cut-off). Nonetheless, the reason and kinetics of thrombocytopenia associated with valemetostat tosylate are not well known. Therefore, thrombopoietin and immature platelet fraction will be centrally assessed to elucidate the mechanism of thrombocytopenia.[77,78,79,80,81]

Markers of Platelet Production

Thrombopoietin and immature platelet fraction (IPF) will be assessed.

Blood samples from Cycle 1 Day 1 through Cycle 3 Day 1 will be collected and sent to the central laboratory. At other visits when platelet count is $<75 \times 10^9$/L, the investigator may submit samples after consultation with the Sponsor Medical Monitor.

Cytomegalovirus Tests

In the ongoing open-label Phase 1 study (DS3201-A-J101, 25 Dec 2019 data cut-off), CMV infection as an AE was reported from 3 subjects. The etiology of this opportunistic infection was unclear. To characterize the CMV infection, blood samples will be collected and sent to the central laboratory for CMV viral load by quantitative polymerase chain reaction (PCR).

8.4.4. Other Safety

Physical Examinations

A complete physical examination should include a weight measurement and an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality

identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits (or as clinically indicated), limited symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be collected in the subject's study record. New or worsened clinically relevant abnormalities should be recorded as AEs on the Adverse Event eCRF.

Vital Signs

Vital signs will include the measurements of heart rate, systolic and diastolic blood pressures, temperature, height (obtained once, prior to dosing), body weight, and BSA (calculated in the eCRF using the Du Bois formula).[55]

Blood pressure and pulse rate will be measured after the subject has rested for 5 minutes or more.

Electrocardiograms

Triplicate 12-lead ECGs will be performed and recorded for every subject per the SoE (Table 1.1).

The ECG will be measured after the subject has rested for 5 minutes or more.

At each time point, triplicate ECGs are required. The 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes. All ECGs must be performed within 15 minutes (Cycle 1 only) or within 30 minutes (Cycles 2 to 5) prior to the collection of all PK samples collected up to Cycle 5 Day 1. If it is not possible, then ECG should be performed 30 minutes or more after the PK sample collection. For ECG assessments without time-matched PK samples, ECG should be performed before any blood collection.

At any visit during which a subject exhibits a heart rate ≤50 bpm or other clinical indications for ECG, the ECG will be repeated. Abnormal, clinically relevant findings occurring post-baseline will be reported as AEs. Whether or not the measurement is performed, the date the ECG is to be performed, heart rate, PR interval, RR interval, QRS amplitude, QT interval, QTcF interval, and results will be transmitted electronically to a central ECG laboratory.

ECOG Performance Status

The subject's ECOG PS should be assessed and recorded (Table 10.3).

Karnofsky Performance Status

For subjects who permanently discontinue the study drug with the intent to undergo HCT, the subject's Karnofsky PS should be assessed and recorded at the EOT visit, prior to the date of the planned HCT (Section 10.3.4).

8.5. Pharmacokinetic Assessments

Blood samples for PK and α-1-acid glycoprotein (AAG) analyses will be obtained at the time points shown in Table 8.3. Cycle 1 Day 8, Day 15, and Day 1 of Cycle 2 to Cycle 5 predose blood samples should be collected as close as possible to 24 hours after the prior dose. Subjects must be instructed not to take the day's dose of valemetostat tosylate until after the predose sample is collected. The actual time of study drug administration and the exact time of blood

sampling collection for PK of valemetostat, its major metabolite (CALZ-1809a), and AAG analysis must be recorded on the eCRF.

Plasma concentrations of valemetostat and major metabolite (CALZ-1809a) will be measured using a validated assay method. Plasma protein binding for valemetostat will be determined as a free fraction (fu) by equilibrium dialysis. The fu will be used to derive unbound plasma concentration of valemetostat.

Alpha-1 Acid Glycoprotein Measurement

Valemetostat binds to AAG in plasma and the level of AAG varies among subjects. Measuring levels of AAG may help in understanding the intersubject variability in the PK of valemetostat.

In order to measure AAG, blood will be collected from each subject.

Details for blood sampling, processing, storage, and shipment for PK and AAG samples will be provided in the Study Laboratory Manual.

Table 8.3: Schedule of PK/AAG Sample Collection

Cycle	1							2 to 5
Day	1					8	15	1
	Predose	Postdose (Time Relative to Dose)				Predose[a]	Predose[a]	Predose[a]
Hours		1	2	4	5			
Window	-24 h	±15 min	±15 min	±20 min	±20 min			
Sample Collected								
PK	X	X	X	X	X	X	X	X
AAG	X					X	X	X

AAG = α-1-acid glycoprotein; h = hour; min = minutes; PK = pharmacokinetics
[a] The predose sample should be collected as close as possible to 24 hours after the prior dose.

8.5.1. Pharmacokinetic Sample Collection for Co-Administration with Strong/Moderate CYP3A Inhibitors or Inducers and/or P-gp Inhibitors

When drugs with a strong/moderate CYP3A inhibitory or inducing effect and/or P-gp inhibitory effect are coadministered with the study drug, additional PK and AAG samples are required to be collected 10 days (or up to 14 days) after the initiation date of the inhibitor or inducer. Three PK samples (1 predose and 2 postdose samples) and 1 AAG sample (predose) will be collected. Specifically, for the PK postdose samples, 1 sample between 0.5 hour and 4 hours postdose and 1 sample between 4 hours and 8 hours postdose of valemetostat tosylate will be collected. If collecting 3 PK samples is difficult, at least 2 PK samples (1 predose and 1 postdose sample) will be collected. In this case, it is ideal to collect the sample closer to 4 hours postdose, but 1 PK sample at 0.5 hour to 8 hours will be acceptable. Note: More than 2 postdose PK samples will be acceptable as multiple postdose samples could increase the predictability of PK parameters and 1 blood sample collection for AAG measurement at predose on the same day of PK blood sampling back in the procedure. AAG data will be used for population PK (PopPK) modeling.

Refer to Table 10.4 for a list of strong/moderate CYP3A inhibitors or inducers and P-gp inhibitors.

The actual dose, actual date, and time of dosing for the comedications mentioned above must be recorded on the eCRF.

An example for 3 PK samples and 1 AAG sample:

- Fluconazole, a moderate CYP3A inhibitor, initiated on 01 Aug.
- Collect 1 AAG sample (predose prior to valemetostat tosylate administration) on 11 Aug.
- Collect 3 PK samples (predose and 2 postdose samples) on 11 Aug:
  - 1 predose PK sample prior to valemetostat tosylate administration
  - 1 postdose PK sample between 0.5 hour and 4 hours (eg, 3 hours) after valemetostat tosylate administration
  - Additional 1 postdose PK sample between 4 hours and 8 hours (eg, 6 hours) after valemetostat tosylate administration

An example for 2 PK samples and 1 AAG sample:

- Fluconazole, a moderate CYP3A inhibitor, initiated on 01 Aug.
- Collect 1 AAG sample (predose prior to valemetostat tosylate administration) on 11 Aug.
- Collect 2 PK samples on 11 Aug:
  - 1 predose prior to valemetostat tosylate administration
  - 1 postdose PK sample between 0.5 and 8 hours (eg, 4 hours) after valemetostat tosylate administration. When only 1 postdose PK sample is collected, it is ideal to collect the sample closer to 4 hours postdose.

8.6. Biomarker Assessments

8.6.1. Analysis of Biopsied Tumor Tissue

Fresh samples obtained during Screening and/or previously collected archival tumor tissue will be used. On Cycle 1 Day 1, oral mucosa swabs will also be collected for subjects who have provided informed consent for oral mucosa collection. Oral mucosa will be used as reference specimens to identify tumor-specific somatic mutations. The analyses can be conducted using fresh tumor samples from biopsies, which are performed at unscheduled time points after the first dose of valemetostat tosylate and optionally submitted.

The analyses of biopsied tumor tissue will include the following assays depending on the availability of the tumor tissue. First, comprehensive gene alteration profiling with next-generation sequencing (NGS) or other assay at baseline and at unscheduled points will be performed to analyze the mechanism of action and mechanism of resistance to valemetostat tosylate. This will include EZH1 and EZH2 mutational status at baseline to investigate its

potential impact on the activity of valemetostat tosylate. In the analysis of gene mutations, oral mucosa will be used as reference specimens to identify tumor-specific somatic mutations. Second, CD30 and other molecules will be evaluated using immunohistochemistry (IHC). Last, H3K27me3 status in biopsied tumor tissue with IHC will be performed in order to assess correlation between any methylation levels and clinical response. The remaining biopsied tumor samples will be used for further analysis to address scientific questions related to the efficacy and/or safety of valemetostat tosylate.

8.6.2. Minimal Residual Disease (MRD) Assessment Using Peripheral Blood Samples

Peripheral blood samples will be collected to evaluate the depth of response. Peripheral blood samples will be analyzed by PhasED Sequence, PCR, and flow cytometry to detect tumor-derived cell-free DNA and residual tumor cells.

A sample will be collected at these time points: Day 1 of Cycle 1, Cycle 2, Cycle 5, Cycle 13, and every 6 cycles onward starting Day 1 of Cycle 19 (ie, Day 1 of Cycle 19, Cycle 25, Cycle 31, and so on). In addition, peripheral blood samples will be collected at the time of the first CR or, if not obtainable, at the subsequent visit after the first CR when the first CR is determined by investigator per CT-based assessment (for primary efficacy analysis) or FDG-PET based-assessment (for primary exploratory analysis; see Table 1.1).

