Title: A Randomized, Open-Label, Phase 3 Trial of brentuximab vedotin (SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma

NCT Number: NCT01578499

Protocol Approve Date: 02 December 2014

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CLINICAL STUDY PROTOCOL C25001 AMENDMENT 5

Brentuximab vedotin (SGN-35)

A Randomized, Open-Label, Phase 3 Trial of brentuximab vedotin (SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma

Protocol Number:	C25001
Indication:	CD30 Positive Cutaneous T-Cell Lymphoma
Phase:	3
Sponsor:	Millennium Pharmaceuticals, Inc.
EudraCT Number:	2010-024215-14
Therapeutic Area:	Oncology

Protocol History

Original	11 July 2011
Amendment 1	21 December 2011
Amendment 2	24 February 2012
Amendment 3	04 March 2013
Amendment 4	03 July 2013
Amendment 5	02 December 2014

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Note: If this document was approved electronically, the electronic approval signatures may be found at the end of the document.

PPD

Rationale for Amendment 5

Amendment 5 to the protocol includes updated safety information and revises the existing eligibility criteria regarding patients at risk for pancreatitis. Acute pancreatitis has been reported with brentuximab vedotin in clinical trials and postmarketing experience. Language has been added to the benefit and risk section of this amendment summarizing the potential risk of pancreatitis in this population of patients with cutaneous T-cell lymphoma (CTCL), a non-life threatening disease. In addition, eligibility criteria have been updated to include the exclusion of patients with an elevated lipase value $\geq 3 \times$ the upper limit of normal (ULN) with an amylase level > ULN. Lipase and amylase have also been added to the chemistry lab panel.

As part of the screening requirements for this study, fludeoxyglucose positron emission tomography (FDG-PET) scans and computed tomography (CT) scans of the neck, chest, abdomen, and pelvis are performed at screening. Amendment 5 allows for FDG-PET scans that were taken within 8 weeks before signing the informed consent form (ICF) to be used as the screening FDG-PET, and CT scans taken within 4 weeks before signing the ICF to be used as the screening CT scan provided pre-specified conditions are met. This change is made in the interest of patient safety (to avoid unnecessary duplicate scans).

Purposes for Amendment 5

The purposes of this amendment are to:

- Add safety language regarding the potential risk of pancreatitis
- Add lipase values and amylase levels to pancreatitis exclusion criterion
- Add lipase and amylase to the chemistry lab panel
- Revise text regarding timing of FDG-PET and CT scans
- Clarify text regarding follow-up for objective response
- Clarify text regarding timing of clinical laboratory assessments
- Revise timing for exclusion of oral retinoid therapy
- Add a statement regarding the scheduling of pregnancy tests
- Revise the definition of relapse in the text to align with the definition in the response tables
- Add relapse to the list of global response score (GRS) responses
- Clarify text regarding the collection of pharmacokinetic parameters
- Clarify text regarding the amount of blood to be collected for germline DNA assessments
- Clarify text regarding the discontinuation of study drug
- Revise text describing safety analysis
- Revise text describing monitoring of adverse events
- Revise text regarding the recording and reporting of adverse events and serious adverse events (SAEs)

- Replace references to PPD with Millennium Pharmacovigilance or designee
- Update contact information for reporting SAEs
- Correct errors in Background and Study Rationale text and in-text references
- Correct typographical errors, punctuation, grammar, and formatting

For specific examples of changes in text and where the changes are located, see Section 15.6.

PROTOCOL SUMMARY

Study Title: A Randomized, Open-Label, Phase 3 Trial of brentuximab vedotin (SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma

Indication: Patients with CD30-positive (CD30+) cutaneous T-cell lymphoma (CTCL) including those with primary cutaneous anaplastic large cell lymphoma (pcALCL) or mycosis fungoides (MF)

Study Objectives

Primary

- To determine objective response rate (ORR), lasting at least 4 months, with brentuximab vedotin in patients with CD30+ MF or pcALCL compared to that achieved with therapy in the control arm

Key Secondary

- To determine complete response (CR) rate with brentuximab vedotin compared to that achieved with therapy in the control arm
- To determine progression-free survival (PFS) with brentuximab vedotin compared to that achieved with therapy in the control arm
- To determine burden of symptoms during treatment with brentuximab vedotin compared to that achieved with therapy in the control arm

Other Secondary

- To assess duration of response with brentuximab vedotin
- To assess duration of skin response with brentuximab vedotin
- To determine event-free survival (EFS) with brentuximab vedotin compared to that achieved with therapy in the control arm
- To describe the pharmacokinetics (PK) of brentuximab vedotin and monomethylauristatin E (MMAE) in blood
- To determine the immunogenicity of brentuximab vedotin
- To assess patient-reported quality of life outcomes
- To assess the safety of brentuximab vedotin

Overview of Study Design: This is an open-label, randomized, multicenter study. All patients must have histologically-confirmed CD30+ MF or pcALCL by central pathology review. CD30 positivity 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.) Patients are to be stratified by diagnosis: primary cutaneous anaplastic large cell lymphoma (pcALCL) or mycosis fungoides (MF), and randomized to treatment with brentuximab vedotin monotherapy (Arm 1) up to 16 cycles total (48 weeks), or methotrexate (MTX) or bexarotene per physician's choice (Arm 2) up to a total of 48 weeks.

