Clinical Study Protocol

NCT Number: NCT05442554

Title: A Phase 4, Single Arm, Open Label, Multicenter Study of Brentuximab Vedotin Treatment of Chinese Patients With CD30-Positive Cutaneous T-Cell Lymphoma

Study Number: C25029

Document Version and Date: Amendment , 31 Jan 2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

PROTOCOL

A Phase 4, Single Arm, Open Label, Multicenter Study of Brentuximab Vedotin Treatment of Chinese Patients With CD30-Positive Cutaneous T-Cell Lymphoma

Sponsor:	Takeda Development Center Americas, Inc.
Study Number:	C25029
EudraCT Number:	Not Applicable
Compound:	Brentuximab vedotin (SGN-35)
Date:	31 January 2022

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

The names and contact information for the medical monitor and responsible medical officer are in the study manual.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practice (GCP): Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

[redacted], MD Date
Project Clinician,
Clinical Science, [redacted]

[redacted], PhD Date
Project Statistician,
Biostatistics, [redacted]

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, prescribing information, and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- ICH, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.0 of this protocol.
- Terms outlined in the clinical study site agreement.
- Responsibilities of the investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix B of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor: Takeda Development Center Americas, Inc.	**Compound:** Brentuximab vedotin (SGN-35)
Title of Protocol: A Phase 4, Single Arm, Open Label, Multicenter Study of Brentuximab Vedotin Treatment of Chinese Patients With CD30-Positive Cutaneous T-Cell Lymphoma	**EudraCT No.:** Not Applicable
Study Number: C25029	**Phase:** 4

Study Design:

This is a phase 4, open-label, single-arm, multicenter, postapproval commitment study to be conducted in China. All patients must have histologically-confirmed CD30-positive (CD30+) mycosis fungoides (MF) or primary cutaneous anaplastic large cell lymphoma (pcALCL) by local pathology assessment. CD30+ is defined as ≥10% target lymphoid cells demonstrating membrane, cytoplasmic, and/or Golgi staining pattern for CD30 at any intensity above background staining as noted on the corresponding negative control. Patients will receive treatment with brentuximab vedotin monotherapy on Day 1 of each 21-day cycle for up to 16 cycles total.

Patients will receive study drug for up to 16 cycles of treatment with brentuximab vedotin. Patients with progressive disease (PD) at any time during the study will be discontinued from study drug. Patients with increasing modified severity weighted assessment tool (mSWAT) before assessment at the end of Cycle 3 will be allowed to continue therapy until the Cycle 3 assessment if, in the investigator's opinion, the findings are due to tumor flare rather than PD.

Objective response over the course of the study, per investigator assessment, will be assessed by global response score, which consists of skin evaluation (mSWAT), nodal and visceral radiographic assessment, and detection of circulating Sézary cells (MF only). Objective response will be evaluated at the end of Cycles 3, 6, 9, 12, and 15, and at the end of treatment (EOT) visit.

Safety will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0, by the incidence of treatment-emergent adverse events (TEAEs), severity and type of adverse events (AEs), and by changes from baseline in the patient's vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and clinical laboratory results in the safety population. The study will be closed when all patients complete the EOT visit.

Primary Objective:

To determine the objective response rate (ORR) lasting at least 4 months with brentuximab vedotin in patients with CD30+ MF or pcALCL.

Secondary Objectives:

- To determine the complete response (CR) rate with brentuximab vedotin
- To determine the ORR with brentuximab vedotin
- To assess the duration of response (DOR) with brentuximab vedotin.

Safety Objective:

- To assess the safety of brentuximab vedotin.

Subject Population: Male or female Chinese patients at least 18 years of age with a diagnosis of CD30+ pcALCL who have received at least 1 prior systemic therapy or prior radiation therapy, or CD30+ MF who have received at least 1 prior systemic therapy for their disease.

Number of Subjects: Approximately 10 evaluable patients	**Number of Sites:** Approximately 3 to 5 investigative sites in China
Dose Level: Brentuximab vedotin 1.8 mg/kg of each 21 day treatment cycle	**Route of Administration:** Intravenous (IV)
Duration of Treatment: Up to 16 cycles	**Period of Evaluation:** Patients will be screened up to 28 days before first dose of the study drug, receive study drug for up to 16 cycles, and will have an EOT assessment visit 30±2 days after receiving the final dose of study drug. The study will be closed when all patients complete the EOT visit.

Main Criteria for Inclusion:

Patients ≥18 years of age with diagnosis of MF or pcALCL.

Eligible histologies include:

- Histologically-confirmed CD30+ disease for MF or pcALCL at screening, defined as ≥10% CD30 expression.
- Patients with pcALCL who have received prior radiation therapy or at least 1 prior systemic therapy; patients with MF who have received at least 1 prior systemic therapy.

Other inclusion criteria include:

- Adequate bone marrow reserve and renal and hepatic function based on the laboratory parameters.
- Radiographically or clinically measurable or evaluable disease.

Main Criteria for Exclusion:

- Concurrent diagnosis of systemic anaplastic large cell lymphoma, or other non-Hodgkin lymphoma (excluding lymphomatoid papulosis).
- Patients with a history of progressive multifocal leukoencephalopathy or known active cerebral/meningeal disease related to the underlying malignancy.

Main Criteria for Evaluation and Analyses:

Efficacy:

The primary efficacy endpoint for this study is the ORR lasting at least 4 months with brentuximab vedotin in Chinese patients with CD30+ MF or pcALCL.

The secondary efficacy endpoints for this study are: CR rate with brentuximab vedotin, ORR with brentuximab vedotin, DOR with brentuximab vedotin.

Safety:

The secondary safety endpoints for this study are: incidence of TEAEs, SAEs, changes from baseline in the, patient's vital signs, ECOG performance status, clinical laboratory results.

Statistical Considerations:

For all efficacy and safety assessments, descriptive summaries and analyses will be performed.

Sample Size Justification: Per China Health Authority requirement, approximately 10 evaluable patients with CD30+ MF or pcALCL are needed for this postapproval commitment study. All efficacy analyses will be based on the full analysis set (FAS), which is defined as all enrolled patients identified as CD30+ and received at least 1 dose of the study drug. The response-evaluable population will include a subset of the FAS patients with measurable disease at baseline and with at least 1 post-baseline response assessment. The safety analysis set will consist of all enrolled patients who receive at least 1 dose of study drug.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the clinical supplier list in the study manual. The identified vendors will perform specific study-related activities either in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a signatory coordinating investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research, and study participation. The signatory coordinating investigator will be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

AE(s)	adverse event(s)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CD30+	CD30-positive
CR	complete response
CSR	clinical study report
CT	computed tomography
CTCL	cutaneous T-cell lymphoma
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
FAS	full analysis set
FDG	fluorodeoxglucose
GCP	Good Clinical Practice
GRS	Global Response Score
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee
IRB	institutional review board
IV	intravenous
IxRS	Interactive Response System
JCV	John Cunningham virus
LPD	lymphoproliferative disorders
LyP	lymphomatoid papulosis
MF	mycosis fungoides
MRI	magnetic resonance imaging
mSWAT	modified severity weighted assessment tool
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
pcALCL	primary cutaneous anaplastic large cell lymphoma
PD	progressive disease/disease progression

PET	positron emission tomography
PML	progressive multifocal leukoencephalopathy
PR	partial response
QOL	quality of life
SAE(s)	serious adverse event(s)
sALCL	systematic anaplastic large cell lymphoma
SAP	statistical analysis plan
SD	stable disease
SDTs	skin-directed therapies
SS	Sézary syndrome
SUSAR	suspected unexpected serious adverse reactions
TBSA	total body surface
TEAE(s)	treatment-emergent adverse event(s)
TNMB	tumor-node-metastasis-blood (classification)
TSEBT	total skin electron beam therapy
ULN	upper limit of the normal range
US	United States
USP	United States Pharmacopeia
WHO	World Health Organization

3.4 Corporate Identification

TDC Americas Takeda Development Center Americas, Inc.

4.0 INTRODUCTION

4.1 Background

4.1.1 Overview of Cutaneous T-cell lymphoma

Cutaneous T-cell lymphoma (CTCL) is a subset of extranodal non-Hodgkin lymphoma arising from malignant transformation of mature skin-resident or skin-infiltrating T cells (Girardi et al. 2004). Clinical manifestations in the skin are variable, but the burden of the skin disease is considerable. Patches and plaques may persist for years and eventually spread and progress to tumors; dissemination to lymph nodes and visceral organs is a late manifestation associated with poor prognosis (Agar et al. 2010). In Europe, CTCL represents 75% to 80% of cutaneous lymphomas, but this distribution is known to vary worldwide (Willemze et al. 2005).

4.1.2 CD30+ CTCL Subtypes

CTCL is classified into several major subtypes according to clinical, histological, and cytogenetic features (Swerdlow et al. 2008; Swerdlow et al. 2016). Subtypes that are commonly associated with CD30 expression include mycosis fungoides (MF), Sézary syndrome (SS), and the primary cutaneous CD30+ T-cell lymphoproliferative disorders (LPDs), primary cutaneous anaplastic large cell lymphoma (pcALCL) and lymphomatoid papulosis (LyP).

4.1.2.1 CTCL Subtypes

The common subtypes MF and CD30+ T-cell LPDs constitute more than 70% of CTCL cases. MF accounts for 44% of all cutaneous lymphomas and approximately 55% of all CTCL cases (Bradford et al. 2009; Imam et al. 2013). A chronic, relapsing disease with a protracted course, it occurs most often in middle-aged to elderly adults, with a higher incidence in men than in women; this difference increases with age. Classic MF typically presents with well-defined, often pruritic and/or erythematous patches and plaques that may eventually evolve to tumors; all of these lesion types can be present concomitantly (Jawed et al. 2014). Individuals with MF can develop a morphologic transformation from small-and intermediate-sized cerebriform tumor cells to a large cell variant (transformed MF) that is also associated with a more aggressive disease course and reduced overall survival (OS) (Arulogun et al. 2008). CD30 expression in MF is variable and heterogeneous, but the available data suggest that it may be present in most cases (Edinger et al. 2009).