8.6.3. Profiling of T-cells in Freshly Collected Peripheral Blood Samples Using Flow Cytometry Assay

Fresh peripheral blood samples will be collected for flow cytometry assay to evaluate the impact of valemetostat tosylate on immune cells on Day 1 of Cycle 1, Cycle 2, Cycle 3, Cycle 5, and Cycle 7. If further evaluation is required for immune cells, sample collection at additional time points is allowed (see Table 1.1).

8.6.4. Pharmacogenomic (Inherited Genetic) Analysis

An oral mucosa swab for optional future pharmacogenetic analysis will be collected predose on Cycle 1 Day 1 from each subject who consented to this analysis. Detailed instructions for the collection, handling, and shipping of samples are outlined in the Study Laboratory Manual. Participation in this part of the study is optional for all subjects. Subjects who do not wish to participate in this part may still participate in the study.

If subjects agree, the remaining DNA will be stored, as outlined in Section 8.6.4.1, for performing pharmacogenetic analysis in the future; otherwise, all remaining DNA samples will be destroyed.

8.6.4.1. Banking of Specimens for Inherited Genetic Analysis

Subjects' samples will be banked for future biomarker analyses, which may include comprehensive gene mutation and expression profiling with NGS and RNA sequencing.

Procedures for the long-term preservation (banking) of blood and/or DNA specimens extracted from subjects' blood samples for each subject who consented are described in the Study Laboratory Manual.

The banked samples may be analyzed for genes involved in the absorption, distribution, metabolism, elimination, safety, and efficacy of valemetostat tosylate. Additionally, samples may be analyzed for genes involved in valemetostat tosylate-related signaling pathways or to examine diseases or physiologic processes related to valemetostat tosylate. DNA samples will not be immortalized or sold to anyone. This information may be useful in increasing the knowledge of differences among individuals in the way they respond to the study drug, as well as helping in the development of new drugs or improvement of existing drugs.

Storage and Disposal of Specimens

Banked DNA samples will be stored for a maximum of 15 years after the finalization of the clinical study report for this protocol. These specimens will be kept for pharmacogenetic analysis in case new genomic or genetic information is obtained in the future regarding the response (PK or pharmacodynamic) to valemetostat tosylate or in case serious adverse drug reactions are noted in a clinical study and pharmacogenetic analysis is to be conducted for investigation into the cause.

During the storage period, the samples will be coded with labels having no personal information and will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent and have their sample destroyed at any time. However, the data will not be discarded if analysis has been completed before the subject withdraws consent.

Disclosure of the Results of Future Pharmacogenetic Analysis

Because the nature and value of future pharmacogenetic analysis cannot be known at this time, any results obtained from research involving pharmacogenetic samples will not be disclosed to the subject or investigators now or in the future.

8.6.5. Storage of Specimens

In consideration of the possibility that the relationship between the biomarker and the efficacy or safety of valemetostat tosylate may be additionally analyzed based on newly obtained knowledge, the submitted specimens may be stored in the central laboratory or sample storage facility for a maximum of up to 15 years after the start of the clinical study (ie, the time of submission of the clinical trial plan notification).

9. STATISTICAL CONSIDERATIONS

9.1. General Statistical Considerations

The statistical analysis plan (SAP) will be developed and finalized before the first subject is enrolled and will describe the subject populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data.

9.2. Statistical Hypothesis

Valemetostat tosylate is efficacious in subjects with R/R PTCL.

9.3. Sample Size Determination

Cohort 1

The total number of Cohort 1 is approximately 128 R/R PTCL subjects. Assuming 90% of enrolled R/R PTCL subjects will have PTCL histology confirmed by central pathology review, the sample size of 115 R/R PTCL subjects will provide sufficient statistical precision for the inference of the ORR. With a sample size of 115 subjects, the probability of observing the lower bound of the 95% CI >27% (historical ORR rate) is at least 90%, if the expected ORR with valemetostat tosylate is 42%.

Table 9.1 shows the 95% exact CI (based on the Clopper-Pearson method) at different observed ORRs. The maximum half width of 95% CI for ORR will be approximately 9.5%.

Table 9.1: 95% Confidence Interval at Various Observed ORRs (R/R PTCL Subjects)

Responders	Total Sample Size	Observed ORR	95% Exact CI	
42	115	36.5%	27.7%	46.0%
47	115	40.9%	31.8%	50.4%
52	115	45.2%	35.9%	54.8%

CI = confidence interval; ORR = objective response rate

Cohort 2

A total sample size of approximately 20 R/R ATL subjects is expected at the time of enrollment closing. This sample size is not based on statistical considerations.

9.4. Population for Analysis Sets

Analysis Sets

- The **Safety Analysis Set** will include all subjects who received at least 1 dose of study drug.

Efficacy Population:

Cohort 1: Defined as all subjects who received at least 1 dose of valemetostat tosylate and had an eligible PTCL subtype that was confirmed by central hematopathology review.

Cohort 2: Defined as all subjects who received at least 1 dose of valemetostat tosylate and had an eligible ATL subtype.

- The **PK Analysis Set** will include all subjects in the Safety Analysis Set who had measurable plasma concentrations of valemetostat.
- The **Biomarker Analysis Set** will include all subjects who received at least 1 dose of the study drug, who provided specimens for the biomarker study, and whose measurement data obtained for the specimens are usable.

9.5. Statistical Analysis

The SAP will be developed and finalized before the first subject is enrolled and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.5.1. Efficacy Analyses

Table 3.1 lists the primary and secondary endpoints and their corresponding definitions of all endpoints. Additional details for the analysis and censoring rules are noted in the following sections. Detailed censoring rules for the primary and applicable secondary efficacy endpoints will be specified in the SAP.

Analysis will be conducted separately for PTCL and ATL cohorts.

9.5.1.1. Primary Efficacy Analysis – Cohort 1 Only

The primary efficacy analysis will be based on the data from the Cohort 1 efficacy population.

- ORR (CR + PR) based on CT-based BICR assessment

The primary efficacy analysis will be performed on the ORR in R/R PTCL subjects with centrally confirmed eligible PTCL subtype. The exact 95% CIs for the ORR will be calculated using the Clopper-Pearson method. Any response assessment after initiating a subsequent lymphoma therapy or a preparative regimen for a HCT will not be included into the primary efficacy analysis.

Sensitivity and supportive analyses of the primary efficacy analysis may be performed based on a subset of subjects from the efficacy population.

9.5.1.2. Secondary Efficacy Analyses – Cohort 1 Only

- DoR based on CT-based BICR assessment
- CR rate based on CT-based BICR assessment
- PR rate based on CT-based BICR assessment

- Duration of CR (DoCR) based on CT-based BICR assessment
- ORR, DoR, CR/PR rate, and DoCR based on investigator assessment

Summary statistics will be provided for DoR/DoCR based on BICR and investigator assessments as well as ORR based on investigator assessments. Kaplan-Meier curves will be provided, and the median survival and 95% CI will be calculated for DoR/DoCR assessed by both BICR and investigator. For the primary analysis of DoR/DoCR based on the BICR assessment, subjects who start subsequent therapy or HCT before BICR-assessed disease progression will be censored at the last evaluable tumor assessments prior to or on the date of initiation of the subsequent anticancer therapy or HCT. There will be a sensitivity analysis of DoR/DoCR based on the BICR and investigator assessment performed without censoring HCT. The censoring rules for the primary and sensitivity analyses for DoR/DoCR will be the same with the rules of PFS analysis.

- PFS based on BICR and investigator assessments
- OS
- DoCR, CR, and PR rates by BICR and investigator assessments.

9.5.1.3. Exploratory Analyses

An EZH2 inhibitor has different clinical activity in EZH2 wildtype and mutated follicular lymphoma.[56] The potential impact of EZH1 and EZH2 mutational status on the activity of valemetostat tosylate in PTCL is unknown. Therefore, EZH1 and EZH2 mutational status at baseline will be evaluated and its impact on the activity of valemetostat tosylate treatment will be analyzed based on mutational status.

Although the primary efficacy analysis for Cohort 1 will be performed according to CT-based response assessment of the 2014 Lugano criteria[1], the BICR and investigators will also conduct PET-CT-based response assessment for exploratory efficacy analysis. Unlike classical Hodgkin lymphoma or diffuse large B cell lymphoma, the role of FDG-PET scans in PTCL has not been fully established yet due to limited data.[57,58,59,60,61] PTCLs can be variably FDG avid, but the higher uptake was in aggressive subtypes.[60,62,63] Thus, FDG-PET scan-based response assessment may be informative to the utility of FDG-PET scans for measuring the therapeutic outcome in PTCL including ATL.

Exploratory analyses of efficacy for Cohort 2 subjects will be summarized in a descriptive manner.

9.5.1.4. Subgroup Analysis

Subgroup analyses will be performed for ORR based on age categories, gender, race, geographic region, PTCL subgroup, and number of prior regimens.

9.5.1.5. Multiplicity Adjustment

Not applicable.

9.5.2. Safety Analyses

Safety analyses will be performed using the Safety Analysis Set, and subjects will be analyzed according to their actual treatment received.

Safety will be measured by the incidence of all clinical and laboratory safety assessments, including TEAEs; TESAEs; severe events (Grades 3 and Grade 4); fatal events; TEAEs associated with treatment discontinuation, interruption, or reduction; and AESIs (as noted above in common toxicities/AEs of special interest).

Adverse Events

TEAEs are defined as new AEs or pre-existing conditions that worsen in NCI-CTCAE grade after the first dose of study drug and up to 30 days after the last dose of study drug. AEs collected after 30 days after the last dose of study drug will not be considered TEAEs unless they are treatment-related. TEAEs will be tabulated. TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology and tabulated by body organ group using the MedDRA system organ class and by AE term using preferred terms.