Patients with documented partial response (PR) or CR at the completion of, and after Cycle 3, may continue to receive study drug for up to 16 cycles of treatment with brentuximab vedotin, or 48 weeks of treatment with bexarotene or methotrexate; patients with stable disease (SD) may continue therapy at the discretion of the investigator. Patients with progressive disease (PD) at any time during the study will be discontinued from study treatment (see Section 7.7). Patients with increasing mSWAT prior to 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 disease progression.

Objective response over the course of the study, per independent review facility (IRF), will be assessed by global response score (GRS), which consists of skin evaluation (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 EOT. All treated patients without disease progression at EOT/ET will then be followed for objective response every 12 weeks for a minimum of 24 months, then every 6 months; or until disease progression or study closure.

All randomized patients will also be followed for survival every 12 weeks for a minimum of 24 months after the EOT visit, and then every 6 months until patient withdrawal, death, or study closure.

Safety will be evaluated by the incidence of treatment-emergent adverse events (TEAEs), severity and type of AEs, and by changes from baseline in the patient's vital signs, ECOG performance status, and clinical laboratory results using the safety population.

Statistical Analysis and Sample Size Determination: The primary endpoint, the proportion of patients achieving an objective response that lasts at least 4 months, per IRF, will be analyzed using a Cochran-Mantel-Haenszel test stratified by baseline disease diagnosis (pcALCL or MF) based on ITT population. The 95% confidence interval of the difference in ORR that lasts at least 4 months per IRF between the 2 treatments will be provided.

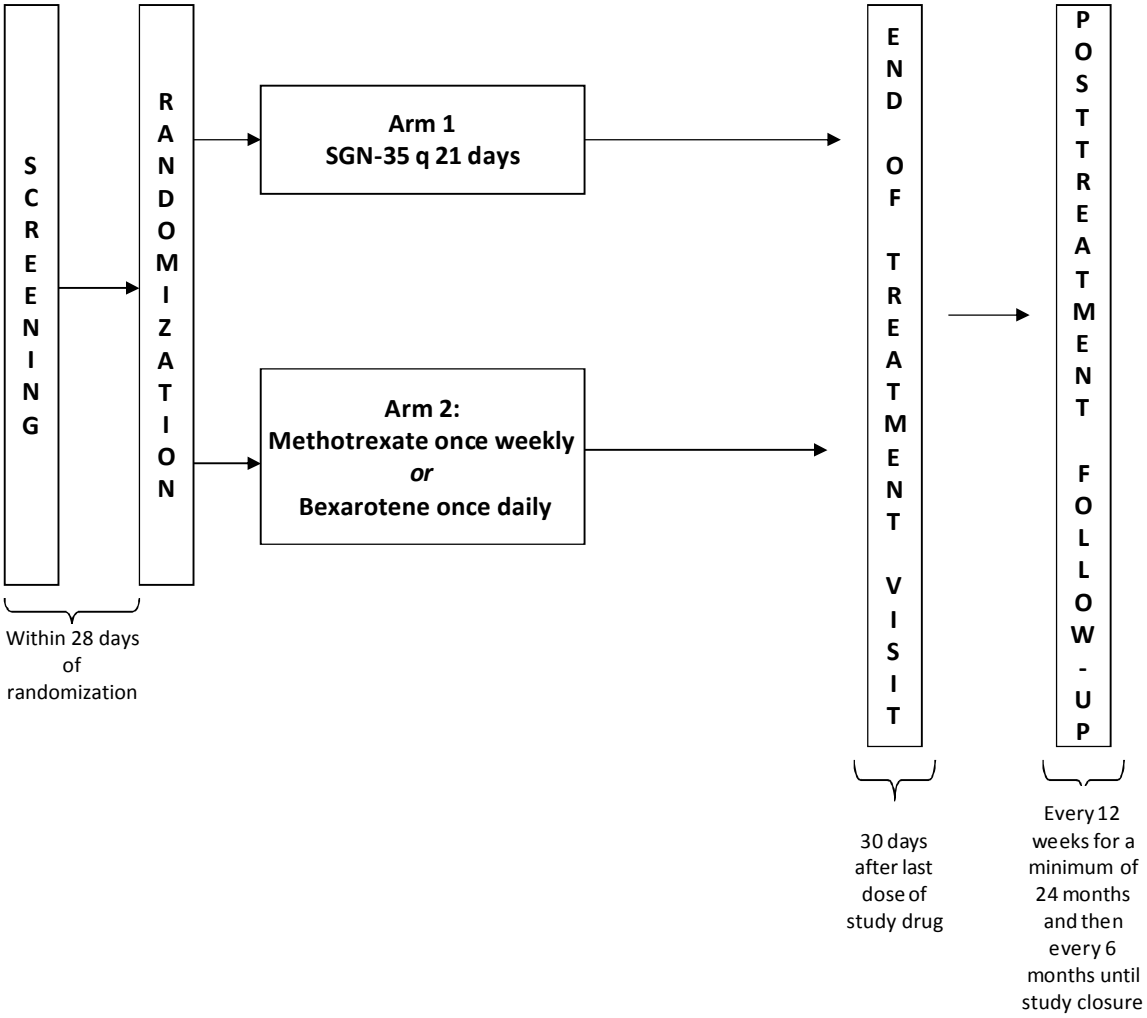
CR rate, progression-free survival, and changes in symptom domain per Skindex-29 assessment tool are designated as key secondary endpoints. A fixed sequential testing procedure will be used to test between the primary endpoint and the key secondary endpoints; that is, the key secondary endpoints will be tested only if the primary endpoint is statistically significant. To test the key secondary endpoints, a weighted Holm's procedure will be used.