Primary cutaneous CD30+ T-cell LPDs are the second most common CTCL subtype, accounting for approximately 15% of all CTCL cases (Bradford et al. 2009; Imam et al. 2013). pcALCL presents in adults as solitary or localized nodules that may undergo partial necrosis and resolution but do not spontaneously regress. The tumor cells involve the dermis extensively and may infiltrate subcutaneous tissue but show little infiltration of the epidermis (Kempf et al. 2011). A diffuse infiltrate of anaplastic, strongly CD30+ tumor cells is typical of pcALCL lesions (Willemze et al. 2005), and diagnostic criteria for pcALCL require CD30 expression by ≥75% of tumor cells (Kempf et al. 2011; Willemze et al. 2005).

4.1.2.2 Other CD30+ CTCL Subtypes

LyP is a rare primary cutaneous CD30+ T-cell LPD with a waxing and waning clinical course defined by CD30+ lesions that may spontaneously regress (Wieser et al. 2016). Although LyP is considered by the World Health Organization (WHO) to be an indolent lymphoma, various reports have described a cumulative risk for progression of LyP to lymphoma between 2% and 14% after 5 years, and between 30% and 80% after 20 years (Bekkenk et al. 2000; Cabanillas et al. 1995; el-Azhary et al. 1994; Sanchez et al. 1983). CD30+ T-cell LPD subtypes pcALCL and LyP are histologically similar, and the differential diagnosis is often dependent upon clinical presentation and disease course; cases in which a definite distinction between pcALCL and LyP cannot be made are designated "borderline" (Kempf et al. 2011; Swerdlow et al. 2008).

SS is a rare, aggressive, leukemic form of CTCL that is distinguished from MF primarily on the basis of the presence of high levels of circulating atypical T cells (Sézary cells), extensive skin erythema (erythroderma), and severe pruritus (Jawed et al. 2014; Whittaker et al. 2016). While SS is generally considered separate from MF, progression from MF to SS is occasionally observed (Arulogun et al. 2008).

Primary cutaneous gamma-delta T-cell lymphoma is a form of CTCL that accounts for less than 1% of all primary cutaneous lymphomas, though this may be because of limitations in diagnostic capabilities. Primary cutaneous gamma-delta T-cell lymphoma is associated with a more aggressive clinical course, and CD30 expression is variable (Guitart et al. 2012).

4.1.2.3 Prognosis and Staging

CTCL is a disfiguring, incurable, and frequently debilitating disease characterized by a relapsing and progressive clinical course. CD30+ CTCL generally follows an indolent course in the early stages, but it commonly becomes refractory after repeated exposure to treatment and more aggressive with progression to advanced-stage systemic disease. Certain histologic findings and clinical presentations can distinguish patients who are at higher risk for aggressive disease and inferior outcomes.

Classification and staging of MF is most commonly based on the tumor-node-metastasis-blood (TNMB) classification criteria proposed by the International Society for Cutaneous Lymphomas (ISCL)/the United States Cutaneous Lymphoma Consortium (USCLC)/European Organisation for Research and Treatment of Cancer (EORTC) (Kim et al. 2007; Olsen et al. 2011b). For MF, disease stage at diagnosis dictates both prognosis and choice of treatment. Early-stage MF is generally associated with excellent prognosis; estimates of 5-year disease-specific survival range from 89% to 98% in patients with Stage IA through IIA disease (Agar et al. 2010). However, more advanced-stage MF is associated with substantially increased risk of mortality, with 5-year disease-specific survival falling to 18% to 39% in patients with Stage IVB disease (Agar et al. 2010; Scarisbrick et al. 2015). Poor prognostic features in MF include the presence of large-cell transformation, folliculotropism, cutaneous tumors, extensive skin erythema (erythroderma), and extracutaneous disease in the blood, lymph nodes, or visceral organs (Agar et al. 2010; Arulogun et al. 2008; Horwitz et al. 2008; Kempf et al. 2011; Kim et al. 2003; Scarisbrick et al. 2015; Trautinger et al. 2006).

The ISCL/USCLC/EORTC staging proposal for non-MF CTCL, including pcALCL, uses the tumor-node-metastasis (TNM) nomenclature for classification; however, because the prognostic and therapeutic value of this system remains to be validated in this setting, TNM classification is generally used descriptively for patients with primary cutaneous CD30+ T-cell LPDs (Kim et al. 2007). Because of the chemosensitive and radiosensitive nature of the disease, OS in patients with primary cutaneous CD30+ T-cell LPDs is generally very good: 5-year disease-specific survival estimates range from 95% to 96% for pcALCL and from 73% to 100% for LyP (Bekkenk et al. 2000; Bradford et al. 2009; Willemze et al. 2005). However, survival prognosis does not reflect the disease burden that these patients suffer, which can be extremely disfiguring and debilitating, greatly affecting patients' quality of life (QOL). Indications of advanced-stage disease at diagnosis, which portends a worse clinical course in pcALCL, include the presence of multifocal or extensive lesions, extensive limb involvement, and extracutaneous disease (Kempf et al. 2011; Trautinger et al. 2006; Woo et al. 2009). For patients with advanced/disseminated pcALCL, clinical features, prognosis, and treatment paradigms are similar to those with systematic anaplastic large cell lymphoma (sALCL).

4.1.2.4 Symptom Burden

CTCL symptoms can be severely debilitating, and the overall burden of disease is substantial across disease stage and subtype. Skin involvement is frequently accompanied by cutaneous tumor formation, ulceration, exfoliation, pruritus, and pain (Rosen and Querfeld 2006). Furthermore, skin lesions are often complicated by infections, cause cosmetic disfigurement, and result in a loss of function in regular daily activities (Demierre et al. 2006; Horwitz et al. 2008; Rosen and Querfeld 2006).

Results from a 2005 survey of 630 patients in the United States (US) with CTCL indicated that striking health distress was prevalent in almost all respondents, with more than half reporting depression, frustration, anger, or lost sleep (Demierre et al. 2006). Most respondents were bothered by itching (88%), scaling (83%), skin redness (94%), or pain (53%); 82% reported that their disease interfered with work or school, 80% reported that it prevented them from meeting family needs, and 80% worried about dying from their disease. Demierre et al (2006) note that CTCL, being both a dermatologic disease and a cancer, may have a more profound effect on patients' QOL than a purely dermatologic disease (Demierre et al. 2006).

In a study of 95 patients in Italy with CTCL, both aspects of the disease were evaluated with different QOL instruments. The most frequent items reported using the Skindex-29 dermatology-focused instrument were itching and sensitive skin, being annoyed by the disease, worry that it could get worse, affected interactions, and impairment in sexual life; the most frequent items reported using the EORTC QLQ-C30 oncology-focused instrument were fatigue, pain, and insomnia (Sampogna et al. 2009).

4.1.3 Standard of Care

Common treatment goals in patients with CTCL include achieving symptom control, reducing disease burden, and minimizing treatment-related toxicity; however, there is no single drug or regimen considered to be standard of care, owing to the diversity of clinical presentations

(Kempf et al. 2011; Trautinger et al. 2006; Zinzani et al. 2016). Early-stage CTCL is typically managed using a variety of skin-directed therapies (SDTs). For early-stage MF (Stages IA-IIA), available SDTs include topical corticosteroids or mechlorethamine, local radiation, topical retinoids, and phototherapy. For patients with extensive plaque, tumor, or erythrodermic disease, total skin electron beam therapy (TSEBT) can also be effective. For pcALCL, surgical excision and local radiotherapy (but not TSEBT) are common treatments for patient with solitary or localized disease.

Although SDTs are often effective for managing early-stage CTCL, patients frequently require repeated treatment courses and maintenance regimens for ongoing disease control (Horwitz et al. 2008). With advancing disease, response rates and progression-free intervals decrease (Dreyling et al. 2013; Herrmann et al. 1995). Systemic agents are commonly incorporated into the therapeutic regimen for patients with advanced-stage disease or other adverse prognostic features.

Methotrexate and bexarotene are widely used treatments across CTCL diagnoses. A recent multicenter, collaborative review of more than 800 patients with Stage IIB or higher MF found that bexarotene and methotrexate were the most commonly used systemic therapies worldwide (Quaglino et al. 2016). Bexarotene was approved in the European Union in 2001 (EMEA/H/C/000326) for the treatment of patients with advanced stage CTCL who are refractory to at least 1 prior systemic therapy. Methotrexate was licensed in 2002 in the United Kingdom for use in non-Hodgkin lymphoma. Methotrexate is widely used off-label across the European Union for the treatment of CTCL. There have been no recent advances in standard of care treatment of CTCL. Overall, achievement of durable responses in patients with advanced CTCL has been elusive. In a retrospective analysis of 198 patients with MF or SS requiring systemic therapy, Hughes et al (2015) reported that the median number of systemic treatments administered was 3, with median time to next treatment of 3.9 months for all systemic chemotherapies and 5.4 months for all treatments considered (Hughes et al. 2015).

4.1.4 Rationale for the Use of Brentuximab Vedotin to Treat CTCL

Brentuximab vedotin is selected for treatment of CTCL on the basis of:

- Favorable benefit: risk profiles observed in pivotal studies of brentuximab vedotin for the treatment of sALCL (SG035-0004) (Pro et al. 2012) and Hodgkin lymphoma (SG035-0003 and SGN35-005) (Moskowitz et al. 2015; Younes et al. 2012).
- Cutaneous responses observed in patients with sALCL with cutaneous manifestations in pivotal Study SG035-0004 (Advani et al. 2012; Pro et al. 2012).
- Positive results from an investigator-initiated phase 2 study of SGN30 (the unconjugated anti-CD30 antibody component of brentuximab vedotin) in patients with pcALCL, LyP, or transformed MF (Duvic et al. 2009).
- Positive results from the phase 3 C25001 study in patients with CD30-positive (CD30+) CTCL. Treatment of CTCL with brentuximab vedotin led to a highly statistically significant improvement in the primary endpoint (the proportion of patients with objective response

lasting at least 4 months [ORR4]), as determined by an independent review of the Global Response Score (GRS), compared with the physician's choice comparator arm (56.3% vs 12.5%, p<0.001).