All AEs will be coded using the MedDRA dictionary. An AE will be assigned to the study period in which it started, even if it resolved in a subsequent period. The number and percentage of subjects reporting TEAEs will be calculated overall, by system organ class, by preferred term, and by treatment group.

Treatment-emergent adverse events will be further summarized by NCI-CTCAE Version 5.0 grade and relationship to study drug. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs and related treatment-emergent SAEs, treatment-emergent AESIs, and TEAEs leading to discontinuation of study drug will be tabulated.

A by-subject AE (including treatment-emergent) data listing, including, but not limited to verbatim term, preferred term, system organ class, NCI-CTCAE grade, and relationship to study drug will be provided. Deaths, all SAEs, AESIs, and AEs associated with study drug discontinuation will be listed.

Clinical Laboratory Evaluation

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation and by treatment group, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study drug, that is, the most current result prior to the first dose of the study drug will serve as the baseline values. In addition, mean change from baseline will be presented by treatment group for the maximum and minimum post-treatment values and the values at the EOT Visit.

Abnormal clinical laboratory results will be graded according to NCI-CTCAE Version 5.0, if applicable, and the grade will be presented in a by-subject data listing. A shift table, presenting by treatment group the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided for clinical laboratory tests. A listing of abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or Grade 4 will be generated.

Electrocardiogram

Descriptive statistics will be provided for the ECG measurements by scheduled time of evaluation and by treatment group, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study drug. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (eg, QTc ≤450 ms, >450 ms to ≤480 ms, >480 ms to ≤500 ms, and >500 ms, increase from baseline >30 ms to 60 ms, and increase from baseline >60 ms).

A listing of ECG data will be generated.

Vital Signs

Descriptive statistics will be provided for the vital signs measurements by scheduled time of evaluation and by treatment group, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study drug. A listing of vital sign data will be generated.

Other

Listings of all other safety endpoints (eg, physical examination findings, including ECOG PS, echocardiogram/multigated acquisition, and ophthalmologic findings) will be generated.

9.5.3. Other Analyses

The following other analyses are planned in this study.

Pharmacokinetics

Pharmacokinetics analyses will be performed using the PK Analysis Set.

Total and unbound concentrations for valemetostat in plasma and total concentration of CALZ-1809a in plasma will be listed and summarized using descriptive statistics at each time point.

Population PK analysis and exposure-response analyses for key efficacy and safety endpoints will be performed. Results from the PopPK analysis and exposure-response will be reported separately.

Biomarker

Peripheral blood and tumor biopsies will be collected at various time points including at baseline, on treatment and/or at the EOT, and/or at the time of relapse in order to characterize associated biomarkers in peripheral blood and tumor biopsies that may predict the effect of valemetostat on safety and efficacy measures. Those exploratory biomarkers will be used to evaluate any potential relationship between clinical outcome and biomarkers, including CD markers, changes in H3K27me3 status, immune cell population, gene mutation, and expression profiles. Other specimens aside from peripheral blood and tumor biopsies at several time points will also be collected and banked for future exploratory biomarker research.

9.6. Unacceptable Toxicities and Stopping Criteria

Unacceptable toxicities are defined as excessive toxicities in any of the following:

- Rate of Grade 4 (hematologic or non-hematologic toxicity) ≥30% or
- Rate of AESI (thrombocytopenia Grade ≥3) ≥35% or
- Rate of Grade 5 (hematologic or non-hematologic toxicity) ≥5%, when the primary cause of death is not reported as disease progression.

The stopping rules for the unacceptable toxicities are derived using the Pocock-type boundary.[64] The Pocock boundary allows stopping as early as possible for use in the stopping rule for excessive toxicity. These stopping boundaries for unacceptable toxicity will be applied separately to both Cohort 1 (see prespecified stopping boundaries in Appendix 3, Section 10.3.8, Table 10.6 through Table 10.8) and Cohort 2 (see prespecified stopping boundaries in Appendix 3, Section 10.3.8, Table 10.9 through Table 10.11).

Patient accrual will be halted, and the DMC meeting will be immediately triggered to make a recommendation based upon their comprehensive evaluation if excessive numbers of toxicities are observed (per each category above), that is, if the number of toxicities is equal to or exceeds stopping boundary out of the number of subjects with full follow-up.

See Section 10.1.4 for the frequency of assessments by the DMC.

9.7. Interim Analyses

Futility interim analysis will be conducted for both cohorts based on the primary endpoint, ORR.

Cohort 1: A non-binding futility interim analysis will be conducted when the first 46 (40%) subjects with histology-confirmed PTCL, by central pathology review, complete a minimum of 4 months of follow-up from the first dose of valemetostat tosylate. The futility criterion of BICR-assessed ORR is 23.9% or lower, that is, 11 or fewer responders from the first 46 subjects with R/R PTCL. The futility boundary is calculated using the spending function of Lan-DeMets with a parameter of O'Brien-Fleming, assuming an ORR rate of 27% (historical rate) and 42% (expected treatment effect rate) for valemetostat. This boundary only provides the conditional power of 0.1% if the null hypothesis is true for the future coming patients. If the alternative hypothesis is true for the future coming patients, it provides the conditional power of 40%. This cohort may be terminated based on the totality of the evidence (response rate, safety, and benefit/risk), with consideration of the futility boundaries. Additional interim analyses may be conducted if it is necessary to make decisions regarding further development.

An internal DMC, independent of the study team, will evaluate the safety and efficacy data for these interim analyses according to statistical procedures defined a priori and for periodic safety reviews. Based on the results of the interim analysis, the DMC will recommend that the study be terminated early for safety and/or efficacy (futility) or continue as planned.

10. APPENDICES – SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1 Regulatory and Ethical Considerations

10.1.1. Regulatory Compliance

The study protocol, the IB, available safety information, recruitment procedures (eg, advertisements), subject information and consent form, any subject written instructions to be given to the subject, information about payments and compensation available to the subjects, and documentation evidencing the investigator's qualifications should be submitted to the independent IRB or EC for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP. Written approval of all protocol amendments and changes to any of the above listed documents must be obtained from the IRB or EC.

The investigator should notify the IRB or EC of deviations from the protocol or SAEs occurring at the study site and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

The Sponsor will appoint a coordinating investigator. Among other possible duties, the coordinating investigator will be responsible for reviewing the final clinical study report and testifying to the accuracy of the description of the study conduct. Because the coordinating investigator should have personal knowledge of the conduct of the study, he/she will normally be chosen from among those investigators who have enrolled and treated at least 1 subject. However, where an investigator has special knowledge of the field or of the study, the coordinating investigator can be chosen prior to the enrollment of the first subject. In all cases, the coordinating investigator must be chosen prior to locking the database.

Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 Apr 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC and/or;
- European Commission Directive (2001/20/EC Apr 2001) and/or;
- European Commission Directive (2005/28/EC Apr 2005) and/or;
- US Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate and/or;

- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 (27 Mar 1997) and/or;
- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 (25 Nov 2014);
- Other applicable local regulations.

In addition, the investigator will inform the Sponsor in writing within 24 hours of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP non-compliance that the investigator becomes aware of.

Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all investigators involved in the clinical study, IECs/IRBs, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The Investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the independent ethics committee/institutional review board (IEC/IRB). The investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

10.1.2. Informed Consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The ICF and any revision(s) should be approved by the IEC/IRB prior to being provided to potential subjects.

The subject's written informed consent should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed ICF should be provided to the subject. The date and time (if applicable) that informed consent was given must be recorded in the eCRF.

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject has consented to their participation. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately

explained to and apparently understood by the subject and that informed consent was freely given by the subject.

A separate special consent for inherited genetic analysis will be obtained from subjects in accordance with health authorities in their particular region/country.

Suggested model text for the ICF for the study and any applicable subparts (PK, pharmacodynamic, etc) is provided in the Sponsor's ICF template for the investigator to prepare the documents to be used at his or her study site. Updates to applicable forms will be communicated via letter from the Sponsor.

For study sites in the US, included with the ICF, an additional consent is required for the Health Insurance Portability and Accountability Act.

10.1.3. Subject Confidentiality

The investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

For EU study sites, the Sponsor will observe the rules laid down in the European Data Protection Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the free movement of such data.

The Investigator must ensure that the subject's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique SID as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (eg, signed ICF) should be kept in strict confidence by the investigator.

In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the independent IRB/EC direct access to review the subject's original medical records for verification of study-related procedures and data. The investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

10.1.4. Data Integrity and Quality Assurance

Monitoring and Inspections

The Sponsor/CRO monitor and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, eCRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review and verification of study data remotely. The Sponsor intends to implement remote source data verification (SDV) of medical records in the study conduct if in compliance with national and local regulations. The investigator or study site, in consultation with their data protection officer, if applicable, must confirm their agreement to remote SDV, which should be compliant with all applicable local guidance documents and national regulations. Investigators and study sites that

must comply with "EMA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19" should inform each study subject that their study records may be reviewed remotely and document their agreement or disagreement.[66]

The frequency of the monitoring visit and remote SDV will vary based on the activity at each study site. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. Detailed information is provided in the monitoring plan.

The Sponsor/designee will monitor for study drug accountability, reconciliation, and record maintenance (ie, Receipt of Shipment Form, dispensation/return record, and certificate of destruction/return receipt).

The monitor will communicate deviations from the protocol, SOPs, GCP and applicable regulations to the investigator and will ensure that appropriate action (s) designed to prevent recurrence of the detected deviations is taken and documented.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the Sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor. Audit of study site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study-related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The Investigator should respond to audit findings.