Approximately 124 patients (approximately 62 patients per treatment arm) will be randomized to the study, including a minimum of 30 patients (15 per treatment arm) with pcALCL. The sample size was calculated based on providing 90% power to detect a 30% improvement in ORR, lasting at least 4 months, in the brentuximab vedotin treatment group, assuming ORRs lasting at least 4 months for brentuximab vedotin treatment group and for the MTX or bexarotene alone treatment group are 70% and 40%, respectively. This calculation is based on a two-sided χ^2 test with significance level of $\alpha = 0.05$, and a 10% dropout rate using nQuery Advisor 7.0.

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

Duration of Study: Patients will be screened up to 28 days, receive study drug up to 48 weeks, and have follow-up assessments performed every 12 weeks for a minimum of 24 months after EOT, and then every 6 months until patient withdrawal, death, or study closure, for a total time on study of up to 5 years.

Study Overview Diagram



Schedule of Events

		Screening[a]	Enrollment	Cycle 1 (21-Day Cycle)			Cycle 2 (21-Day Cycle)	Cycle 3-16 (21-Day Cycle)		EOT/ET	PTFU[b]
	Cycle (C) Day (D) Visit Window	-28 to D1	Within 72 hours of first dose	C1 D1	C1 D2 & 4	C1 D3 & 5	C2 D1	Cx D1	Cx D16-21	30 days (±2 days) after last dose	Minimum of 24 months
Baseline	Informed consent	X	Randomization to Study Treatment Arm Arm 1 - brentuximab vedotin or Arm 2 - Methotrexate or Bexarotene								
	Inclusion/exclusion	X									
	Demographics	X									
	Medical history	X									
	Complete physical exam	X									
	Height	X									
	Weight[c]	X		X			X	X		X	
	Pregnancy test[d]	X		X			X	X			
	Archived tissue[e]	X									
Safety Assessments	Vital signs[f]	X		X[f]			X	X		X	
	Physical exam including focused lymphoma assessment			X[g]			X	X		X	X
	ECOG performance status	X		X			X	X		X	
	Hematology/serum chemistry[h]	X					X	X		X	
	Urinalysis	X									
	12-lead ECG	X		X[i]							
	Immune reconstitution assessment[j]			X			X	X		X	
Disease Assessment	mSWAT and photography[k]	X		X			X	X	X	X	X
	Circulating Sézary cells	X		X[l]				X[l]		X	X
	FDG-PET[m]	X									
	CT[n]	X							X[n]	X[n]	X[n]
	Quality of life assessments[o]			X			X	X		X	X

		Screening[a]	Enrollment	Cycle 1 (21-Day Cycle)			Cycle 2 (21-Day Cycle)	Cycle 3-16 (21-Day Cycle)		EOT/ET	PTFU[b]
	Cycle (C) Day (D) Visit Window	-28 to D1	Within 72 hours of first dose	C1 D1	C1 D2 & 4	C1 D3 & 5	C2 D1	Cx D1	Cx D16-21	30 days (±2 days) after last dose	Minimum of 24 months
	Healthcare Utilization	X		X			X	X		X	X
	Skin biopsy[p] (CD30 Expression)	X							X[p]	X[p]	X[p]
	Biopsies for disease assessment[q]			X							
	Disease status/survival[r]								X	X	X
Treatment	Brentuximab vedotin administration			X			X	X			
	Methotrexate administration[s]			X			X	X			
	Bexarotene administration[t]			Bexarotene is dosed once a day for the course of the study							
	Monitoring of concomitant medications and procedures	Recorded from screening through 30 days after the last dose of study drug.									
	Adverse event reporting[u]		Recorded from first dose of study drug through 30 days after the last dose of study drug.								
	Serious adverse events	Serious adverse events[v] will be collected from signing of the informed consent form through 30 days after the last dose of study drug									
PK/PD	PK sample[w]			X[w]	X[w]	X[w]		X[w]		X	
	CCI										
	Immunogenicity[y]			X				X		X	
	CCI										

Abbreviations: CT = computed tomography; CTACK = cutaneous T cell-attracting chemokine; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ET = early termination; EOT = end of treatment; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; mSWAT = modified severity weighted assessment tool; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; PTFU = posttreatment follow-up; TARC = thymus and activation regulated chemokine.

Tests and procedures should be performed on schedule, but occasional changes are allowable (± 2 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 prior to randomization.

b All treated patients without disease progression at EOT/ET will be followed for objective response every 12 weeks (± 2 weeks) for a minimum of 24

		Screening[a]	Enrollment	Cycle 1 (21-Day Cycle)			Cycle 2 (21-Day Cycle)	Cycle 3-16 (21-Day Cycle)		EOT/ET	PTFU[b]
	Cycle (C) Day (D) Visit Window	-28 to D1	Within 72 hours of first dose	C1 D1	C1 D2 & 4	C1 D3 & 5	C2 D1	Cx D1	Cx D16-21	30 days (±2 days) after last dose	Minimum of 24 months

months after the EOT visit, and then every 6 months (± 1 month); or until progressive disease or study closure. All randomized patients will also be followed for survival every 12 weeks (± 2 weeks) for a minimum of 24 months after the EOT visit, then every 6 months (± 1 month) until patient withdrawal, death, or study closure.

c 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

d A serum beta-human chorionic gonadotropin (B-hCG) 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 Independent Ethics Committee (IEC)/Institutional Review Board (IRB), or if required by local regulations.

e If available and consistent with local regulations, tumor tissue collected at the time of original diagnosis (unstained slides or a paraffin-embedded block) will be obtained during screening after the patient has signed the informed consent form. The sample may be used in the evaluation of a diagnostic test to determine CD30 expression.