4.2 Rationale for the Proposed Study

The indication of brentuximab vedotin treatment in patients with CD30+ MF or pcALCL who have received prior systemic treatment has been approved in China based on the global pivotal ALCANZA (C25001) study with local Chinese data waiver. This study is a postapproval commitment study required by the China Health Authority to collect efficacy and safety data in Chinese patients in this indication. Per China Health Authority requirement, at least 10 evaluable patients with CD30+ MF or pcALCL are needed for this postapproval commitment study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective is to determine the objective response rate (ORR) lasting at least 4 months with brentuximab vedotin in patients with CD30+ MF or pcALCL.

5.1.2 Secondary Objectives

The secondary objectives are:

- To determine the complete response (CR) rate with brentuximab vedotin
- To determine the ORR with brentuximab vedotin
- To assess the duration of response with brentuximab vedotin.

5.1.3 Safety Objective

The safety objective is:

- To assess the safety of brentuximab vedotin.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary efficacy endpoint for this study is the ORR lasting at least 4 months with brentuximab vedotin in Chinese patients with CD30+ MF or pcALCL.

5.2.2 Secondary Endpoints

The secondary efficacy endpoints for this study are:

- CR rate with brentuximab vedotin.

- ORR with brentuximab vedotin.
- Duration of response (DOR) with brentuximab vedotin.

5.2.3 Safety Endpoints

The secondary safety endpoints for this study are:

- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs).
- Changes from baseline in the patient's vital signs.
- Eastern Cooperative Oncology Group (ECOG) performance status.
- Clinical laboratory results.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This is a phase 4, open-label, single-arm, multicenter, postapproval commitment study to be conducted in China. All patients must have histologically-confirmed CD30+ MF or pcALCL by local pathology assessment. CD30+ is defined as ≥10% target lymphoid cells demonstrating membrane, cytoplasmic, and/or Golgi staining pattern for CD30 at any intensity above background staining as noted on the corresponding negative control. Patients will receive treatment with brentuximab vedotin monotherapy on Day 1 of each 21-day cycle for up to 16 cycles total.

Objective response over the course of the study, per investigator assessment, will be assessed by global response score, which consists of skin evaluation (a modified severity weighted assessment tool [mSWAT]), nodal and visceral radiographic assessment, and detection of circulating Sézary cells (MF only). Objective response will be evaluated at the end of Cycles 3, 6, 9, 12, and 15, and at the end of treatment (EOT) visit.

Safety will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0, by the incidence of TEAEs, severity and type of adverse events, and by changes from baseline in the patient's vital signs, ECOG performance status, and clinical laboratory results in the safety population. The study will be closed when all patients complete the EOT visit.

Toxicity will be evaluated according to NCI CTCAE, Version 5.0, effective 27 November 2017 (NCI 2017).

6.2 Number of Patients

Approximately 10 evaluable patients will be enrolled and dosed in this study from approximately 3 to 5 study centers in China. Enrollment is defined as a patient who has been confirmed as eligible to participate in the study and completed the related registration in the Interactive Response System (IxRS).

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients will receive treatment with brentuximab vedotin monotherapy on Day 1 of each 21-day cycle for up to 16 cycles total.

Patients with progressive disease (PD) at any time during the study will be discontinued from study drug. Patients with mSWAT before assessment at the end of Cycle 3 will be allowed to continue therapy until the Cycle 3 assessment if, in the investigator's opinion, the findings are due to tumor flare rather than PD.

Duration of Follow-up: Patients will be screened up to 28 days before first dose of the study drug, receive study drug for up to 16 cycles, and will have an EOT assessment visit 30±2 days after receiving the final dose of study drug.

6.3.2 End of Study/Study Completion Definition and Planned Reporting

The study will be closed when all patients complete the EOT visit.

The final analyses for the CSR will be performed after the last patient has completed the EOT visit, and the report will be prepared and submitted within the timeframe that is required by regulatory authorities.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosures information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame
Primary efficacy endpoint	ORR lasting at least 4 months with brentuximab vedotin in patients with CD30+ MF or pcALCL	Up to 48 weeks
Secondary efficacy endpoints	CR rate with brentuximab vedotin, the ORR with brentuximab vedotin, and the DOR with brentuximab vedotin	Up to 48 weeks
Safety endpoints	Incidence of TEAEs, severity and type of AEs (by NCI CTCAE, Version 5.0), changes from baseline in the patient's vital signs, ECOG performance status, and clinical laboratory results	Up to 48 weeks

AEs: adverse events; CR: complete response; DOR: duration of response; ECOG: Eastern Cooperative Oncology Group; MF: mycosis fungoides; NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; ORR: objective response rate; pcALCL: primary cutaneous anaplastic large cell lymphoma; TEAE: treatment-emergent adverse events.

6.3.4 Total Study Duration

It is anticipated that this study will last for approximately 36 months – including enrollment, treatment, and follow-up (EOT visit 30±2 days after receiving the final dose of study drug).

6.3.5 Posttrial Access

Posttrial access to brentuximab vedotin is not planned for this study because patients will receive study drug until PD, unacceptable toxicity, or completion of up to 16 cycles of brentuximab vedotin during the study, whichever occurs first.

7.0 STUDY POPULATION

Procedures for rescreening patients are intended to be identical to the screening procedures. Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 more time which requires signing the informed consent form (ICF) again and repeating the screening procedures.

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Patients aged 18 years or older with diagnosis of MF or pcALCL.
2. Histologically- confirmed CD30+ disease by local laboratory assessment and pathology review. CD30+, defined as ≥10% target lymphoid cells demonstrating membrane, cytoplasmic, and/or Golgi staining pattern for CD30 at any intensity above background staining as noted on the corresponding negative control. (A minimum of 10% staining in at least 1 sample is required. Percent positivity should be determined using percent neoplastic cells staining first. If neoplastic cells cannot be easily distinguished from non-neoplastic, then percent positivity should be determined using percent total lymphocytes staining.)
3. Patients with pcALCL who have received prior radiation therapy or at least 1 prior systemic therapy, or patients with MF who have received at least 1 prior systemic therapy for their disease.
4. ECOG performance status of ≤2 (refer to Appendix C).
5. Patients with uterus and ovary/ies who:
    - Are postmenopausal for at least 1 year before the screening visit, OR
    - Are surgically sterile, OR
    - If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 6 months after the last dose of study drug, OR
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are

not acceptable methods of contraception. Female and male condoms should not be used together.)

Patients with testis/es, even if surgically sterilized (ie, status postvasectomy), who:

- Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

6. Voluntary written consent must be given before performance of any study-related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
7. Suitable venous access for the study-required blood sampling.
8. Clinical laboratory values as specified below within 4 days before the first dose of study drug:
   - Total bilirubin must be <1.5 × the upper limit of the normal range (ULN).
   - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) must be <3 × ULN. AST and ALT may be elevated up to 5 × ULN if their elevation can be reasonably ascribed to the presence of metastatic disease in liver.
   - Serum creatinine must be <2.0 mg/dL and/or creatinine clearance or calculated creatinine clearance >30 mL/minute. (The Cockcroft-Gault formula is provided in Section 9.0.)
9. Patients must have radiographically or clinically measurable or evaluable disease.
10. A 3-week washout period is required from previous treatments (with the exception of a 12-week washout for antibody-directed or immunoglobulin-based immune therapy, or other monoclonal antibody therapies), unless it is not in the best interest of the patient in the opinion of the investigator. Individual cases should be discussed with the project clinician before enrollment.
11. Recovered (ie, Grade ≤1 toxicity) from the reversible effects of prior antineoplastic therapy.

7.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

1. Patients who are lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.

2. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
3. Treatment with radiotherapy or other skin-directed therapy or any investigational products within 3 weeks before the first dose of study drug.
4. A concurrent diagnosis of systemic anaplastic large cell lymphoma (ALCL), or other non-Hodgkin lymphoma (excluding LyP).
5. A concurrent diagnosis of SS or B2 disease.
6. Corticosteroid therapy for the treatment of CTCL within 3 weeks of first dose of study drug.
7. Known hypersensitivity to recombinant proteins, murine proteins, or any excipient contained in the drug formulation.
8. Life-threatening illness unrelated to cancer.
9. Severe central nervous system (CNS), pulmonary, renal, or hepatic disease not related to the patient's cancer.
10. Known active cerebral/meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy (PML).
11. Known human immunodeficiency virus (HIV) positive.
12. Known hepatitis B surface antigen positive or known or suspected active hepatitis C infection.
13. Any severe active systemic viral, bacterial, or fungal infection within 1 week before first study drug dose requiring systemic antimicrobial therapy. (Oral antibiotics for prophylaxis are allowed.)
14. Receiving antibody-directed or immunoglobulin-based immune therapy (eg, immunoglobulin replacement, other monoclonal antibody therapies) within 12 weeks of first study drug dose.
15. Any of the following cardiovascular conditions or values within 6 months before the first dose of study drug:
    - Myocardial infarction within 6 months of enrollment.
    - New York Heart Association (NYHA) Class III or IV heart failure (see Appendix D).
    - Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure (CHF), angina, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
16. History of another primary malignancy not in remission for at least 3 years. The following are exempt from the 3-year limit: completely resected in situ carcinoma, such as nonmelanoma skin cancer and cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on Pap smear.
17. Oral retinoid therapy for any indication within 3 weeks of the first dose of study drug.

18. Systemic therapy with Vitamin A in doses of greater than 15,000 IU (5,000 mcg) per day (equivalent to approximately 3 times recommended daily allowance [RDA]) within 3 weeks before the first dose of study drug.
19. History of pancreatitis or significant risk factors for developing pancreatitis (eg, prior pancreatitis, uncontrolled hyperlipidemia, excessive alcohol consumption, uncontrolled diabetes mellitus, biliary tract disease, and medications known to increase triglyceride levels or to be associated with pancreatic toxicity).
20. Any other condition that, in the opinion of the investigator or project clinician, would interfere with a patient's ability to receive or complete the study.
21. Previous receipt of brentuximab vedotin.

8.0 STUDY DRUG

Investigational medicinal product: brentuximab vedotin.