In the event that a regulatory authority informs the investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

Data Collection

An eCRF must be completed for each subject who signs an ICF and undergoes any screening procedure. If a subject is not treated, the reason must be recorded on the eCRF. All data collected during the study will be recorded in this individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via an "audit trail."

The eCRF should be kept current to enable the study monitor to review the subject's status throughout the course of the study. Upon completion of the subject's eCRF, it will be reviewed and signed off by the investigator via the EDC system's electronic signature. Throughout the study, the investigator may also be required to confirm ongoing review of the subject's eCRF. This signature will indicate that the investigator inspected or reviewed the data in the subject-specific eCRF, the data queries, and the site notifications and agrees with the eCRF content.

Data Management

Each subject will be identified in the database by a unique SID.

To ensure the quality of clinical data across all subjects and study sites, a Sponsor/CRO Clinical and Data Management review will be performed on subject data according to specifications developed by the Sponsor. Data will be vetted both electronically by programmed data rules within the application and manually. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, completeness and any apparent discrepancies.

Data received from external sources such as central laboratories will be reconciled to the clinical database.

All AEs will be coded using MedDRA. Serious adverse events in the clinical database will be reconciled with the safety database.

All concomitant medications and prior cancer therapies will be coded using the World Health Organization Drug Reference (WHODRUG) Dictionary.

Safety Monitoring

The Sponsor will monitor the subjects' safety on an ongoing basis during this study.

- The safety of subjects on this study are reviewed, on a systematic and continuous basis, by the study physicians (medical monitor and safety lead). This includes a review of serious and non-serious adverse events, including hematological and nonhematological events.
- The safety data across the entire valemetostat tosylate program is reviewed at regular intervals throughout the study by the Safety Management Team (SMT). The SMT is responsible for reviewing data from all sources, including nonclinical and clinical studies, which include but are not limited to this study.
- In addition, study-wide accrual stopping criteria will be based upon excess occurrences of "unacceptable toxicities" and will be performed every 3 months. If any of the unacceptable toxicities occur in excess of the predefined stopping boundaries, this will prompt enrollment of new subjects into the study to be paused and a comprehensive review of the safety data by the adhoc DMC. See Section 9.6 for the definition of unacceptable toxicities details on the study-wide stopping boundaries.

10.1.5. Committees

Blinded Independent Central Review Committee

A BICR will be utilized in this study for Cohort 1 for the determination of BICR-assessed endpoints such as ORR, CR rate, PR rate, and associated durations of response. The BICR will review all available tumor assessment scans for all Cohort 1 treated subjects and, when applicable, relevant clinical data (at minimum, bone marrow results and tumor biopsy results). Copies of de-identified local pathology report for bone marrow or tumor biopsies performed in the study (with SID noted) may be collected, upon request by the BICR. Details of BICR responsibilities and procedures will be specified in the BICR charter.

Data Monitoring Committee

An internal DMC, independent of the study team, will evaluate the safety and efficacy data for this interim analysis according to statistical procedures defined a priori, and for periodic safety reviews, which includes the review of unacceptable toxicities (Section 9.6 and Section 10.1.4). Members of the DMC are independent of the study and will consist of both internal Sponsor experts (including safety physician, hematologist(s)/oncologist(s), and biostatistician) and external experts (including hematologist(s)/oncologist(s) with expertise in malignant lymphoma). Other external experts may be included if additional expertise is needed.

Based on the review of the data, the DMC will recommend that the study be terminated early for safety and/or efficacy (futility) or continue as planned. Details of DMC responsibilities and procedures will be specified in the DMC charter.

10.1.6. Study Documentation and Storage

The investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to obtain informed consent and make entries and/or corrections on eCRFs will be included on the Signature List.

Investigators will maintain a confidential Screening Log of all potential study candidates that includes limited information of the subjects, date and outcome of the screening process.

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential SID code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the investigator to reveal the identity of any subject when necessary.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IEC/IRB correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site (site specific Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by local laws or regulations or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing via email to DSPDRecords@dsi.com and be given the opportunity to provide further instruction.

Record Keeping

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (site specific Trial Master File) of all study-related (essential) documentation,

suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. Essential documents include:

- Subject files containing completed eCRFs, ICFs, and supporting source documentation (if kept).
- Study files containing the protocol with all amendments, IB, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the independent IRB/EC and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at study site, accountability records and final reconciliation and applicable correspondence.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

All essential documentation will be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have lapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by the applicable laws or regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

Subjects' medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

No study document should be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor in writing via email to DSPDRecords@dsi.com of the new responsible person and/or the new location.

10.1.7. Finances

Prior to starting the study, the Principal Investigator and/or Institution will sign a clinical study agreement with Sponsor or designee. This agreement will include the financial information agreed upon by the parties.

Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

10.1.8. Publication and Public Disclosure Policy

The Sponsor is committed to meeting the highest standards of publication and public disclosure of information arising from clinical studies sponsored by the company. The Sponsor will comply with US, EU, and Japanese policies for public disclosure of the clinical study protocol and clinical study results, and for sharing of clinical study data. The Sponsor will follow the principles set forward in "Good Publication Practice for Communicating Company-Sponsored

Medical Research (GPP3)", and publications will adhere to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" established by the International Council of Medical Journal Editors (ICMJE).

In order to ensure compliance with the public disclosure policies and the ICMJE recommendations, and to protect proprietary information generated during the study, all publications (manuscripts, abstracts, or other public disclosure) based on data generated in this study must be reviewed and approved in writing by the Sponsor prior to submission.

10.1.9. Protocol Deviations

The investigator should conduct the study in compliance with the protocol agreed to by the Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IECs/IRBs.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject.

The Sponsor must be notified in writing of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) within 24 hours and in accordance with the clinical study agreement between the parties.

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or study treatment, and had at least one administration of study drug, data should be collected for safety purposes.

If applicable, the investigator should notify the IEC/IRB of deviations from the protocol in accordance with local procedures.

10.1.10. Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the investigator
- Discontinuation of further study intervention development

The internal DMC will determine if potential early termination of the study, based on pre-specified criteria noted in the DMC charter, is warranted.

Study termination may also be requested by (a) competent authority/ies.

10.1.11. Product Complaints

A product complaint is any dissatisfaction with a product that may be attributed to the identity, quality, durability, reliability, or safety of the product. Individuals who identify a potential product complaint situation should immediately report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a quality representative from the Sponsor.

For product complaints, refer to the Pharmacy Manual for instructions and details.

10.2. Appendix 2: Central and/or Local Laboratory

The clinical laboratory tests listed in Table 10.1 are to be performed in this study.

Table 10.1: Clinical Laboratory Tests

Local Laboratory Used Unless Otherwise Indicated		
Test	**Analytes**	
Blood Chemistry	Albumin Alanine aminotransferase (ALT) Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Bilirubin (total) Bilirubin (direct) Blood urea nitrogen (BUN) (Urea if BUN cannot be performed) Calcium (Ca) Chloride (Cl) Creatinine	Gamma-glutamyl transaminase (GGT) Glucose, random Lactate dehydrogenase (LDH) Magnesium (Mg) Phosphorus Potassium (K) Protein (total) Sodium (Na) Uric acid
Serology	C-reactive protein (CRP) Immunoglobulin (Ig) G IgA	IgM β2 microglobulin
Hematology	Hemoglobin Hematocrit Platelet count Red blood cell (RBC) count White blood cell (WBC) count Reticulocyte	Differential WBC count: Basophils Eosinophils Lymphocytes Monocytes Neutrophils Abnormal lymphocytes [tumor cells] (optional for Cohort 1)
Lipid Profile	Cholesterol (total) Lipoprotein, high density (HDL) Lipoprotein, low density (LDL) Triglycerides	

Local Laboratory Used Unless Otherwise Indicated		
Test	**Analytes**	
Coagulation	Prothrombin time (PT) or PT ratio Activated partial thromboplastin time (aPTT) or APTT ratio International normalized ratio (INR)	
Urinalysis	Glucose Occult blood Protein	Urobilinogen
Hepatitis B and C	Hepatitis B surface antigen Hepatitis B core antibody hepatitis B surface antibody (Hepatitis B virus DNA level may be performed if necessary)	Hepatitis C antibody (Hepatitis C virus RNA testing may be performed if necessary)
Central Laboratory Tests		
Markers of Platelet Production	Markers of Platelet Production (thrombopoietin and immature platelet fraction)	
HTLV-1 antibody	HTLV-1 antibody (Cohort 2 only)	
Cytomegalovirus	CMV viral load by quantitative polymerase chain reaction (PCR)	

10.3. Appendix 3: Reference Standards

10.3.1. Cockcroft-Gault Equation

The estimated creatinine clearance (CrCl; mL/min) will be calculated using the Cockcroft-Gault equation based on actual weight in kilograms (1 kilogram = 2.2 pounds):[67]

Conventional – serum creatinine in mg/dL

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in mg/dL)} \times 72} \times 0.85$$

International System of Units – serum creatinine in µmol/L

Male:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in µmol/L)} \times 72 \times 0.0113}$$

Female:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in µmol/L)} \times 72 \times 0.01} \times 0.85$$

10.3.2. New York Heart Association

The NYHA classifications are summarized in Table 10.2.[68]

Table 10.2: New York Heart Association Classifications

Class	Functional Capacity	Objective Assessment
I	Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

Source: American Heart Association. Classification of Functional Capacity and Objective Assessment, Ninth edition 14 Mar 1994.
http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp

10.3.3. Eastern Cooperative Oncology Group Performance Status

The ECOG PS scale scores are summarized in Table 10.3.[69]