CCI

f Perform vital signs measurement at screening, prior to 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.

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

h 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 randomization, and do not need to be repeated before dosing.

Hematology panel includes complete blood count (CBC) with differential consisting of the following: hemoglobin, hematocrit, platelet count, leukocytes with differential, and neutrophils (absolute neutrophil count [ANC]). Machine counts are acceptable.

Serum chemistry panel includes: sodium, potassium, carbon dioxide, chloride, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), albumin, glucose, urate (uric acid), calcium, phosphate, magnesium, GGT, amylase, and lipase.

Hemoglobin A1C will be obtained at screening and on Day 1 of Cycles 1, 4, 7, 10, and 16.

Lipid panel (total cholesterol, HDL, LDL, triglycerides) and thyroid panel (TSH, free T4, free T3) should be obtained at screening and on Day 1 of Cycles 1, 2, 3, 6, 9, 12, and 16.

i 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 and before any closely timed PK blood collection.

		Screening[a]	Enrollment	Cycle 1 (21-Day Cycle)			Cycle 2 (21-Day Cycle)	Cycle 3-16 (21-Day Cycle)		EOT/ET	PTFU[b]
	Cycle (C) Day (D) Visit Window	-28 to D1	Within 72 hours of first dose	C1 D1	C1 D2 & 4	C1 D3 & 5	C2 D1	Cx D1	Cx D16-21	30 days (±2 days) after last dose	Minimum of 24 months

j Lymphocytes counts, phenotypic T, B, and natural killer (NK) cell subsets ($CD4^+$ T cells counts, $CD8^+$ T cells counts, CD8/CD4 ratio, $CD19^+$ B cells counts); NK cells ($CD3^-$ CD56 CD16+ vs $CD3^-$ CD56 $CD16^-$).

k The mSWAT should follow guidelines from Olsen, et al, 2011, 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; and at posttreatment follow-up visits. Full body global photographs including head, trunk, legs, front, back, and side, will be taken at the same time points indicated above.

l 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; and every 12 weeks (± 2 weeks) for a minimum of 24 months after the EOT visit, and then every 6 months (± 1 month); or until progressive disease or study closure. If the screening sample was obtained within 4 days before randomization, it does not need to be repeated on Cycle 1, Day 1. The Sézary cell sample will be evaluated per independent pathology review 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 prior to dosing.

m 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 informed consent form (ICF) may be used as the screening FDG-PET scan.

n CT scans of the neck, chest, abdomen, and pelvis will be obtained at screening. CT scans taken within 4 weeks before signing the ICF may be used for the screening CT scan if all of the following conditions are met:

- There is no nodal or visceral involvement noted
- There is no clinically evident lymphadenopathy or splenogegaly by physical exam at the time of screening
- The scan meets all quality criteria as outlined in the Imaging Manual

For patients without nodal or visceral involvement (as determined by baseline CT scans), CT scans will be performed:

- During the cycle following the first skin response, ideally corresponding to the confirmation of the skin response, and 6 cycles (a minimum or 4 months) after that confirmed skin response
- If there is a question of new or progressive disease in the LN/viscera

For patients with baseline nodal/visceral disease, CT scans will be performed:

- At the end of Cycles 3, 6, 9, 12, and 15 (Days 16-21 or on Day 1 of the subsequent cycle), and per the follow-up schedule until disease progression
- If there is a question of new or progressive disease in the LN/viscera
- At EOT if the previous CT scan was performed more than 8 weeks before EOT

o All questionnaires should be completed on Day 1 of Cycles 1, 2, 4, 6, 8, 10, 12, 14, and 16 before any other study procedures are performed, at EOT, and during posttreatment follow-up. EQ-5D, FACT-G, and Skindex-29 questionnaires will be employed for health-related quality of life (HRQoL) assessment from the patient's perspective. Questionnaires may be collected by phone or by mail for patients not required to return to clinic for posttreatment follow-

		Screening[a]	Enrollment	Cycle 1 (21-Day Cycle)			Cycle 2 (21-Day Cycle)	Cycle 3-16 (21-Day Cycle)		EOT/ET	PTFU[b]
	Cycle (C) Day (D) Visit Window	-28 to D1	Within 72 hours of first dose	C1 D1	C1 D2 & 4	C1 D3 & 5	C2 D1	Cx D1	Cx D16-21	30 days (±2 days) after last dose	Minimum of 24 months

up.

p 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 prior to randomization) to confirm tumor specific CD30+ expression and again at the end of Cycle 3, and at the time of disease progression (EOT or during the posttreatment follow-up period). If possible, repeat skin biopsies should be taken from the same lesions as the samples obtained at screening. At the time of PD, an effort should be made to take an additional sample from a new lesion. In the event that a patient is rescreened, repeat skin biopsies should be discussed with the sponsor, project clinician, or designee.

q If applicable, biopsies for response assessment may be needed as outlined in Section 7 (refer to the following tables):

- Bone marrow: Refer to Table 7-5
- Lymph node: Refer to Table 7-3
- Skin: Refer to Table 7-2
- Viscera: Refer to Table 7-4

r 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; and then every 12 weeks for a minimum of 24 months, and then every 6 months; or until disease progression or study closure. All randomized patients will also be followed for survival every 12 weeks for a minimum of 24 months after the EOT visit, then every 6 months until patient withdrawal, death, or study closure. Additional unscheduled GRS determinations may occur following a change in response in skin or at the time of a CT scan. Information may be collected by phone for patients with progressive disease.