8.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

Study drug will be administered by intravenous (IV) infusion given over approximately 30 minutes on Day 1 of each 21-day cycle. In the absence of infusion toxicities, the infusion rate for all patients must be calculated in order to achieve a 30-minute (approximate) infusion period. Brentuximab vedotin must not be administered as an IV push or bolus. Study drug will be administered through a dedicated IV line and cannot be mixed with other medications.

The dose of brentuximab vedotin is 1.8 mg/kg. Dosing is based on patients' weight according to the institutional standard; however, doses will be adjusted for patients who experience a ≥10% change in weight from baseline. Actual weight will be used except for patients weighing greater than 100 kg; dose will be calculated based on 100 kg for these individuals. The dose will be rounded to the nearest whole number of milligrams.

Further brentuximab vedotin administration information can be found in the pharmacy manual.

8.2 Dose Modification Guidelines

No dose escalation of brentuximab vedotin is permitted in this study.

8.2.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle, and Discontinuation of Study Drug

Treatment with brentuximab vedotin will use a cycle length of 21 days. Dose modification guidelines are provided in Table 8.a.

Table 8.a Recommended Brentuximab Vedotin Dose Modifications for Treatment-Associated Toxicity

	Nonhematologic (Excluding Neuropathy)	Hematologic	Peripheral Neuropathy
Grade 1	Continue at same dose level	Continue at same dose level	Continue at same dose level
Grade 2	Continue at same dose level	Continue at same dose level	For Grade 2 neuropathy, withhold dose until toxicity is Grade ≤1 or has returned to baseline, then restart treatment at a reduced dose of 1.2 mg/kg every 3 weeks.
Grade 3	Withhold dose until toxicity is Grade ≤1 or has returned to baseline, then resume treatment at the same dose level a.	Withhold dose until toxicity is Grade ≤2, or has returned to baseline, then resume treatment at the same dose level b. Consider growth factor support (G-CSF or GM-CSF) for treatment of neutropenia and prophylaxis in subsequent cycles.	Withhold dose until toxicity returns to Grade ≤1 or baseline, then restart treatment at a reduced dose of 1.2 mg/kg every 3 weeks.
Grade 4	Withhold dose until toxicity is Grade ≤1 or has returned to baseline, then reduce dose to 1.2 mg/kg and resume treatment, or discontinue at the discretion of the investigator after discussion with the sponsor a.	Withhold dose until toxicity is Grade ≤2, then resume treatment at the same dose level. Consider growth factor support (G-CSF or GM-CSF) for treatment of neutropenia and prophylaxis in subsequent cycles. For the second occurrence of Grade 4 toxicity (if neutropenia, while receiving growth factor support), withhold dose until toxicity is Grade ≤2, then reduce the dose to 1.2 mg/kg and resume treatment after discussion with the sponsor b.	Discontinue brentuximab vedotin

CTCAE: Common Terminology Criteria for Adverse Events; G-CSF: granulocyte-colony stimulating factor; GM-CFS: granulocyte macrophage-colonystimulating factor; NCI: National Cancer Institute.

Grading based on the NCICTCAE, Version 5.0.

[a] Patients who develop clinically insignificant Grade 3 or 4 electrolyte laboratory abnormalities may continuestudy drug without interruption.

[b] Patients who develop clinically insignificant Grade 3 or 4 lymphopenia may continue study drug without interruption.

Please refer to Table 8.a for guidelines regarding discontinuation of study drug.

8.2.2 Criteria for Dose Reduction

Intrapatient dose reduction to 1.2 mg/kg brentuximab vedotin will be allowed depending on the type and severity of toxicity.

Doses reduced for drug-related toxicity should generally not be resumed. However, patients may resume the previous dose level at the discretion of the investigator after discussion with the sponsor.

8.3 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Any investigational agent other than brentuximab vedotin, including agents that are commercially available for indications other than CTCL (including bleomycin, where use is contraindicated due to pulmonary toxicity).
- Any antineoplastic treatment with activity against CTCL other than study drug.
- Any phototherapy including psoralen with ultraviolet light A (PUVA).
- Any immunotherapy (eg, immunoglobulin replacement, any other monoclonal antibody therapy).
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates PD).
- Long-term systemic steroids.

8.4 Permitted Concomitant Medications and Procedures

Patients may receive concomitant hormonal therapy provided they have been on a stable dosage for at least 1 month before enrollment. The use of platelet and/or red blood cell supportive growth factors or transfusions when applicable is allowed. The use of colony stimulating factors for the treatment of neutropenia per institutional practice is permitted during therapy. The use of systemic, topical, or inhaled corticosteroids during the study for reasons other than CTCL should be reviewed by the investigator and project clinician. The use of corticosteroids for the management of complications from infusion reactions and/or anaphylaxis is permitted. Topical corticosteroids to relieve CTCL symptoms are permitted on an as-needed basis. Patients may receive treatment for prior comorbidities and AEs which are expected not to interfere with the trial's evaluation.

8.5 Precautions and Restrictions

It is not known what effects brentuximab vedotin has on human pregnancy or development of the embryo or fetus; therefore, patients participating in this study should avoid becoming pregnant or avoid impregnating a partner. Nonsterilized patients of reproductive age with a uterus and/or ovaries and nonsterilized patients with testes/testis should use effective methods of contraception through defined periods during and after study treatment as specified below.

Reproductively female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, OR
- Surgically sterile, OR

- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing of the ICF through 6 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Reproductively male patients, even if surgically sterilized (ie, status postvasectomy), must agree to 1 of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

8.6 Management of Clinical Events

8.6.1 Nausea and/or Vomiting

Although this study will not initially employ prophylactic anti-emetics, there is no prohibition against their use in the management of a patient who develops nausea and/or vomiting. As in the prophylactic setting, 5-hydroxytryptamine 3 serotonin receptor (5-HT3) antagonists should be tried first.

8.6.2 Diarrhea

Prophylactic antidiarrheals (eg, loperamide) are not recommended in this protocol; however, patients may be instructed to take antidiarrheal medications at physician's discretion until they are diarrhea-free for at least 12 hours. Fluid intake should be maintained to avoid dehydration.

8.6.3 Management of Infusion-Related Reactions

Infusion-related reactions may occur during the infusion of brentuximab vedotin. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. The patient should be observed closely during and for 60 minutes following the infusion of brentuximab vedotin. During this observation period, the IV line should remain open for at least 1 hour to allow administration of IV drugs if necessary. All supportive measures consistent with optimal patient care will be given throughout the study according to institution standards. Medications for infusion-related reactions, such as epinephrine and antihistamines should be available for immediate use.

Patients who experience a Grade 1 or 2 infusion-related reaction may receive subsequent brentuximab vedotin infusions with premedication consisting of acetaminophen (650 mg orally) and diphenhydramine (25-50 mg orally or 10-25 mg IV) or according to institutional standards,

administered 30 to 60 minutes before each 30-minute (approximate) brentuximab vedotin infusion. The planned use of steroids as premedication is prohibited.

If anaphylaxis occurs, brentuximab vedotin administration should be immediately and permanently discontinued.

8.6.4 Management of Peripheral Neuropathy

AEs of peripheral neuropathy will be monitored closely and recorded throughout the study. Events that are greater than Grade 1 in severity will result in brentuximab vedotin dose modification which shown in Table 8.a.

8.6.5 Management of PML

Signs and symptoms of PML may include altered mental status; motor deficits, such as hemiparesis or ataxia; visual disturbances; or higher cortical dysfunction, such as dysphasia or agnosia. See the Investigator's Brochure for further details.

If PML is suspected, hold further brentuximab vedotin dosing and undertake a diagnostic work-up that may include (but is not limited to):

- Neurologic examinations, as warranted.
- Brain magnetic resonance imaging (MRI): features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, which are typically nonenhancing and do not have mass effect.
- Polymerase chain reaction analysis: John Cunningham virus (JCV) DNA detectable in cerebrospinal fluid or there is evidence of JCV in a brain biopsy.
- Neurology consultation.

If PML is confirmed, treatment with brentuximab vedotin should be discontinued permanently.

8.7 Blinding and Unblinding

This is an open-label and single-arm study.

8.7.1 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at the time points specified in the schedule of events.

8.8 Description of Investigational Agents

Brentuximab vedotin for injection is a sterile, preservative-free, white to off-white lyophilized cake for reconstitution for IV administration. Brentuximab vedotin for Injection is supplied by the sponsor in single-use, Type 1 borosilicate glass vials with FluroTec-coated butyl rubber stoppers and aluminum seals. Each vial of the product contains brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80. The lyophilized product, after reconstitution with 10.5 mL

sterile Water for Injection, United States Pharmacopeia (USP), yields 11 mL of brentuximab vedotin solution (5 mg/mL).

8.9 Preparation, Reconstitution, and Dispensation

Recommended safety measures for handling and preparation include masks, protective clothing, gloves, and vertical laminar airflow safety cabinets.

Study drug vials are single-use containers. Any partially used vials or diluted dosing solutions are to be discarded using appropriate institutional drug disposal procedures according to the guidelines in the pharmacy manual.

The required volume of 5 mg/mL reconstituted brentuximab vedotin solution needed must be calculated and withdrawn from the vials. The reconstituted solution should be added immediately to an infusion bag containing a minimum volume of 100 mL. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg.

Study drug must be reconstituted with the appropriate amount of Sterile Water for Injection, USP (see pharmacy manual for details).

There are no known incompatibilities between study drug and polyvinyl chloride (PVC), ethyl vinyl acetate (EVA), polyolefin, or polyethylene (PE) bags.

The formulation contains no preservative and is intended for single use only; infusion solutions should be prepared and transferred using aseptic technique in a biosafety hood.

Refer to the pharmacy manual for more specific instructions on reconstitution and use.

8.10 Packaging and Labeling

Vials of study drug will be packaged in cardboard kits. Each kit will contain 1 vial of investigational product. Vials and kits will be labeled to meet country-specific regulatory requirements.

8.11 Storage, Handling, and Accountability

Vials containing study drug must be refrigerated at 2oC to 8oC in a secure location (eg, locked room) accessible only to the pharmacist, the investigator, or a duly designated person.