Table 10.3: Eastern Cooperative Oncology Group Performance Status

Score	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (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: Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-55

10.3.4. Karnofsky Performance Status Scale Definitions Rating (%) Criteria

The Karnofsky PS scale scores are summarized below.[70]

	Rating	Description
Able to carry on normal activity and to work; no special care needed.	**100**	Normal; no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	**70**	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	**40**	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Source: Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: reliability, validity, and guidelines. J Clin Oncol. 1984 Mar;2(3):187-93

10.3.5. CYP3A/P-gp Inhibitors and Inducers

Please note that the following list (Table 10.4) of CYP3A inhibitors/inducers and P-gp inhibitors is not all inclusive.[71]

Table 10.4: CYP3A/P-gp Inhibitors and CYP3A Inducers

CYP3A/P-gp Inhibitors	CYP3A Inducers[a]
Drugs having a strong CYP3A inhibitory effect and a P-gp inhibitory effect Clarithromycin Itraconazole Ritonavir Lopinavir and ritonavir Saquinavir and ritonavir Telaprevir Tipranavir and ritonavir Strong CYP3A inhibitors Boceprevir Cobicistat Danoprevir and ritonavir Elvitegravir and ritonavir Grapefruit juice Idelalisib Indinavir and ritonavir Ketoconazole Nefazodone Nelfinavir Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) Posaconazole Troleandomycin Voriconazole Mibefradil Telithromycin Moderate CYP3A inhibitors Aprepitant Ciprofloxacin Crizotinib Cyclosporine Conivaptan Diltiazem Dronedarone Erythromycin Fluconazole Fluvoxamine Imatinib Isavuconazole Tofisopam Verapamil	Strong CYP3A inducers Apalutamide Carbamazepine Enzalutamide Mitotane Phenytoin Rifampicin St. John's wort Avasimibe Rifapentine Moderate CYP3A inducers Bosentan Efavirenz Etravirine Phenobarbital Primidone Rifabutin Weak CYP3A inducers Armodafinil Rufinamide Modafinil

CYP3A/P-gp Inhibitors	CYP3A Inducers[a]
Weak CYP3A Inhibitors Chlorzoxazone Cilostazol Cimetidine Clotrimazole Fosaprepitant Istradefylline Ivacaftor Lomitapide Ranitidine Ranolazine Ticagrelor P-gp inhibitors (no strong CYP3A inhibition) Amiodarone Carvedilol Dronedarone Lapatinib Propafenone Quinidine Ranolazine Verapamil Topical medicine is excluded.	

CYP3A = cytochrome P450 3A; P-gp = P-glycoprotein

[a] If currently used, these medications need to be discontinued at least 14 days prior to valemetostat tosylate administration (substitution by alternative medications should be considered).

Sources:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table2-2,table3-3,table5-2
https://www.druginteractionsolutions.org

10.3.6. Highly Effective Contraception

Methods considered to be highly effective contraception include the following:[72]

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system

- Bilateral tubal occlusion
- Vasectomized partner
- Complete sexual abstinence
  - Note: sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

    Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception and therefore must not be used in this clinical study.

10.3.7. ATL Subtypes

Criteria for ATL subtypes are provided in Table 10.5.

Table 10.5: Diagnostic Criteria for Clinical Subtype of ATL[73]

	Smoldering	Chronic	Lymphoma	Acute
Anti-HTLV-1 antibody	+	+	+	+
Lymphocyte (× 10 y/L)	<4	≥4[a]	<4	*
Abnormal T-lymphocytes	≥5%	+[b]	≤1%	+[b]
Flower cells of T-cell marker	Occasionally	Occasionally	No	+
LDH	≤1.5 N	≤2 N	*	*
Corrected Ca (mmol/L)	<2.74	<2.74	*	*
Histology-proven lymphadenopathy	No	*	+	*
Tumor lesion				
Skin	**	*	*	*
Lung	**	*	*	*
Lymph node	No	*	Yes	*
Liver	No	*	*	*
Spleen	No	*	*	*
CNS	No	No	*	*
Bone	No	No	*	*
Ascites	No	No	*	*
Pleural effusion	No	No	*	*
GI tract	No	No	*	*

Ca = calcium; CNS = central nervous system; GI = gastrointestinal; LDH = lactate dehydrogenase; N = normal upper limit
* No essential qualification, except for terms required for other subtype(s).
** No essential qualification if other terms are fulfilled, but histology-proven malignant lesion is required in case abnormal T-lymphocytes are <5% in the peripheral blood.
[a] Accompanied by T-lymphocytosis (3.5 × 10 y/L or more).
[b] In case abnormal T-lymphocytes are <5% in the peripheral blood, histology-proven tumor lesion is required.

Eligibility criteria of clinical types for enrollment into **Cohort 2** in this study are indicated below.

Smoldering Type (Ineligible)

- ≥5% or more abnormal lymphocytes of T-cell nature in the peripheral blood.
- Normal lymphocyte level (<4 × 10^9/L).
- No hypercalcemia (corrected calcium level <2.74 mmol/L).
- Lactate dehydrogenase (LDH) value of up to 1.5 × the normal upper limit.
- No lymphadenopathy; no involvement of the liver, spleen, CNS, bone and gastrointestinal tract; and neither ascites nor pleural effusion. Skin and pulmonary lesion(s) may be present.
- In case of <5% abnormal T-lymphocytes in the peripheral blood, at least 1 of the histologically-proven skin and pulmonary lesions should be present.

Chronic Type (Ineligible Other Than Unfavorable)

- Absolute lymphocytosis (≥4 × 10^9/L) with T-lymphocytosis >3.5 × 10^9/L.
- LDH value up to twice the normal upper limit.
- No hypercalcemia.
- No involvement of CNS, bone and gastrointestinal tract, and neither ascites nor pleural effusion. Lymphadenopathy and involvement of the liver, spleen, skin, and lung may be present.
- In case of <5% abnormal T-lymphocytes in the peripheral blood, at least 1 of the histologically-proven tumor lesions should be present.

a. Favorable (ineligible)

- Absence of any 3 unfavorable prognostic factors

b. Unfavorable (eligible)

Presence of at least 1 of the 3 unfavorable prognostic factors:

- Serum blood urea nitrogen level > normal upper limit
- Serum LDH level > normal upper limit
- Serum albumin levels < normal lower limit

Lymphoma Type (Eligible)

- No lymphocytosis (<4 × 10^9/L), 1% or less abnormal T-lymphocytes, and histologically proven lymphadenopathy with or without extranodal lesions.

Acute Type (Eligible)

- Remaining ATL subjects who have usually leukemic manifestation and tumor lesions, but are not classified as any of the 3 other types.[65]

10.3.8. Prespecified Stopping Boundaries

Table 10.6: Cohort 1: Probability of Grade 4 (hematologic or non-hematologic toxicity) = 30% (Sample Size = 128 & Desired probability of early stopping = 0.05)

No. of subject enrolled	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Stopping boundary	**-**	**-**	**-**	**-**	**5**	**6**	**6**	**7**	**7**	**8**	**8**	**9**	**9**	**10**	**10**	**10**
No. of subject enrolled	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Stopping boundary	**11**	**11**	**12**	**12**	**13**	**13**	**13**	**14**	**14**	**15**	**15**	**15**	**16**	**16**	**17**	**17**
No. of subject enrolled	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
Stopping boundary	**17**	**18**	**18**	**19**	**19**	**19**	**20**	**20**	**21**	**21**	**21**	**22**	**22**	**23**	**23**	**23**
No. of subject enrolled	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64
Stopping boundary	**24**	**24**	**24**	**25**	**25**	**26**	**26**	**26**	**27**	**27**	**27**	**28**	**28**	**29**	**29**	**29**
No. of subject enrolled	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
Stopping boundary	**30**	**30**	**30**	**31**	**31**	**31**	**32**	**32**	**33**	**33**	**33**	**34**	**34**	**34**	**35**	**35**
No. of subject enrolled	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96
Stopping boundary	**35**	**36**	**36**	**37**	**37**	**37**	**38**	**38**	**38**	**39**	**39**	**39**	**40**	**40**	**41**	**41**
No. of subject enrolled	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112
Stopping boundary	**41**	**42**	**42**	**42**	**43**	**43**	**43**	**44**	**44**	**44**	**45**	**45**	**45**	**46**	**46**	**47**
No. of subject enrolled	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128
Stopping boundary	**47**	**47**	**48**	**48**	**48**	**49**	**49**	**49**	**50**	**50**	**50**	**51**	**51**	**51**	**52**	**52**

Table 10.7: Cohort 1: Probability of AE of Special Interest (thrombocytopenia, Grade ≥3) = 35% (Sample Size = 128 & Desired probability of early stopping = 0.05)

No. of subject enrolled	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Stopping boundary	**-**	**-**	**-**	**-**	**5**	**6**	**7**	**7**	**8**	**8**	**9**	**9**	**10**	**10**	**11**	**11**
No. of subject enrolled	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Stopping boundary	**12**	**12**	**13**	**13**	**14**	**14**	**15**	**15**	**16**	**16**	**17**	**17**	**17**	**18**	**18**	**19**
No. of subject enrolled	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
Stopping boundary	**19**	**20**	**20**	**21**	**21**	**22**	**22**	**22**	**23**	**23**	**24**	**24**	**25**	**25**	**25**	**26**
No. of subject enrolled	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64
Stopping boundary	**26**	**27**	**27**	**28**	**28**	**28**	**29**	**29**	**30**	**30**	**31**	**31**	**31**	**32**	**32**	**33**
No. of subject enrolled	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
Stopping boundary	**33**	**34**	**34**	**34**	**35**	**35**	**36**	**36**	**36**	**37**	**37**	**38**	**38**	**39**	**39**	**39**
No. of subject enrolled	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96
Stopping boundary	**40**	**40**	**41**	**41**	**41**	**42**	**42**	**43**	**43**	**44**	**44**	**44**	**45**	**45**	**46**	**46**
No. of subject enrolled	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112
Stopping boundary	**46**	**47**	**47**	**48**	**48**	**48**	**49**	**49**	**50**	**50**	**50**	**51**	**51**	**52**	**52**	**52**
No. of subject enrolled	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128
Stopping boundary	**53**	**53**	**54**	**54**	**54**	**55**	**55**	**56**	**56**	**57**	**57**	**57**	**58**	**58**	**59**	**59**