s Methotrexate will be administered once weekly as an oral dose.

t Patients taking bexarotene will receive fenofibrate for a total of 7 days before the start of bexarotene dosing.

u 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.

v Including serious pretreatment events; see Section 10.1.1 and Section 10.3 of the study protocol.

w Patients randomized to brentuximab vedotin will be assigned to Group A or Group B at the time of randomization for PK sampling. PK blood samples will be obtained at the following times:

All brentuximab vedotin-treated patients:

Cycles 1, 3, 5, 7, 9, 11, 13, and 15

Day 1: within 4 hours before the start of the brentuximab vedotin infusion and 30 minutes (± 25 minutes) after the end of the brentuximab vedotin infusion

End of Treatment Visit

Group A (consisting of half the brentuximab vedotin-treated patients):

		Screening[a]	Enrollment	Cycle 1 (21-Day Cycle)			Cycle 2 (21-Day Cycle)	Cycle 3-16 (21-Day Cycle)		EOT/ET	PTFU[b]
	Cycle (C) Day (D) Visit Window	-28 to D1	Within 72 hours of first dose	C1 D1	C1 D2 & 4	C1 D3 & 5	C2 D1	Cx D1	Cx D16-21	30 days (±2 days) after last dose	Minimum of 24 months

Cycles 1 and 3

Day 1: within 4 hours before the start of the brentuximab vedotin infusion and 30 minutes (± 25 minutes) after the end of the brentuximab vedotin infusion

Day 2: 24 hours (± 4 hours) from the start of the Day 1 dose infusion

Day 4: 72 hours (± 4 hours) from the start of the Day 1 dose infusion

Group B (consisting of half the brentuximab vedotin-treated patients):

Cycles 1 and 3

Day 1: within 4 hours before the start of the brentuximab vedotin infusion and 30 minutes (± 25 minutes) after the end of the brentuximab vedotin infusion

Day 3: 48 hours (± 4 hours) from the start of the Day 1 dose infusion

Day 5: 96 hours (± 4 hours) from the start of the Day 1 dose infusion

x CCI [redacted]

y Immunogenicity samples in patients receiving brentuximab vedotin will be collected before dosing on Day 1 of Cycles 1, 3, 5, 7, 9, 11, 13, and 15 and at EOT.

z CCI [redacted]

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
ADC	antibody-drug conjugate
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
BSA	body surface area
BUN	blood urea nitrogen
pcALCL	primary cutaneous anaplastic large cell lymphoma
CBC	complete blood count
CD30+	CD30-positive
C_{max}	maximum plasma concentration
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CT	computed tomography
CTCL	cutaneous T-cell lymphoma
CTACK	cutaneous T cell-attracting chemokine
DME	drug metabolizing enzymes
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assay
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study (visit)

Abbreviation	Term
EOT	End of Treatment (visit)
EU	European Union
EVA	ethyl vinyl acetate
FDA	United States Food and Drug Administration
FDG	Fludeoxyglucose
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
GRS	global response score
Hb	Hemoglobin
Hct	Hematocrit
HDAC	histone deacetylase
HDACi	histone deacetylase inhibitor
HDL	high-density lipoprotein
HED	human equivalent dose
hERG	human ether-à-go-go related gene
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
HRQoLHU	health-related quality of lifehealthcare utilization
HU	healthcare utilization
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRF	independent review facility
ISCL	International Society for Cutaneous Lymphoma
ITT	intent-to-treat

Abbreviation	Term
IV	intravenous; intravenously
IVRS	interactive voice response system
IWRS	interactive web response system
JCV	John Cunningham virus
LDH	lactic dehydrogenase
LDL	low density lipoprotein
LyP	lymphomatoid papulosis
MF	mycosis fungoides
MMAE	monomethylauristatin E
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
mSWAT	modified severity weighted assessment tool
MTD	maximum tolerated dose
MTX	methotrexate
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse effect level
NYHA	New York Heart Association
ORR	objective response rate
ORR4	objective response rate lasting at least 4 months
pcALCL	primary cutaneous anaplastic large cell lymphoma
PD	progressive disease (disease progression)
PE	polyethylene
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PO	*per os*; by mouth (orally)
PP	per protocol
PR	partial response
PRO	patient-reported outcome
PUVA	psoralen with ultraviolet light A
PVC	polyvinyl chloride

Abbreviation	Term
RBC	red blood cell
RR	response rate
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
CCI	[redacted]
SD	stable disease
SDT	skin-directed therapy
SmPC	Summary of Product Characteristics
SS	Sézary Syndrome
SWAT	severity weighted assessment tool
TARC	thymus and activation regulated chemokin
TEAE	treatment-emergent adverse event
tMF	transformation mycosis fungoides
TNMB	Tumor-Node-Metastasis-Blood
TNM	Tumor-Node-Metastasis
TSEBT	total skin electron beam therapy
ULN	upper limit of the normal range
US	United States
UVA	ultraviolet light A
UVB	ultraviolet light B
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment: Cutaneous T-cell Lymphoma

Cutaneous T-cell lymphoma (CTCL) is the most common cutaneous lymphoma, accounting for 72% of cases. From 1973 to 2002, reported CTCL incidence rates in the United States (US) have steadily increased. The incidence rate of CTCL from 1998 through 2002 was 9.6 per million person-years, up from 2.8 per million person-years in 1973 through 1977. CTCL incidence increases with age; it is quite low in those under 20 years (0.3 per million person-years) and it peaks in the 70- to 79–year age group (24.6 per million person-years). Cutaneous T-cell lymphoma also has notable racial and ethnic incidence differences, with much higher rates among blacks than among whites.[1, 2, 3]