Study drug does not contain preservatives; therefore, opened and reconstituted vials of study drug must be used within 24 hours when stored under refrigeration at 2oC to 8oC. Reconstituted study drug should not be stored at room temperature. It is recommended that study drug vials and solutions be protected from direct sunlight until the time of use. **Reconstituted vials must not be shaken**.

Drug accountability instructions are provided in the pharmacy manual.

9.0 STUDY CONDUCT

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), applicable regulatory requirements, and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines.

9.1 Study Personnel and Organizations

The contact information for the project clinician for this study, the local laboratory, the coordinating investigator for each member state/country, and may be found in the Investigator Site File. A full list of investigators is available in the sponsor's investigator database.

For 24-hour contact information, please refer to the Patient identification (ID) Card.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/ independent ethics committee (IEC).

9.3 Study Procedures

Refer to the schedule of events (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow.

9.3.1 Informed Consent

Each patient must provide written informed consent before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

9.3.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during screening.

9.3.3 Medical History

During the screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy and include a description of prior therapies for it. In addition, concomitant medications will be recorded as specified in Section 9.3.9.

9.3.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the schedule of events (Appendix A). A complete physical examination must be performed at screening, the extent of which should be consistent with medical history and the patient's underlying disease. Subsequent physical examinations may be directed to relevant findings.

9.3.5 Patient Height

Height will be measured only during screening.

9.3.6 Patient Weight

Weight will be measured at screening, on Day 1 of each treatment cycle, and at EOT.

9.3.7 Vital Signs

Vital signs measurement will be performed at the times specified in the Schedule of Events (Appendix A). Vital sign measurements include measurements of diastolic and systolic blood pressure, heart rate, and body temperature. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

9.3.8 Pregnancy Test

A serum pregnancy (choriogonadotropin beta) test will be completed for all reproductively female patients of childbearing potential during screening; this test must be negative for the patient to be enrolled. A urine pregnancy test will be performed before dosing on Day 1 of all cycles. The results of any pregnancy test must be negative before dosing on Day 1 of all cycles.

Additional pregnancy tests may be performed during the study at the discretion of the investigator, if requested by an IEC/IRB or if required by local regulations.

9.3.9 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will recorded in the electronic case report form (eCRF) from screening through 30 days after the last dose of brentuximab vedotin. See Section 8.3 and Section 8.4 for a list of medications and therapies that are prohibited or allowed during the study.

9.3.10 Adverse Events

Monitoring of adverse events (AEs), serious and nonserious, will be conducted throughout the study as specified in the schedule of events. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of AEs and SAEs.

9.3.11 Enrollment

A patient is considered to be enrolled in the study when they have been confirmed as eligible to participate in the study and completed the related registration in IxRS system.

Procedures for completing enrollment information are described in the study manual.

Patients who screen fail may later be rescreened once with prior sponsor approval. Any patient who is rescreened after screen failure must, in addition to the failed test, repeat only those screening tests that have fallen outside the specified screening period, as outlined in the Schedule of Events (Appendix A).

9.3.12 ECG

A 12-lead ECG will be administered at the time points specified in the Schedule of Events (Appendix A). ECG assessments are to be performed with the patient supine and rested for 5 minutes.

9.3.13 Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed locally. Clinical laboratory evaluations will be performed as outlined in Section 9.3.13.1.

Sézary cell results must be available from the local lab to determine eligibility and treatment decisions.

9.3.13.1 Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the clinical chemistry and hematology parameters shown in Table 9.a and urine samples for analysis of the parameters shown in Table 9.b will be obtained as specified in the Schedule of Events (Appendix A).

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry	
Hematocrit	Albumin	Chloride
Hemoglobin	ALP	GGT)
Leukocytes with differential	ALT	Glucose
ANC	AST	LDH
Platelet (count)	Bilirubin (total)	Magnesium
	BUN	Phosphate
	Calcium	Potassium
	Creatinine	Sodium
	Lipase	Urate
		Amylase

ANC: absolute neutrophil count; ALP: alkaline phosphatase; ALT: alanine aminotransferase; aspartate aminotransferase; BUN: blood urea nitrogen; GGT: gamma glutamyl transferase; LDH: lactate dehydrogenase.

Table 9.b Clinical Urinalysis Tests

Urinalysis	
Bilirubin	pH
Glucose	Protein
Ketones	Specific gravity
Leukocytes	Turbidity and color
Nitrite	Urobilinogen
Occult blood	

If creatinine clearance is to be estimated, the Cockroft-Gault formula will be employed as follows:

For female patients, the result of the formula above should be multiplied by 0.85.

For transgender patients, use the sex at birth for patients not using hormone therapy or for patients who have used hormone therapy for <6 months; use the current gender for patients who have used hormone therapy for ≥6 months.

9.3.14 Disease Assessment

A GRS of CR, partial response (PR), stable disease (SD), PD, and relapse will be determined based on sequential tumor burden assessments of body compartments (skin, lymph nodes, viscera, and blood for MF patients) as further described below.

Response will be determined by a composite assessment of total tumor burden:

- Cutaneous disease (mSWAT) (Section 9.3.15.1.1).
- Lymph node involvement (Section 9.3.15.1.3).
- Visceral involvement (Section 9.3.15.1.3).
- Blood (MF patients only) (Section 9.3.15.1.4).
  - Sézary cells will be enumerated by morphology and immunophenotyping.

9.3.15 Response Assessment

9.3.15.1 Cutaneous Disease Response Assessment

9.3.15.1.1 mSWAT

mSWAT will be used for MF and pcALCL and will be performed as specified in the Schedule of Events.

The mSWAT score calculation method and skin lesion definitions for MF and pcALCL are provided in Table 9.c.

Table 9.c mSWAT

Body Region	% BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch[a]	Plaque[b]	Tumor[c]
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of lesion BSA				
Weighting factor		x1	x2	x4
Subtotal lesion BSA x weighting factor				

BSA: body surface area; mSWAT: modified Severity Weighted Assessment Tool.
mSWAT score equals summation of each column line.

[a] Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.

[b] Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.

[c] Any solid or nodular lesion ≥ 1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

The mSWAT score will be calculated as follows:

Sum percentage of total body surface (TBSA) from all body regions affected by patches x severity-weighting factor of 1

+ Sum percentage of TBSA from all body regions affected by plaques x severity-weighting factor of 2

+ Sum percentage ofTBSA from all body regions affected by tumors x severity-weighting factor of 4

= Total mSWAT (maximum score = 400)

Figure 9.a presents the mSWAT percentage of TBSA for the 12 main body areas to assess disease burden in MF and pcALCL (Mann et al. 2007; Stevens et al. 2002). The body is divided into 12 regions with preassigned percentage of TBSA based on methodology used to assess burns (Lund and Browder 1944). The extent of skin disease is assessed for each region and

quantified using the patient's palm as a "ruler" to measure the percentage of TBSA involvement within each region:

Patient's palm with 4 fingers and including the thumb, and measured from wrist to fingertips, is approximately 1% of TBSA.

Figure 9.a mSWAT Percentage of TBSA for 12 Main Body Areas

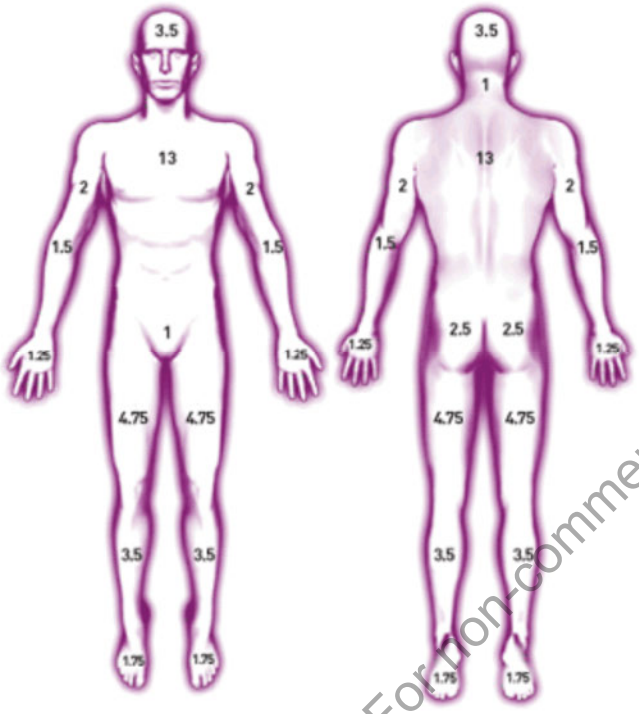

Table 9.d Response in Skin

Response	Definition
CR	100% clearance of skin lesions[a]
PR	50%-99% clearance of skin disease from baseline No new tumors in patients without tumors at baseline (MF) No new tumors (pcALCL)
SD	<25% increase to <50% clearance in skin disease from baseline No new tumors in patients without tumors at baseline (MF)
PD[b]	≥25% increase in skin disease from baseline, or Loss of response: in those with CR or PR, increase of skin score of greater than the sum of nadir plus 50% baseline score, or New tumors in patients without tumors at baseline (MF)
Relapse	Any disease recurrence in those with complete response

Source: Response criteria for MF are per Olsen 2011 (Olsen et al. 2011b), and for pcALCL per Kempf 2011 (Kempf et al. 2011).
CR: complete response; MF: mycosis fungoides; pcALC: primary cutaneous anaplastic large cell lymphoma; PD: progressive disease; PR: partial response; SS: Sézary syndrome.
[a] A biopsy of normal appearing skin is unnecessary to assign a complete response. However, a skin biopsy should be performed on a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist. If histologic features are suspicious or suggestive of MF/SS, the response should be considered a PR only.
[b] Whichever criterion occurs first.

9.3.15.1.2 Photographs

Each of the designated index lesions (up to a total of 5) and lesions selected for biopsy will be serially photographed at screening; before dosing on Day 1 of Cycles 1, 2, and 3; at the end of every cycle beginning at Cycle 3 (Days 16-21, or before dosing on Day 1 of subsequent cycles); within 30 days after the last dose of study drug. Full body global photographs, including head, trunk, legs, front, back, and side, will be taken at the same time points indicated above.