Table 10.8: Cohort 1: Probability of Grade 5 (hematologic or nonhematologic toxicity) = 5% (Sample Size = 128 & Desired probability of early stopping = 0.05)

No. of subject enrolled	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Stopping boundary	**-**	**2**	**2**	**3**	**3**	**3**	**3**	**3**	**3**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
No. of subject enrolled	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Stopping boundary	**4**	**4**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**6**	**6**	**6**	**6**	**6**
No. of subject enrolled	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
Stopping boundary	**6**	**6**	**6**	**6**	**6**	**6**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
No. of subject enrolled	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64
Stopping boundary	**7**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**8**	**9**	**9**	**9**
No. of subject enrolled	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80
Stopping boundary	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**9**	**10**	**10**	**10**	**10**	**10**	**10**
No. of subject enrolled	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96
Stopping boundary	**10**	**10**	**10**	**10**	**10**	**10**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**	**11**
No. of subject enrolled	97	98	99	100	101	102	103	104	105	106	107	108	109	110	111	112
Stopping boundary	**11**	**11**	**11**	**11**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**	**12**
No. of subject enrolled	113	114	115	116	117	118	119	120	121	122	123	124	125	126	127	128
Stopping boundary	**12**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**13**	**14**

Table 10.9: Cohort 2: Probability of Grade 4 = 30% (hematologic or non-hematologic toxicity) (sample size = 20 and desired probability of early stopping = 0.05)

No. of Subjects Enrolled	1	2	3	4	5	6	7	8	9	10
Stopping boundary	-	-	-	4	5	5	6	6	7	7
No. of subject enrolled	11	12	13	14	15	16	17	18	19	20
Stopping boundary	7	8	8	9	9	10	10	10	11	11

Table 10.10: Cohort 2: Probability of AE of Special Interest (thrombocytopenia, Grade ≥3) = 35% (sample size = 20 and desired probability of early stopping = 0.05)

No. of Subjects Enrolled	1	2	3	4	5	6	7	8	9	10
Stopping boundary	-	-	-	4	5	6	6	7	7	8
No. of subject enrolled	11	12	13	14	15	16	17	18	19	20
Stopping boundary	8	9	9	10	10	11	11	11	12	12

Table 10.11: Cohort 2: Probability of Grade 5 (hematologic or non-hematologic toxicity) = 5% (sample size = 20 and desired probability of early stopping = 0.05)

No. of Subjects Enrolled	1	2	3	4	5	6	7	8	9	10
Stopping boundary	-	2	2	2	2	3	3	3	3	3
No. of subject enrolled	11	12	13	14	15	16	17	18	19	20
Stopping boundary	3	3	3	3	4	4	4	4	4	4

The method generates a Pocock-type boundary for repeated testing for toxicity.[74]

10.3.9. GVHD Grading and Staging

Table 10.12: Acute GVHD Grading and Staging

Stage	Skin	Liver	Gut
1	Rash on <25% of skin[a]	Bilirubin 2-3 mg/dL[b]	Diarrhea >500 mL/day[c] or persistent nausea[d] *Pediatric*: 280-555 mL/m^2/day or 10-19.9 mL/kg/day
2	Rash on 25-50% of skin	Bilirubin 3-6 mg/dL	Diarrhea >1000 mL/day *Pediatric*: 556-833 ml/m^2/day or 20-30 mL/kg/day
3	Rash on >50% of skin	Bilirubin 6-15 mg/dL	Diarrhea >1500 mL/day *Pediatric*: >833 mL/m^2/day or >30 mL/kg/day
4	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dL	Severe abdominal pain, with or without ileus, and/or grossly bloody stool

Stage	Skin	Liver	Gut
Grade[e]			
I	Stage 1-2	None	None
II	Stage 3	Stage 1	Stage 1
III	—	Stage 2-3	Stages 2-4
IV[f]	Stage 4	Stage 4	—

GVHD = graft-versus-host disease
[a] Use "Rule of Nines" (see Table 10.13 below) or burn chart to determine extent of rash.
[b] Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.
[c] Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Downgrade one stage if an additional cause of diarrhea has been documented.
[d] Persistent nausea with or without histologic evidence of GVHD in the stomach or duodenum.
[e] Criteria for grading given as minimum degree of organ involvement required to confer that grade.
[f] Grade IV may also include lesser organ involvement with an extreme decrease in performance status.

Table 10.13: Percent Body Surfaces

Body Area	Percentage	Total Percentage
Each Arm	9%	18%
Each Leg	18%	36%
Chest & Abdomen	18%	18%
Back	18%	18%
Head	9%	9%
Pubis	1%	1%

Table 10.14: Organ Scoring of Chronic GVHD

Organ	Score 0	Score 1	Score 2	Score 3
Skin % BSA[a]	No BSA involved	1%-18% BSA	19%-50% BSA	>50% BSA
Skin Features	No sclerotic features	N/A	Superficial sclerotic features but not "hidebound"	Deep sclerotic features; "hidebound;" impaired mobility; ulceration
Mouth	No symptoms	Mild symptoms **with** disease signs but not limiting oral intake significantly	Moderate symptoms with disease signs **with** partial limitation of oral intake	Severe symptoms with disease signs **with** major limitation of oral intake
Eyes	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant drops ≤3×/day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant drops >3×/day or punctal plugs) **WITHOUT** new vision impairment due to	Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS

Organ	Score 0	Score 1	Score 2	Score 3
			keratoconjunctivitis sicca (KCS)	
GI Tract	No symptoms	Symptoms without significant weight loss (<5%)	Symptoms associated with mild to moderate weight loss (5-15%) within 3 months **OR** moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss (>15%) within 3 months, requires nutritional supplement for most calorie needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
Liver	Normal total bilirubin and ALT or AP <3 × ULN	Normal total bilirubin with ALT ≥3 to 5 × ULN or AP ≥3 × ULN	Elevated total bilirubin but ≤3 mg/dL or ALT >5 × ULN	Elevated total bilirubin >3 mg/dL
Lungs Symptom Score:	No symptoms	Mild symptoms (SOB after climbing one flight of steps)	Moderate symptoms (SOB after walking on flat ground)	Severe symptoms (SOB at rests; requires O_2)
Lungs Lung Score:	FEV1 ≥80%	FEV1 60-79%	FEV1 40-59%	FEV1 ≤39%
Joints and Fascia	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion **AND** not affecting ADL	Tightness of arms or legs **OR** joint contractures, erythema thought to be due to fasciitis, moderate decrease of range of motion **AND** mild to moderate limitation of ADL	Contractures **WITH** significant decrease of range of motion **AND** significant limitation of ADL (unable to tie shoes, button shirts, dress self, etc)
Genital Tract[b]	No signs	Mild signs and females with or without discomfort on exam	Moderate signs and may have signs of discomfort on exam	Severe signs with or without symptoms
Other Features[c]	No GVHD	Mild	Moderate	Severe

ADL = activities of daily living; ALT = alanine aminotransferase; AP = alkaline phosphatase; BSA = body surface area; FEV1 = forced expiratory volume in the first second; GVHD = graft versus host disease; N/A = not applicable; O_2 = oxygen; SOB = shortness of breath; ULN = upper limit of normal

[a] Features to be scored by BSA: Maculopapular rash, lichen planus-like features, sclerotic features, papulosquamous lesions or ichthyosis, keratosis pilaris-like GVHD.

[b] Scoring is based on severity of the signs instead of symptoms, based on limited available data and the opinions of experts. Female or male genital GVHD is not scored if a practitioner is unable to examine the patient.

[c] May include ascites, pericardial effusion, pleural effusion(s), nephrotic syndrome, myasthenia gravis, peripheral neuropathy, polymyositis, weight loss without GI symptoms, eosinophilia >500/µL, platelets <100,000/µL, others.

Source: NIH Consensus Criteria, 2014[75]

10.4. Appendix 4: Response Criteria

10.4.1. Target Lesions

Definition of Target Lesions

Selection of Target Nodal and Extranodal Lesions (up to 6 in total) for Cohort 1 (PTCL) and Cohort 2 (ATL)

Definition of target lesions is provided in Table 10.15 for Cohort 1 (PTCL) and Cohort 2 (ATL), and additional lesions/disease for response assessment is provided in Table 10.16 for Cohort 2 (ATL).

Up to 6 of the largest target nodal lesions that are measurable in 2 diameters (longest diameter [LDi] and shortest diameter [SDi]) should be identified from different body regions representative of the subject's overall disease burden and include mediastinal and retroperitoneal disease, if involved. Extranodal disease (eg, hepatic nodules) may be included in the 6 representative, measured lesions.

All other lesions (including nodal and extranodal lesions that were not selected as target lesions) should be followed as non-target lesions (eg, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, and ascites). Splenomegaly, hepatomegaly, and bone marrow involvement are not considered as target lesions. Tumor lesions situated in a previously irradiated area are not considered target lesions unless there is an apparent exacerbation of the lesion after radiotherapy.