CTCL is characterized by clonal expansions of mature, post-thymic T cells that infiltrate the skin. The current World Health Organization (WHO) classification includes 7 major subtypes: mycosis fungoides (MF), Sézary syndrome (SS), primary cutaneous CD30-positive (CD30+) lymphoproliferative disorders (comprising primary cutaneous anaplastic large cell lymphoma [pcALCL] and Lymphomatoid papulosis [LyP]), subcutaneous panniculitis-like T-cell lymphoma, primary cutaneous γδ T-cell lymphoma, primary cutaneous aggressive epidermotropic CD8+cytotoxic T-cell lymphoma, and primary cutaneous small/medium CD4+ T-cell lymphoma.

Brentuximab vedotin is an anti-CD30 targeted antibody-drug conjugate (ADC). Two major CD30-expressing CTCL subtypes have been selected for this study: MF and pcALCL.[4]

1.1.1.1 Mycosis Fungoides

Mycosis fungoides, the most common form of CTCL, accounts for approximately 44% of all cutaneous lymphomas. An indolent disease with a protracted course, it occurs most often in middle-aged to elderly adults, with a male (66%) predominance. The 10-year disease-specific survival for patients who have progressed to the tumor stage is approximately 42%; this drops to 20% with histologically proven lymph-node involvement.[5] The skin lesions of MF tend to be on the trunk and include erythematous patches, thickened plaques, nodular tumors, and generalized erythroderma. 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.

Although the clinical course of MF is usually indolent, occasionally, individuals with MF develop a morphologic transformation (tMF) from small- to intermediate-sized cerebriform cells to a large cell variant. Large cells in excess of 25% of the total lymphoid infiltrate typically characterize large-cell transformation and incidence of such transformation reportedly ranges between 8% and 55%.[6, 7] Approximately 30% to 50% of tMF cases express CD30 by large cells, with a positivity of more than 75% in approximately 15% of tMF cases.[5] Edinger et al showed that in 47 nontransformed MF biopsies, at least rare dermal CD30-positive cells were present in all cases. More than 25% CD30-positive lymphoid cells were present in the epidermis and dermis in 12 (25%) and 2 (4%) cases, respectively, indicating that CD30 staining can be prominent in MF without transformation.[8]

1.1.1.2 Primary Cutaneous Anaplastic Large Cell Lymphoma

The incidence of primary cutaneous ALCL (pcALCL) peaks in the 6th decade. The disease-specific survival rate for pcALCL patients at 5 years is 85% to 90%.[9, 10] pcALCL usually presents in adults as solitary or localized nodules that may undergo partial necrosis and resolution, but it does not spontaneously regress. It has a 5-year OS of approximately 90%. The tumor cells involve the dermis extensively, may infiltrate subcutaneous tissue, and have little epidermotropism. In contrast to nodal ALCL, primary cutaneous forms of ALCL lack epithelial membrane antigen and express the cutaneous lymphocyte antigen (HECA-452). Anaplastic lymphoma kinase [ALK-1 (p80)] and t(2;5) translocation are usually absent in pcALCL. If these are present, one needs to be highly suspicious of the lesions being a cutaneous manifestation of underlying systemic ALCL.[11]

1.1.2 Disease Treatment and Staging

1.1.2.1 Mycosis Fungoides Treatment and Staging

Mycosis fungoides survival is dependent on stage, and patients with limited patch and plaque disease have survival equal to age-matched controls. MF is staged based on clinical features of skin involvement and degree of infiltration of the lymph nodes and viscera. The most common staging system for MF is based on a tumor (T)-node (N)-metastasis (M)-blood (B) classification (Section 15.4). Staging is based on modified American Joint Committee on Cancer (AJCC) criteria according to the International Society for Cutaneous Lymphomas (ISCL)/European Organisation for Research and Treatment of Cancer (EORTC) Tumor-Node-Metastasis-Blood (TNMB) classification.[12]

Disease stage dictates prognosis and choice of treatment in MF.[13] Early-stage patients with mycosis fungoides often respond to skin-directed therapies (SDTs) alone. For patients with extensive/refractory skin disease or more advanced-stage disease, biologic systemic therapies (often combined with SDTs) are utilized initially, and chemotherapies are reserved for later. Because of the chronic and recurrent nature of CTCL, patients frequently require repeat treatment courses and maintenance regimens for disease control.

Phototherapy, including broadband ultraviolet B (280–320 nm wavelength), narrowband UVB (311 nm wavelength, NBUVB), and photochemotherapy (psoralen and ultraviolet A [PUVA]) are useful for whole-body SDT for CTCL. However, with advancing disease stage, response rates decrease and recurrent disease becomes all but certain.[14] Responses to SDT have been described in treatment resistant stage IA to IIB mycosis fungoides, but 38% to 50% of patients experience recurrence. It is less effective in tumor stage mycosis fungoides or folliculotropic mycosis fungoides due to lesion depth.[15, 16, 17, 18]

Total skin electron beam therapy (TSEBT) is effective for extensive plaque, tumor, or erythrodermic disease. A recent retrospective review of 18 cases of advanced refractory CTCL (stage IIB–IV) treated with palliative TSEBT demonstrated a CR in 50% and a limited response in 39%. Twenty-four percent of patients exhibited progression-free survival. Four patients (22%) had a median continuing remission of 6 months (range 2-14 months). The overall 1-year survival was 48%, and most patients relapsed within 1 year after completing treatment.[19]