9.3.15.1.3 Lymph Node and Visceral Evaluation

Lymph nodes and visceral involvement will be assessed by a computed tomography (CT) scan, and responses are defined in Table 9.e and Table 9.f.

Table 9.e Response in Lymph Nodes [a]

Response	Definition
CR	All lymph nodes are now ≤1.5 cm [b] in greatest transverse (long axis) diameter by method used to assess lymph nodes at baseline or biopsy negative for lymphoma. In addition, lymph nodes that show lymphoma involvement by biopsy [c] and ≤1.5 cm [b] in long axis diameter and >1 cm in short axis at baseline, must now be ≤1 cm in diameter of the short axis or biopsy negative for lymphoma
PR	Cumulative reduction ≥50% of the SPD of each abnormal lymph node at baseline and no new lymph node >1.5 cm [b] in the diameter of the long axis or >1.0 cm in the short axis if the long axis is 1-1.5 cm diameter
SD	Fails to attain the criteria for CR, PR, and PD
PD [d]	(1) ≥50% increase in SPD from baseline of lymph nodes, or (2) Any new node >1.5 cm [b] in greatest transverse diameter or >1 cm in the short axis diameter if 1-1.5 cm in long axis that is proven to be lymphoma histologically [c], or (3) Loss of response: in those with PR (or CR if pcALCL), >50% increase from nadir in SPD of lymph nodes
Relapse	Any new lymph node >1.5 cm [b] in the long axis diameter: In those with CR (pcALCL) In those with CR proven to be lymphoma histologically [c] (MF)

Source: (Olsen et al. 2011a), (Kempf et al. 2011), and (Cheson et al. 2007).

CR: complete response; EORTC: European Organisation for Research and Treatment of Cancer; ISCL: International Society for Cutaneous Lymphomas; MF: mycosis fungoides; pcALCL primary cutaneous anaplastic large cell lymphoma; PD: progressive disease PR: partial response; SD: stable disease; SPD: sum of the maximum linear dimension (major axis) X longest perpendicular dimension (minor axis); USCLC: United States Cutaneous Lymphoma Consortium.

[a] Peripheral and central lymph nodes.

[b] Response criteria are similar for patients with MF and pcALCL. However, per the EORTC, ISCL and USCLC consensus recommendations for the treatment of non-MF primary cutaneous CD30+ lymphoproliferative disorders (Kempf et al. 2011), an abnormal lymph node is considered ≥1.5 cm and should be considered when assessing nodal response in patient with pcALCL.

[c] For patients with MF, lymphoma involvement is defined as N3 (ie, partial or complete effacement of lymph node architecture by atypical or frankly neoplastic cells)

[d] Whichever criterion occurs first.

Table 9.f Response in Viscera

Response	Definition
CR	Liver or spleen or any organ considered involved at baseline should not be enlarged on physical exam and should be considered normal by imaging; no nodules should be present on imaging of liver or spleen. Any posttreatment mass must be determined by biopsy to be negative for lymphoma
PR	≥50% regression in any splenic or liver nodules, or in measurable disease (SPD) in any organs abnormal at baseline. No increase in size of liver or spleen and no new sites of involvement
SD	Fails to attain the criteria for CR, PR, or PD
PD[a]	(1) >50% increase in size (SPD) of any organs involved at baseline, or (2) New organ involvement, or (3) Loss of response: in those with PR (or CR if pcALCL), >50% increase from nadir in the size (SPD) of any previous organ involvement
Relapse	New organ involvement in those with CR

Source: (Olsen et al. 2011b) and (Kempf et al. 2011).

CR: complete response; PR: partial response; SPD: sum of the maximum linear dimension (major axis) X longest perpendicular dimension (minor axis); SD: stable disease; SPD: sum of the maximum linear dimension (major axis) X longest perpendicular dimension (minor axis); PD: progressive disease.

[a] Whichever criterion occurs first.

Contrast CT scans of the neck, chest, abdomen, and pelvis will be obtained at screening and during the study or if clinically indicated as specified in the Schedule of Events (Appendix A) and Section 6.1. All CT scans will be taken with IV contrast (unless contraindicated) and they will be of diagnostic quality. Specific disease sites that cannot be adequately imaged by CT may be documented by MRI. Fluorodeoxyglucose-positron emission tomography (FDG-PET) scans will be performed at screening only, unless clinically indicated. Anatomical measurements (summed across target lesions) will be collected at baseline and each subsequent evaluation using an imaging modality consistent with that used at screening.

Objective assessments will be performed at each time point as described in the Schedule of Events (Appendix A). When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the site, and test results and physician's findings will be filed in patient source documents.

9.3.15.1.4 Blood Assessment

MF involvement in blood is defined in Appendix E. SS is defined as meeting T4 plus B2 criteria, Appendix E (Olsen et al. 2011b).

Table 9.g Response in Blood

Response [a]	Definition
CR [b]	B_0
PR [c]	>50% decrease in quantitative measurements of blood tumor burden from baseline in those with high tumor burden at baseline (B_2)
SD	Fails to attain criteria for CR, PR, or PD
PD [d]	B_0 to B_2 or >50% increase from baseline and at least 5,000 neoplastic cells/µL or Loss of response: in those with PR who were originally B_2 at baseline, >50% increase from nadir and at least 5,000 neoplastic cells/µL
Relapse	Increase of neoplastic blood lymphocytes to ≥B_1 in those with CR

CR: complete response; PD: progressive disease.PR: partial response; SD: stable disease.
[a] As determined by absolute numbers of neoplastic cells/µL.
[b] If a bone marrow biopsy was performed at baseline and determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR where blood assessment now meets criteria for B_0, a repeat bone marrow biopsy must show no residual disease or the response should be considered a PR only.
[c] There is no PR in those with B_1 disease at baseline as the difference within the range of neoplastic cells that define B_1 is not considered significant and should not affect determination of global objective response.
[d] Whichever criterion occurs first.

9.3.15.1.5 Global Response Score

GRS is an assessment whereby each component of the TNM(B) staging (skin, nodes, viscera, and blood for MF), has been given its own definition of response. Due to the primacy of the response in the skin in CTCL, no patient with a global objective response should have less than a PR in the skin. The global response score definition is provided in Table 9.h.

Response to treatment (CR, PR, SD, PD, relapse) will be monitored on a continual basis. For all treated patients, GRS will be assessed at the end of Cycles 3, 6, 9, 12, and 15 (Days 16-21 or before dosing on Day 1 of the subsequent cycle); at EOT. GRS will be determined based upon the most recent disease assessments for each component (mSWAT, CT scans, Sezary cell count for MF patients). For patients without baseline nodal/visceral involvement, the schedule for obtaining CT scans will likely not correlate with the timing of GRS determinations; thus, the nodal/visceral response component should be based upon the most recent CT scan findings before the GRS assessment time point. Additional unscheduled GRS determinations may occur following a change in response in skin or at the time of a CT scan. Relapse will be categorized in the study endpoints definition as recurrent disease in patients with complete response.

Table 9.h Global Response Score

Global Score	Definition	Skin	Nodes	Blood	Viscera
CR	Complete disappearance of all clinical evidence of disease	CR	All categories have CR/NI		
PR	Regression of measurable disease	CR	All categories do not have a CR/NI and no category has a PD		
		PR	No category has a PD and if any other category involved at baseline, at least one has a CR or PR		
SD	Failure to attain CR, PR or PD representative of all disease	PR	No category has a PD and if any other category involved at baseline, no CR or PR in any		
		SD	CR/NI,PR,SD in any category and no category has a PD		
PD	Progressive disease		PD in any category		
Relapse	Recurrence disease in prior CR		Relapse in any category		

CR: complete response; GRS: Global Response Score; NI: noninvolved; PD: progressive disease; PR: partial response; SD: stable disease.

For the purpose of this study, patients with B_1 involvement at baseline (but no node or viscera), who reach a PR in skin and stable B_1, will be considered to have reached PR for the GRS.

9.3.16 Skin Biopsies

For enrollment, patients will be required to undergo skin biopsies, (a total of at least 2 samples from separate lesions for MF, and 1 sample for pcALCL) during screening for confirmation of CD30 expression. Samples may be obtained up to 28 days before the first dose of brentuximab vedotin; in the event that a patient rescreens, repeat skin biopsies should be discussed with the sponsor, project clinician, or designee. CD30+ is defined as ≥10% target lymphoid cells demonstrating membrane, cytoplasmic, and/or Golgi staining pattern for CD30 at any intensity above background staining as noted on the corresponding negative control. A minimum of 10% staining in at least 1 sample is required. Percent positivity should be determined using percent neoplastic cells staining first. If neoplastic cells cannot be easily distinguished from non-neoplastic, then percent positivity should be determined using percent total lymphocytes staining.

9.4 Completion of Study Treatment (for Individual Patients)

Patients will be considered to have completed study treatment if they meet any of the following criteria:

- Complete up to 16 cycles of treatment with brentuximab vedotin.

9.5 Completion of Study (for Individual Patients)

Regardless of the duration of treatment, all patients will remain on study until they complete the EOT visit, or they withdraw consent, are lost to follow-up, death, or until study closure. The study is expected to close approximately 3 years after the first patient starts study drug.

9.6 Discontinuation of Treatment With Study Drug and Patient Replacement

Study drug should be discontinued for patients meeting any of the following criteria:

- Completed 16 cycles of brentuximab vedotin therapy.
- PD.

Treatment with study drug may also be discontinued for any of the following reasons:

- AE.
- Protocol deviation.
- Study terminated by sponsor.
- Withdrawal by patient.
- Lost to follow-up.
- Other.

Once study drug has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the Schedule of Events (Appendix A). The primary reason for study drug discontinuation will be recorded on the eCRF.

Note that some patients may discontinue study drug for reasons other than PD before completing the full treatment course.

Additional patients may be enrolled to ensure an adequate number of evaluable patients in the study, ie, approximately 10 evaluable patients.