Table 10.15: Definition of Target Lesions (Cohorts 1 and 2: PTCL and ATL)

Lesion	Definition of Target Lesions Based on Cross-Sectional CT (or MRI) Scan
Nodal Lesions	Meeting all of the following conditions: • Enlarged lymph nodes (nodal lesions) • Measurable in 2 perpendicular dimensions • LDi >1.5 cm (15 mm)
Extranodal Lesions	Meeting all of the following conditions: • Nodular lesions in extranodal organs • Measurable in 2 perpendicular dimensions • LDi >1.0 cm (10 mm)

CT = computed tomography; LDi = longest diameter; MRI = magnetic resonance imaging

Table 10.16: Additional Lesions/Disease for Response Assessment (Cohort 2: ATL)

Lesion	Definition
Skin Lesions	Cutaneous lesion(s) confirmed by visual inspection. If it is difficult to determine whether it is an ATL lesion or not by visual inspection, a biopsy should be performed to make a histopathological diagnosis.
Disease in Peripheral Blood	• Abnormal lymphocyte count (actual number) is $\geq 1 \times 10^9$/L (1000/μL) and • The abnormal lymphocyte-to-leukocyte ratio is ≥5%

ATL = adult T-cell leukemia/lymphoma

Target Lesions That Split or Become Confluent

Nodes or Extranodal Lesions That Split When Disease is Responding

If a confluent nodal mass splits into several discrete nodes, the individual product of the perpendicular diameters (PPDs) of the nodes should be summed together to represent the PPD of the split lesion; this PPD is added to the sum of the PPDs of the remaining lesions to measure response. If subsequent growth of any or all of these discrete nodes occurs, the nadir of each individual node is used to determine progression (as if each individual node was selected as a target lesion at baseline).

Nodes or Extranodal Lesions That Become Confluent When Disease is Progressing

If a group of target lymph nodes becomes confluent, the PPD of the current confluent mass should be compared with the sum of the PPDs of the individual nodes, with >50% increase in the PPD of the confluent mass compared with the sum of individual nodes necessary to indicate progressive disease. The LDi and SDi are no longer needed to determine progression.

10.4.2. 2014 Lugano Criteria: Cohort 1

Selection of Target and Non-Target Lesions

Criteria are provided in Table 10.17.

A target nodal lesion must have an LDi >1.5 cm (15 mm). Target extranodal disease (eg, hepatic nodules) may be included in the 6 representative, target lesions. A target extranodal lesion should have an LDi greater than 1.0 cm (10 mm). All other lesions (including nodal and extranodal) should be followed as non-target lesions (eg, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, and ascites).

Table 10.17: 2014 Lugano Criteria for Cohort 1 (PTCL)

Response	Site	PET-CT–based Response For Exploratory Efficacy Analysis	CT-based Response For Primary Efficacy Analysis
CR		Complete metabolic response	Complete radiologic response (all of the following)
	Lymph nodes and extranodal sites	Score 1, 2, or 3 with or without a residual mass on 5-PS.[a]	Target nodes/nodal masses regress to ≤15 mm in LDi. No extranodal sites of disease.
	Nonmeasured lesion	Not applicable.	Absent.
	Organ enlargement	Not applicable.	Regress to normal.
	New lesions	None.	None.
	Bone marrow	Normal by morphology; if indeterminate, IHC negative.[a]	Normal by morphology; if indeterminate, IHC negative.

Response	Site	PET-CT–based Response For Exploratory Efficacy Analysis	CT-based Response For Primary Efficacy Analysis
PR		Partial metabolic response	Partial remission (all of the following)
	Lymph nodes and extranodal sites	Score 4 or 5 with a reduced uptake compared with baseline and residual mass(es) of any size.	≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites. When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value. When no longer visible, 0 × 0 mm. For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation.
	Nonmeasured lesions	Not applicable.	Absent/normal, regressed, but no increase.
	Organ enlargement	Not applicable.	Spleen must have regressed by >50% in length beyond normal.
	New lesions	None.	None.
	Bone marrow	A residual uptake higher than the uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy 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 scan.	Not applicable.
Stable Disease		No metabolic response	Stable disease
	Target nodes/nodal masses and extranodal lesions	Score 4 or 5 with no significant change in the FDG uptake from baseline at interim or end of treatment.	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites. No criteria for progressive disease are met.
	Nonmeasured lesions	Not applicable.	No increase consistent with progression.
	Organ enlargement	Not applicable.	No increase consistent with progression.
	New lesions	None.	None.
	Bone marrow	No change from baseline.	Not applicable.

Response	Site	PET-CT–based Response For Exploratory Efficacy Analysis	CT-based Response For Primary Efficacy Analysis
Progressive Disease		Progressive metabolic disease	Progressive disease requires at least 1 of the following
	Individual target nodes/nodal masses and extranodal lesions	Score 4 or 5 with an increase in intensity of the uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment.	PPD progression: An individual node/lesion must be abnormal with: LDi >15 mm and An increase by ≥50% from PPD nadir and an increase in LDi or SDi from nadir: 5 mm for lesions ≤20 mm. 10 mm for lesions >20 mm. In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline or nadir, whichever is smaller (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, the splenic length must increase by at least 2 cm from baseline. New or recurrent splenomegaly.
	Nonmeasured lesions	None.	New or clear progression of preexisting nonmeasured lesions.
	New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection and inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions. A new node >15 mm in any axis with an absolute increase of ≥5 mm from nadir. A new extranodal site >10 mm in any axis. If <10 mm in any axis, its presence must be unequivocal and must be attributable to lymphoma. Assessable disease of any size unequivocally attributable to lymphoma.
	Bone marrow	New or recurrent FDG-avid foci.	New or recurrent involvement.

5-PS = 5-point scale; CR = complete response; CT = computed tomography; FDG = fluorodeoxyglucose; IHC = immunohistochemistry; LDi = longest diameter of a lesion; MRI = magnetic resonance imaging; PET = positron emission tomography; PPD = product of the perpendicular diameter; PR = partial response; PTCL = peripheral T-cell lymphoma; SDi = shortest diameter; SPD = sum of the product of the perpendicular diameters for multiple lesions.

[a] Modification for PTCL

In Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within the spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), an uptake may be greater than the normal 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 a high physiologic uptake.
Source: https://pubmed.ncbi.nlm.nih.gov/25113753/

10.4.3. Modified 2009 ATL Criteria: Cohort 2

Modified ATL criteria are provided in Table 10.18. The modification was made such that there is no requirement for each criterion to be present for a period of at least 4 weeks.

Table 10.18: Modified 2009 ATL Criteria

Antitumor Response	Definition	Target Lesion		Non-target Lesion		Spleen, Liver	Skin[e]	Peripheral Blood	Bone Marrow
		Lymph Node	Extranodal Lesion	Lymph Node	Extranodal Lesion				
CR	Disappearance of disease	Normal	Disappearance	Normal	Disappearance	Normal	Normal	Normal[a]	Normal
CRu	Stable residual mass in bulky lesion	≥75% decrease[b]		Normal	Disappearance	Normal	Normal	Normal[a]	Normal
PR	Regression of disease	≥50% decrease[b]		Normal or no increase	Disappearance or no increase	No increase	≥50% decrease	≥50% decrease	Irrelevant
SD	Failure to attain complete/ partial remission and no progressive disease	No change in size		Not qualifying as CR, PR, or PD	Not qualifying as CR, PR, or PD	No change in size	No change in size	No change	No change
RD/PD	New or increased lesions	New or ≥50% increase[c]		Increase or re-enlargement	Increase or re-appearance	≥50% increase[f]	≥50% increase	New or ≥50% increase[d]	New or re-appearance
NA	—	—	—	—	—	—	—	—	—

CR = complete response; CRu = uncertified complete response; mSWAT = modified severity-weighted assessment tool; NA = not applicable; PD = progressive disease; PR = partial response; RD = relapsed disease; SD = stable disease

[a] Provided that <5% of flower cells remains, complete remission is judged to have been attained if the absolute lymphocyte count, including flower cells, is $<4 \times 10^9$/L.

[b] Calculated by the sum of the products of the greatest diameters of target lesions.

[c] Defined by ≥50% increase from nadir in the sum of the products of target lesions.

[d] Defined by ≥50% increase from nadir in the count of flower cells and an absolute lymphocyte count, including flower cells, of $>4 \times 10^9$/L.

[e] Calculated by the mSWAT score for skin lesions.

[f] In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline or nadir, whichever was smaller (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, the splenic length must increase by at least 2 cm from baseline.

Source: Barrington SF, Mikhaeel NG, Kostakoglu L, et al. Role of imaging in the staging and response assessment of lymphoma: consensus of the International Conference on Malignant Lymphomas Imaging Working Group. J Clin Oncol. 2014 Sep 20;32(27):3048-58. doi: 10.1200/JCO.2013.53.5229. Erratum in: J Clin Oncol. 2016 Jul 20;34(21):2562. PMID: 25113771; PMCID: PMC5015423.

10.4.4. mSWAT Score Calculation: Cohort 2

The total body surface area (TBSA) of humans is regarded as 100, and a sum of the percentage of body surface area (%BSA) of each site is defined in Table 10.19 and Figure 10.1 (eg, head: 7, neck: 2, and anterior trunk: 13).[3,4] By site, lesion type (patch [flat erythema], plaque [elevated area], tumor [dome-shaped nodular lesion with >10-mm elevation], or ulcer [lesion with significant loss of superficial skin, including loss of the entire epidermis or some portion of the upper dermis]), and %BSA of normal skin will be assessed; the percentage total body surface area (%TBSA) will then be calculated by summing the %BSA of each site by lesion type. Furthermore, mSWAT score will be derived by multiplying the %TBSA by weighting factor, and all individual numbers will then be added to produce a total score (0 to 400).