Histone deacetylase inhibitors (HDACi) vorinostat and romidepsin have been used in patients with relapsed and refractory CTCL, with objective response rates (ORR) of 24% to 30 %, and 34%, respectively.[20, 21] HDACi are a novel class of compounds that inhibit the enzyme HDAC, and thus inhibit the deacetylation of histone proteins associated with DNA and nonhistone proteins. Chemotherapy agents with notable activity in patients with relapsed and refractory disease include gemcitabine and liposomal doxorubicin. These agents have moderate to high response rates (70% and 88%, respectively); however, response durations are short.[22, 23] Both methotrexate and bexarotene are approved by the FDA and remain widely used treatments for CTCL across the diagnoses.

1.1.2.2 pcALCL Treatment and Staging

Similar to MF, the ISCL/EORTC proposal for non-MF CTCL uses the Tumor-Node-Metastasis (TNM) nomenclature for classification.[24]

Because it is implicit in the definition of cutaneous lymphomas other than MF that extracutaneous disease (lymph node or visceral) is absent, all patients are N_0 and M_0 at presentation. However, to permit application of the staging system at the time of relapse (as a relapse-stage designation) or disease progression, the N-M-classification is defined as in Kim, et al 2007.[24]

The most common therapies for solitary or localized pcALCL are surgical excision and radiotherapy. Response rates for these therapies are high (90%–100%); relapsed rates range from 41% to 43%. Chemotherapy is used primarily for multifocal pcALCL or relapsed disease. High response rates have been reported with multiagent chemotherapy but the majority of patients relapse, with median remission rates of 6 weeks to 4 months.[11]

1.1.3 Study Drug

Brentuximab vedotin is an antibody-drug conjugate (ADC) consisting of the antibody cAC10 chemically conjugated to monomethylauristatin E (MMAE), a synthetic analog of the naturally occurring cytotoxic agent, dolastatin10. cAC10 binds to a number of CD30+ cancer cell lines including Hodgkin lymphoma (HL), anaplastic large cell lymphoma (ALCL), and other varied lymphoproliferative disorders.

The cAC10 antibody itself (SGN-30) was previously evaluated as a target for immunotherapy in pcALCL, LyP, and tMF. In 2009, Duvic M, et al,[25] reported the results of a phase 2 study of SGN-30 in pcALCL. The overall ORR (complete response [CR] + partial response [PR]) was 70% (16 of 23 patients): 10 patients achieved a CR and another 6 patients achieved a PR. Overall, disease control rate of SGN-30, as assessed by achieving a response to therapy or stable disease (CR + PR + stable disease), was shown by 87% of patients during the study, including all patients (14 of 14) with pcALCL or LyP and 6 of 9 patients (67%) with transformation mycosis fungoides (tMF) or with multiple clinical diagnoses (lymphoma and related lymphoproliferative disorders). Fifteen of 23 patients (65%) experienced at least 1 adverse event during the study, most of which were mild or moderate.[25]

Although cAC10, the unconjugated anti-CD30 antibody, was not further developed, brentuximab vedotin uses cAC10 as the targeting mechanism for delivering its cytotoxic MMAE payload and therefore may be equally, if not more effective, in CD30+ CTCL based upon its mechanism of action.

1.2 Preclinical Experience

Brentuximab vedotin has the potential to target and selectively deliver a potent cytotoxic to tumor cells. It induces cell death of both HL and ALCL cell lines in vitro with subnanomolar concentration producing 50% inhibition (IC_{50}) values and has demonstrated antitumor activity in xenograft models of the same tumors.

Multiple-dose brentuximab vedotin toxicity studies have been performed in monkeys and rats. In both species, hypocellularity of the bone marrow and lymphoid depletion of the thymus were observed. In addition, lesions were seen in the kidneys, liver, and spleen in monkeys and in the liver and testes in rats. Reversibility of toxicity was demonstrated for all of the findings with the exception of the testicular changes in rats. At the recovery sacrifice 4 weeks following the last dose of brentuximab vedotin, testicular changes (diffuse seminiferous tubule degeneration) were still evident. The no observed adverse effect level (NOAEL) for brentuximab vedotin was defined at 1.0 mg/kg in monkeys and 0.5 mg/kg in rats. Human equivalent doses (HED) are 0.32 and 0.08 mg/kg respectively.

Detailed information regarding the nonclinical pharmacology and toxicology of brentuximab vedotin may be found in the Investigator's Brochure (IB).

1.3 Clinical Experience

The safety and efficacy of brentuximab vedotin have been evaluated in more than 300 patients with HL, sALCL, and other CD30+ hematologic malignancies in 11 clinical studies. Clinical data have been collected from 2 completed phase 1 dose escalation studies (SG035-0001 and SG035-0002), a pivotal phase 2 study in relapsed or refractory HL after ASCT (SG035-0003), a pivotal phase 2 study in relapsed or refractory sALCL (SG035-0004), and a phase 1 drug-drug interaction study (SG035-008A). Preliminary and final analyses of safety data indicate that brentuximab vedotin has a tolerable and manageable safety profile in the studied populations.