9.7 Withdrawal of Patients From Study

A patient may be discontinued from the study (during treatment cycle or follow-up) for any of the following reasons:

- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by patient.
- Death.
- Other.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

The sponsor or their designee must be notified if a patient is withdrawn from study drug or from the study. The reason(s) for withdrawal should be documented in the patient's medical records and eCRF. The investigators must make every reasonable effort to keep each patient on the study until all planned treatments and assessments have been performed. Final treatment assessments will be performed before any other therapeutic intervention if possible. Additionally, any planned alternative treatments should be documented on the patient's medical records and eCRF.

9.8 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AE Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.2 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient 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 an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).

- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life-threatening, or require hospitalization, but may be considered serious when, on the basis of appropriate medical judgment, it may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as a single comprehensive event.

Regardless of causality, AEs or SAEs must be reported (see Section 10.3 for the period of observation) by the investigator to the sponsor's Global Pharmacovigilance department or designee within 7 calendar days for AEs, or 24 hours for SAEs, after becoming aware of the event. This will be done by transmitting an electronic data capture (EDC) AE or SAE report. If transmission of an EDC SAE report is not feasible, then a completed Takeda paper-based AE or SAE form will be sent via fax or email. A sample of the paper-based SAE form and processing directions are in the study manual. Information in the AE or SAE report or form must be consistent with the data provided on the eCRF.

If information not available at the time of the first report becomes available at a later date, then the investigator will transmit a follow-up EDC SAE report (or a paper-based SAE form if an EDC SAE report is not feasible) or provide other documentation immediately within 24 hours of receipt, while follow-up AE report is transmitted within 7 days of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All AEs and SAEs should be followed up until resolution, SD, loss to follow up, withdrawal of consent, or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial; eg, surgery was performed earlier or later than planned.

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to study drug administration.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 5.0, effective 27 November 2017 (NCI 2017). The criteria are provided in the study manual.

Relationship of the event to study drug administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: is there a reasonable possibility that the AE is associated with the study drug? The causal assessment can be based on but not limited to suggestive time or dose relationship, plausible temporal association, or biological plausibility (pharmacological and pathological mechanism).

10.3 Monitoring of AEs and Period of Observation

AEs, both nonserious and serious, will be monitored throughout the study as follows:

- AEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug. All events relating to peripheral neuropathy regardless of seriousness will be followed for all changes in severity until resolution to baseline or study closure, whichever occurs first, and recorded in the eCRF.
- Serious pretreatment events will be reported to the sponsor's Department of Pharmacovigilance or designee from the time of the signing of the ICF up to first dose of study drug, but will not be recorded in the eCRF. Investigators will send initial and follow-up paper-based SAE forms of serious pretreatment events within 24 hours of becoming aware of via fax or email.
- Related and unrelated SAEs will be reported to the sponsor's Department of Pharmacovigilance or designee from the first dose of study drug through 30 days after administration of the last dose of study drug and recorded in the eCRF. After this period only related SAEs must be reported to the sponsor's Department of Pharmacovigilance or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor must also be contacted immediately by sending a completed pregnancy form to the sponsor's Global Pharmacovigilance department or designee. The pregnancy must be followed for the final pregnancy outcome.

If a reproductively male patient impregnates a partner during the male patient's participation in this study, the sponsor must also be contacted immediately by sending a completed pregnancy form to the sponsor's Global Pharmacovigilance department or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or email addresses provided below.

A medication error is a preventable event that involves an identifiable patient and leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or email addresses provided below.

Call Center	Phone Number	Email	Fax
DLSS	1-844-662-8532 Non-toll-free number: 1-510-740-1273	GlobalOncologyMedinfo@takeda.com	1-800-881-6092

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or a medication error results in an AE or SAE, then the AE or SAE should be reported.

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs and IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited reports within 7 days for fatal and life-threatening events and within 15 days for other serious events, and serious ADRs will be submitted to the regulatory authorities within 15 days and other ADRs within 30 days, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Independent Data Monitoring Committee

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the data management plan. If selected for coding, AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the WHO Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an ICF.

The sponsor or designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

The sponsor, or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk (CD) or other electronic media will be placed in the investigator's study file.

12.2 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the data approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility and sponsor notified.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

Descriptive summaries and analyses will be performed for all efficacy and safety assessments. A statistical analysis plan (SAP) will be prepared and signed off and will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

The following analysis sets are defined in the study. If a patient will not be included in an analysis set, it should be decided before database lock.

Full analysis set

All efficacy analyses will be based on the full analysis set (FAS), which is defined as all enrolled patients identified as CD30 positive and received at least 1 dose of the study drug.

Response-evaluable set

The response-evaluable population will include a subset of the FAS patients with measurable disease at baseline and with at least 1 post-baseline response assessment. Patients who were discontinued due to death before a post-baseline evaluation happens, will be used for analyses of response.

Safety analysis set

The safety analysis set will consist of all enrolled patients who receive at least 1 dose of study drug.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive statistics will be provided on demographics and baseline characteristics, including gender, age, body weight, height, medical history, prior medication, and other parameters, if needed.

13.1.3 Efficacy Analysis

All primary efficacy evaluations for the primary and secondary efficacy endpoints will be conducted using the FAS. In addition, sensitivity analysis may be performed using response-evaluable population as appropriate.

13.1.3.1 Analysis of Primary Efficacy Endpoints

The primary endpoint, ORR4, proportion of patients achieving an objective response that lasts at least 4 months will be summarized. The 95% CI of the ORR4 will be provided. Patients whose first response occurs after the start of subsequent anti-cancer therapy but otherwise meet the primary endpoint criteria will be excluded. No imputation will be conducted for missing data.

13.1.3.2 Analyses of Secondary Efficacy Endpoints

CR rate is defined as the proportion of patients who achieved a CR as their best response on study. The 95% CI of the CR will be provided. No imputation will be conducted for missing data.

ORR will be analyzed in a similar fashion as the primary endpoint.

Duration of response is defined as the time between first documentation of response and PD. Duration of response will be summarized using the Kaplan-Meier method with the associated

95% CIs when estimable. The analysis will only include responders. Detailed censoring approaches for the analysis of DOR will be provided in the SAP.

13.1.4 Safety Analysis

Safety will be evaluated by the incidence of TEAEs, SAEs, ECOG and by changes from baseline in the patient's vital signs and clinical laboratory results using the safety analysis set. Exposure to study drug, including the number of treated cycles, total amount of doses taken, and dose intensity, will be summarized.

TEAEs, defined as AEs that occur after administration of the first dose of study drug and through 30 days after the last dose of study drug, will be tabulated. A listing of deaths and TEAEs resulting in study drug discontinuation will be provided. All reported AEs will be listed along with the date of onset, date of resolution (if resolved), CTCAE grade, and relationship to study drug. Summary information (the number and percent of patients) by System Organ Class, High Level Term, and Preferred Term will be tabulated for the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- TEAEs leading to study drug modification and discontinuation.
- SAEs.

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters. Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE, grade from baseline to the worst postbaseline value.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs (eg, diastolic and systolic blood pressure, heart rate, and body temperature) and weight over time will be tabulated by scheduled time point. ECG will be presented in a listing. ECOG performance status scores over time will also be tabulated.

Additional and unplanned safety analyses may be performed as the study is conducted. Those additional analyses, if deemed necessary, will be presented in the listing and documented in the CSR and may not need to be prespecified.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

Per China Health Authority requirement, approximately 10 evaluable patients with CD30+ MF or pcALCL are needed for this post approval commitment study.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee including, but not limited to, the investigator's binder, study medication, patient medical records, informed consent documentation, documentation of patient authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of the primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it may be reported to regulatory authorities as a serious breach of GCP and the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by a regulatory agency. If the

study site is contacted for an inspection by a regulatory agency, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual patients (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the responsibilities of the investigator that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable ICH- GCP guidelines, state and federal/local requirements and regulations of each participating region/country. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the ICF, and, if applicable, subject recruitment materials and advertisements and other documents required by all applicable laws and regulations must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study, ie, before shipment of the sponsor-supplied drug or study-specific screening activity. The IRB or IEC approval must refer to the study by its exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. If required by country or regional regulations or procedures, approval from the competent regulatory authority will be obtained before commencement of the study or implementation of a substantial amendment. The sponsor will notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the trial. Until the site receives notification, no protocol activities, including screening, may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor (or designee).

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, and the date informed consent is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the ICF and, if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. If the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether to participate in the study. If the subject, or the subject's legally acceptable representative, determines that he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and before the subject enters into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using a ballpoint pen with either blue or black ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and before the subject enters into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the

signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICFs must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will be linked to the sponsor's clinical study database or documentation only via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US Food and Drug Administration, United Kingdom Medicines and Healthcare Products Regulatory Agency, Japan Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain identifying personal information removed, eg, subject name, address, and other identifier fields not collected on the subject's eCRF.

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in

accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail.

15.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, Takeda will, at a minimum, register interventional clinical trials it sponsors anywhere in the world on www.ClinicalTrials.gov or other publicly accessible websites on or before start of study, as defined by Takeda policy/standards. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

As needed, Takeda and investigator/site contact information may be made public to support participant access to trials via registries. In certain situations/registries, Takeda may assist participants or potential participants in finding a clinical trial by helping them locate trial sites closest to their homes by providing the investigator name, address, and phone number via email/phone or other methods preferred by callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on www.ClinicalTrials.gov, and other publicly accessible websites (including the Takeda corporate site) and registries, as required by Takeda policy/standards, applicable laws, and/or regulations.