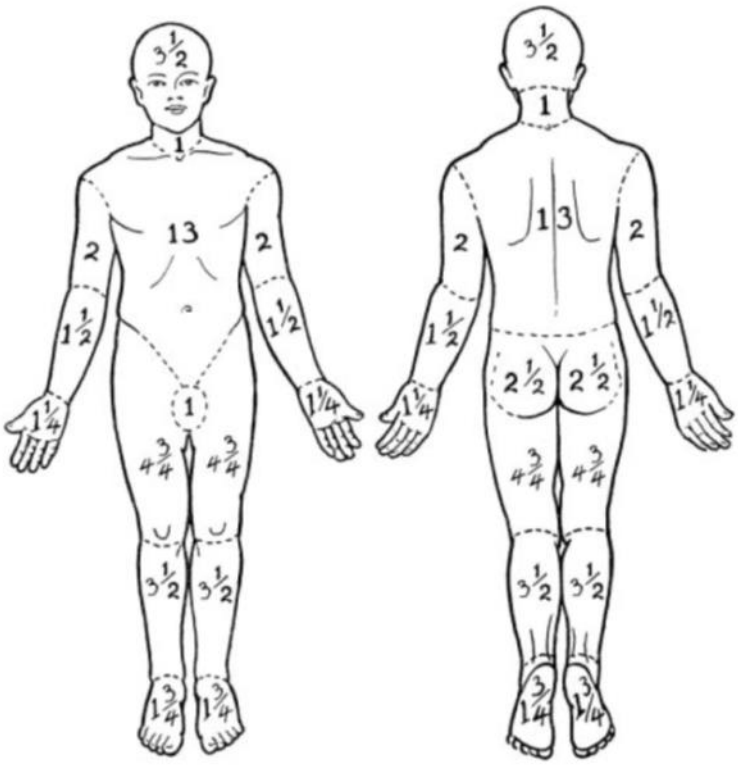
mSWAT score = (patch %TBSA × 1) + (plaque %TBSA × 2) + (tumor and ulcer %TBSA × 4)

Table 10.19: Table for Calculation of Body Surface Area

Body Lesion	%BSA Patch	%BSA Plaque	Tumor or Ulcer %BSA	Normal %BSA	Total %BSA of Each Lesion
Head					7
Neck					2
Anterior trunk					13
Posterior trunk					13
Buttocks					5
Groin					1
Arms					8
Forearms					6
Hands					5
Thighs					19
Legs					14
Feet					7
%TBSA of each lesion					100

BSA = body surface area; TBSA = total body surface area

Figure 10.1: Regional Percent Body Surface Area



10.4.5. 5-Point Scale: Cohort 1 and Cohort 2

The most intense uptake in a site of initial disease:

1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Uptake moderately higher than liver
5. Uptake markedly higher than liver and/or new lesions
6. X. New areas of uptake unlikely to be related to lymphoma

10.5. Appendix 6: General Information - Adverse Events

10.5.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

It is the responsibility of investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings which should be considered AEs.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, and vital signs measurements), including those that worsen from baseline, considered clinically relevant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically relevant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.5.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline or for administration of anticancer therapy after discontinuation of study drug is not considered an AE.
- Results in persistent or significant disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is an important medical event
- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.5.3. Grade Assessment

The severity of AEs will be graded using the latest NCI-CTCAE (version 5.0). For each episode, the highest severity grade attained should be reported.

The NCI-CTCAE guidelines do not allow certain grades for certain AEs. For example, pain can be Grade 1 to 3 only (ie, cannot be life-threatening or fatal), whereas sepsis can only be Grade 4 or 5 (ie, can only be life-threatening or fatal). In addition, alopecia can only be Grade 1 or 2. The NCI-CTCAE guidelines should be followed closely.

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Difference between Severity and Seriousness

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.5.4. Causality Assessment

The investigator should assess causal relationship between an adverse event and the study drug based on his/her clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

- Related:
  - The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

    or
  - The AE follows a reasonable temporal sequence from study drug administration and is a known reaction to the drug under study (or its chemical group) or is predicted by known pharmacology.
- Not Related:
  - The AE does not follow a reasonable sequence from study drug administration or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

10.5.5. Action Taken Regarding Study Drug(s)

- Dose Not Changed: No change in study drug dosage was made.
- Drug Withdrawn: The study drug was permanently stopped.
- Dose Reduced: The dosage of study drug was reduced.
- Drug Interrupted: The study drug was temporarily stopped.
- Not Applicable: Subject died, study drug completed/permanently discontinued prior to reaction/event, or reaction/event occurred prior to the first dose.
- Unknown: Subject is lost to follow-up.

10.5.6. Other Action Taken for Event

- None.
  - No treatment was required.
- Medication required.
  - Prescription and/or over-the-counter medication was required to treat the AE.
- Hospitalization or prolongation of hospitalization was required.
  - Hospitalization was required or prolonged due to the AE, whether or not medication was required.
- Other.

10.5.7. Adverse Event Outcome

- Recovered/Resolved
  - The subject fully recovered from the AE, with no sequelae observed.
- Recovered/Resolved with Sequelae
  - The subject fully recovered from the AE, but with sequelae.
- Recovering/Resolving
  - The AE is improving but not recovered.
- Not Recovered/Not Resolved
  - The AE continues without improving.
- Fatal
  - Fatal should be used when death is a direct outcome of the AE.
- Unknown

10.6. Appendix 7 Key Data Analysis Requirements

Key data analysis requirements are provided in Table 10.20.

Table 10.20: Key Data Requirements

Endpoint/Analysis	Key Data Requirements (assessed both by BICR and investigators)
ORR	The numerator will be the number of subjects who have at least 1 response. The denominator will be the number of the subjects who were dosed with at least 1 dose (regardless whether subjects had 1 assessment). Primary analysis will be performed at least 10 months after the first dose of the last subject in Cohort 1.
DoR/DoCR	The numerator will be the number of subjects who have at least 1 response (CR/CRu only). The denominator will be the number of the subjects who were dosed with at least 1 dose (regardless of whether subjects had 1 assessment). Primary analysis will be performed at least 10 months after the first dose of the last subject in Cohort 1.
CR/PR rate	The numerator will be the number of subjects who have at least 1 CR/PR. The denominator will be the number of the subjects who were dosed with at least 1 dose (regardless of whether subjects had 1 assessment). Primary analysis will be performed at least 10 months after the first dose of the last subject in Cohort 1.

ATL = adult T-cell leukemia/lymphoma; BICR = blinded independent central review; CR = complete response; CRu = uncertified complete remission (response); DoCR = duration of complete response; DoR = duration of response; ORR = objective response rate; PR = partial response
CRu for ATL will be included into ORR or CR rate and DoR/DoCR analysis in Cohort 2.

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12. LIST OF ABBREVIATIONS

Abbreviation	Definition
AAG	α-1-acid glycoprotein
AE	adverse event
AESI	adverse event of special interest
AITL	angioimmunoblastic T-cell lymphoma
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATL	adult T-cell leukemia/lymphoma
AUC	area under the plasma concentration-time curve
BICR	blinded independent central review
BSA	Body surface area
CCR4	Chemokine receptor type 4
CFR	code of federal regulations
CHOP	Cyclophosphamide, Doxorubicin, Vincristine and Prednisone
CI	confidence interval
Cmax	maximum concentration
CMV	cytomegalovirus
CNS	Central nervous system
CR	complete response
CrCl	creatinine clearance
CRO	contract research organization
CRu	uncertified complete remission (response)
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CYP	cytochrome P450
DIMS	drug inventory management system
DLT	dose-limiting toxicity
DMC	data monitoring committee
DoCR	duration of complete response
DoR	duration of response
DS-3201a	Free form of DS-3201b
EC	ethics committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

Abbreviation	Definition
EDC	electronic data capture
EIU	exposure in utero
EOS	End of Study
EOT	End of Treatment
EU	European Union
EZH	enhancer of zeste homolog
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
GCP	Good Clinical Practice
GVHD	graft-versus-host disease
H3K27	lysine 27 of histone H3
HCT	hematopoietic cell transplantation
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
HTLV-1	human T-cell leukemia virus type 1
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Council of Medical Journal Editors
IEC	independent ethics committee
IHC	immunohistochemistry
INN	international non-proprietary name
IPF	immature platelet fraction
IRB	institutional review board
LAM	lactational amenorrhoea method
LDH	lactate dehydrogenase
LDi	longest diameter
LTFU	Long-term Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mSWAT	modified severity weighted assessment tool
NCI	National Cancer Institute
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NOS	not otherwise specified
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival

Abbreviation	Definition
P-gp	P-glycoprotein
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PopPK	population pharmacokinetic
PPD	product of the perpendicular diameter
PR	partial response
PS	performance status
PT	post-transplant
PTCL	peripheral T-cell lymphoma
QTc	corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
RBC	red blood cell
R/R	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SDi	shortest diameter
SDV	source data verification
SID	subject identification
SMT	safety management team
SoE	Schedule of Events
SUSAR	suspected unexpected serious adverse reaction
TBSA	total body surface area
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TFH	T-follicular helper
ULN	upper limit of normal
US	United States

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DS3201-A-U202: Single-arm, Phase 2 Study of Valemetostat Tosylate Monotherapy i

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