Data Sharing

The sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or the patient's disease. The data provided to external researchers will not include information that identifies patients personally.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the clinical study site agreement regarding the sponsor's policy on subject

compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Events

	Screening [a]	Cycle 1 (21-Day Cycle)	Cycle 2 (21-Day Cycle)	Cycle 3-16 (21-Day Cycle)		EOT/ET
Cycle (C) Day (D) Visit Window	**-28 to D-1**	**C1 D1**	**C2 D1**	**Cx D1**	**Cx D16-21**	**30 (±2) days after last dose**
Informed consent	X					
Inclusion/exclusion	X					
Demographics	X					
Medical history	X					
Complete physical exam	X					
Height	X					
Weight [b]	X	X	X	X		X
Pregnancy test [c]	X	X	X	X		
Vital signs [d]	X	X [d]	X	X		X
Physical exam including focused lymphoma assessment		X [e]	X	X		X
ECOG performance status	X	X	X	X		X
Hematology/serum chemistry [f]	X		X	X		X
Urinalysis	X					
12-lead ECG	X	X [g]				
mSWAT and photography [h]	X	X	X	X	X	X
Circulating Sézary cells	X	X [i]		X [i]		X
FDG-PET [j]	X					
CT [k]	X				X [k]	X [k]
Skin biopsy [l] (CD30 expression)	X					
Biopsies for disease assessment		X				

	Screening [a]	Cycle 1 (21-Day Cycle)	Cycle 2 (21-Day Cycle)	Cycle 3-16 (21-Day Cycle)		EOT/ET
Cycle (C) Day (D) Visit Window	**-28 to D-1**	**C1 D1**	**C2 D1**	**Cx D1**	**Cx D16-21**	**30 (±2) days after last dose**
Disease status [m]					X	X
Brentuximab vedotin administration		X	X	X		
Monitoring of concomitant medications and procedures	Recorded from screening through 30 days after the last dose of study drug.					
AE [n]		Recorded from first dose of study drug through 30 days after the last dose of study drug.				

AE: adverse event; CBC: complete blood cell; CR: complete response, CT: computed tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; ET: early termination; FDG: fluorodeoxyglucose; ICF: informed consent form; IEC: independent ethics committee. IRB: institutional review board; MF: mycosis fungoides; mSWAT: modified severity weighted assessment tool; pcALCL: primary cutaneous anaplastic large cell lymphoma; PD: progressive disease; PET: positron emission tomography; PR: partial response; SD: stable disease.

Tests and procedures should be performed on schedule, but occasional changes are allowable (±3 days) for holidays, vacations, and other administrative reasons. If extenuating circumstances prevent a patient from beginning treatment or completing a scheduled procedure or assessment within this time, the patient may continue the study only with the written permission of the project clinician.

[a] Screening must occur within 28 days before enrollment.

[b] Weight will be measured at screening, on Day 1 of each treatment cycle, and at EOT. The brentuximab vedotin dose will be adjusted for patients who experience a ≥10% change in weight from baseline.

[c] A serum beta-human chorionic gonadotropin pregnancy test will be performed during screening only for patients of childbearing potential. A urine pregnancy test will be performed before dosing on Day 1 of all cycles. The results of any pregnancy test must be negative before dosing on Day 1 of all cycles. Additional pregnancy testing may be performed during the study at the discretion of the investigator, upon request of the IEC/IRB, or if required by local regulations.

[d] Perform vital signs measurement at screening, before dosing on Day 1 of each cycle, and at EOT. On Cycle 1 Day 1 only, also perform vital signs measurements at 1 hour (± 10 minutes) postdose for patients receiving brentuximab vedotin. Blood pressure should be determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes.

[e] The Cycle 1 Day 1 physical examination is not required if the complete physical examination performed at screening was conducted within 4 days before treatment. A limited physical exam may be administered at the treating physician's discretion.

[f] A blood sample for hematology and serum chemistry will be obtained at screening, before dosing on Day 1 of all cycles, and at EOT. For screening, labs must be performed within 4 days of treatment, and do not need to be repeated before dosing. Hematology panel includes complete blood count with differential consisting of the following: hemoglobin, hematocrit, platelet count, leukocytes with differential, and neutrophils (absolute neutrophil count). Machine counts are acceptable. Serum chemistry panel includes: sodium, potassium, chloride, blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, aspartate transaminase, alanine transaminase, lactate dehydrogenase, albumin, glucose, urate (uric acid), calcium, phosphate, magnesium, gamma glutamyl transferase,

	Screening [a]	Cycle 1 (21-Day Cycle)	Cycle 2 (21-Day Cycle)	Cycle 3-16 (21-Day Cycle)		EOT/ET
Cycle (C) Day (D) Visit Window	**-28 to D-1**	**C1 D1**	**C2 D1**	**Cx D1**	**Cx D16-21**	**30 (±2) days after last dose**

amylase, and lipase.

[g] A 12-lead ECG will be obtained at screening and on Cycle 1 Day 1 (predose). ECG assessments are to be performed with the patient supine and rested for 5 minutes.

[h] The mSWAT should follow guidelines from Olsen, et al, 2011 (Olsen et al. 2011b), for analysis and response. Each of the designated index lesions (up to a total of 5) and lesions selected for biopsy will be serially photographed at screening; before dosing on Day 1 of Cycles 1, 2, and 3; at the end of every cycle beginning at Cycle 3 (Days 16-21 or before dosing on Day 1 of the subsequent cycle); within 30 days after the last dose of study drug. Full body global photographs including head, trunk, legs, front, back, and side, will be taken at the same time points indicated above.

[i] A blood sample for Sézary cell enumeration in patients with MF will be collected at screening; at the time of response assessments at the end of Cycles 3, 6, 9, 12, and 15 (Days 16-21 or before dosing on Day 1 of the subsequent cycle); at EOT; If the screening sample was obtained within 4 days before treatment, it does not need to be repeated on Cycle 1, Day 1. The Sézary cell sample will be evaluated per pathologist and will not be used for dosing decisions; the slide should be prepared from the same vial of blood sent for CBC testing. Investigators should ensure the result of a Sézary cell sample sent for local testing is available before dosing.

[j] FDG-PET scans will be taken at screening. No further FDG-PET scans will be required unless they are clinically indicated. FDG-PET scans taken within 8 weeks before signing the ICF may be used as the screening FDG-PET scan.

[k] CT scans of the neck, chest, abdomen, and pelvis will be obtained at screening, at the end of Cycles 3, 6, 9, 12, and 15 (Days 16-21 or before dosing on Day 1 of the subsequent cycle); and at EOT. CT scans taken within 4 weeks before screening as routine can be used as screening evaluation.

[l] Skin biopsies with a minimum of 2-mm diameter (at least 2 samples from separate lesions for patients with MF, and at least 1 sample for patients with pcALCL) will be obtained at screening (within 28 days before treatment) to confirm tumor specific CD30+ expression. In the event that a patient is rescreened, repeat skin biopsies should be discussed with the sponsor, project clinician, or designee.

[m] Response to treatment (CR, PR, SD, PD, relapse) will be monitored on a continual basis. For all treated patients, global response score will be assessed at the end of Cycles 3, 6, 9, 12, and 15 (Days 16-21 or before dosing on Day 1 of the subsequent cycle), at EOT. Additional unscheduled global response score determinations may occur following a change in response in skin or at the time of a CT scan.

[n] All events relating to peripheral neuropathy regardless of seriousness will be followed for all changes in severity until resolution to baseline or study closure, whichever occurs first.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations.

The investigator agrees to assume the following responsibilities:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure that this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study-related procedures, including study-specific (nonroutine/nonstandard panel) screening assessments, are NOT performed on potential subjects before the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to ICH and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each ICF should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an ICF does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C ECOG Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. 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	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

Source: (Oken et al. 1982).
ECOG: Eastern Cooperative Oncology Group.

Appendix D NYHA Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients 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.	Objective evidence of minimal cardiovascular disease.
III	Patients 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.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: (The Criteria Committee of New York Heart Association 1994).
NYHA: New York Heart Association.

Appendix E TNMB Classification and Clinical Staging System for MF

Modified ISCL/EORTC Revisions to the TNMB Classification of MF/SS

TNMB Stages	Description of TNMB
Skin*	
T_1	Limited patches, papules, and/or plaques covering <10% of the skin surface; may further stratify into T_{1a} (patch only) *v* T_{1b} (plaque ± patch)
T_2	Patches, papules, or plaques covering ≥10% of the skin surface; may further stratify into T_{2a} (patch only) *v* T_{2b} (plaque ± patch)
T_3	1 or more tumors (≥1 cm diameter)
T_4	Confluence of erythema covering ≥80% body surface area
Node†	
N_0	No clinically abnormal lymph nodes; biopsy not required
N_1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN_{0-2}
N_{1a}	Clone negative
N_{1b}	Clone positive
N_2	Clinically abnormal lymph nodes; histopathology Dutch Grade 2 or NCI LN_3
N_{2a}	Clone negative
N_{2b}	Clone positive
N_3	Clinically abnormal lymph nodes; histopathology Dutch grade 3-4 or NCI LN_4; clone positive or negative
N_x	Clinically abnormal lymph nodes without histologic confirmation or inability to fully characterize the histologic subcategories
Visceral	
M_0	No visceral organ involvement
M_1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
Blood	
B_0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sézary) cells
B_{0a}	Clone negative
B_{0b}	Clone positive

Modified ISCL/EORTC Revisions to the TNMB Classification of MF/SS

TNMB Stages	Description of TNMB
B_1	Low blood tumor burden: >5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B_2
B_{1a}	Clone negative
B_{1b}	Clone positive
B_2	High blood tumor burden: ≥1,000/µL Sézary cells with positive clone‡; one of the following can be substituted for Sézary cells: CD4/CD8 ≥10, CD4+CD7- cells ≥40% or CD4+CD26- cells ≥30%

Source: (Olsen et al. 2011b).

EORTC: European Organisation for Research and Treatment of Cancer ISCL: International Society for Cutaneous Lymphomas; MF: mycosis fungoides; NCI: National Cancer Institute SS: Sézary syndrome; TNMB: tumor-mode-metastasis-blood.

*Patch = any sized lesion without induration or significant elevation above the surrounding uninvolved skin: poikiloderma may be present. Plaque = any sized lesion that is elevated or indurated: crusting or poikiloderma may be present.

Tumor = any solid or nodular lesion ≥1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

† Lymph node classification has been modified from 2007 ISCL/EORTC consensus revisions (Kim et al. 2007) to include central nodes. Lymph nodes are qualified as abnormal if >1.5 cm in diameter.

‡ The clone in the blood should match that of the skin. The relevance of an isolated clone in the blood or a clone in the blood that does not match the clone in the skin remains to be determined.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Clinical Approval	02-Feb-2022 03:17 UTC
[redacted]	Statistical Approval	03-Feb-2022 03:17 UTC