In Study SG035-0001, a total of 45 patients with CD30-positive hematologic malignancies (42 with HL, 2 with sALCL, 1 with angioimmunoblastic T-cell lymphoma) were treated with brentuximab vedotin at dose levels of 0.1 to 3.6 mg/kg administered intravenously every 3 weeks. The primary objectives of the study were to establish a maximum tolerated dose (MTD) of brentuximab vedotin and to assess the associated toxicity profile. The most common adverse events were fatigue (36%), pyrexia (33%), diarrhea, nausea, peripheral neuropathy, and neutropenia (22% each). Notable serious adverse events considered at least

possibly related to treatment included anaphylaxis, myocardial infarction, and peripheral neuropathy.

In Study SG035-0002, 44 patients with CD30-positive hematologic malignancies (38 with HL, 5 with sALCL, and 1 with peripheral T-cell lymphoma) were treated with brentuximab vedotin at dose levels of 0.4 to 1.4 mg/kg administered intravenously weekly for 3 of 4 weeks. The primary objectives explored in this study were to establish the safety profile and MTD of weekly brentuximab vedotin monotherapy in patients with relapsed/refractory CD30+ hematologic malignancies. Although this weekly regimen was designed to enable combination use with gemcitabine, efficacy with brentuximab vedotin monotherapy was deemed sufficient and the planned brentuximab vedotin/gemcitabine combination was not pursued. The most common adverse events were peripheral sensory neuropathy (66%); fatigue (52%); nausea (50%); diarrhea (32%); arthralgia (27%); pyrexia (25%); and decreased appetite, myalgia, and upper respiratory tract infection (23% each). Treatment discontinuations due to adverse events (AEs) were observed in 30% of patients. The most frequent AE that led to dose modification or delay was peripheral sensory neuropathy.

In SG035-0003, a phase 2, single-arm, open-label study in patients with relapsed or refractory HL post ASCT, and SG035-0004, a phase 2 trial conducted in patients with relapsed or refractory sALCL, brentuximab vedotin was administered at a dose of 1.8 mg/kg every 3 weeks. One-hundred two patients with relapsed and refractory HL and 58 patients with relapsed and refractory sALCL were exposed for a median duration of approximately 27weeks (9 cycles) and 20 weeks (6 cycles), respectively. Most patients (89%) in the two phase 2 studies were between the ages of 18 and 65 years. The primary endpoint of both studies was ORR as assessed by an independent radiographic facility. Key secondary endpoints included duration of response, OS, and PFS. The key efficacy results in HL (SG035-0003) include ORR per IRF (75% [95% CI: 64.9%-82.6%]), CR rate (34% [95% CI: 25.2%-44.6%]), B symptom resolution rate (77%), and duration of response (DOR, 29 weeks). Key efficacy points in sALCL (SG035-0004) include ORR (86% [95% CI: 74.6%-93.9%]), CR rate (53% [95% CI: 39.6%-66.7%]), and B symptom resolution rate (82%).

Treatment-emergent AEs occurring in ≥ 20% of patients in phase 2 were peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhea (34%), pyrexia (31%), upper respiratory tract infection (28%), neutropenia (21%), and vomiting (20%). These events were primarily mild to moderate in severity and reversible. Approximately half of patients had treatment-emergent peripheral neuropathy, predominantly sensory neuropathy, with an

onset and severity pattern consistent with a cumulative effect. Dose delay and subsequent reduction to 1.2 mg/kg was generally effective in managing peripheral neuropathy. Grade 3 and 4 neutropenia occurred in 13% and 7% of patients, respectively; these events were typically of short duration and well managed by brief dose delays with growth factor support in some cases.

Infusion-related reactions (IRRs) were reported for 17 patients (11%) in the phase 2 population (Studies SG035-0003 and SG035-0004), and were reported in similar proportions of HL and ALCL patients. The preferred terms reported most frequently were chills in 6 (4%) patients, nausea in 5 (3%) patients, dyspnoea and pruritus in 4 patients each (3%), and cough in 3 (2%) patients. All IRRs in the phase 2 population (Studies SG035-0003 and SG035-0004) were Grade 1 or 2 in severity. No serious IRRs, nor any events of anaphylaxis, were reported in the phase 2 population. All but 1 patient had their first IRR within Cycle 3 (9 patients in Cycle 1; 6 patients in Cycle 2; and 1 patient in Cycle 3); 1 patient had a first IRR in Cycle 15. Of the 17 patients with IRRs reported by the investigator, 7 patients received no IRR prophylaxis and had no further IRRs reported, while 10 received IRR prophylaxis. Of the 10 patients who received IRR prophylaxis, no additional IRRs were reported for 8 of these patients. Incidences of IRRs were also observed in the phase 1 studies. Most IRRs occurred within the first 2 cycles. Most IRRs in the phase 1 studies were Grade 1 or 2. Grade 3 IRRs occurred in 2 patients (both in phase 1 dose-escalation safety studies). Two SAEs of anaphylaxis occurred, both in phase 1 safety (SG035-0001) and clinical pharmacology (SGN35-007) studies. One of these 2 cases of anaphylaxis resulted in treatment discontinuation. The other patient continued treatment with IRR prophylaxis and a longer infusion time.

The clinical laboratory parameters for which the most patients had new or worsening shifts to ≥ Grade 3 were low neutrophils (11%), lymphocytes (11%), platelets (6%), leukocytes (5%), and high glucose (6%). Only 1 patient in the phase 2 studies had Grade 3 ALT and aspartate aminotransferase (AST).

In the phase 2 studies, 31% of patients had a serious adverse event (SAE), 28% had an SAE of Grade 3 or higher, and 15% had an SAE that was determined by the investigator to be related to brentuximab vedotin. The most common SAEs, reported in ≥ 2% of patients, were abdominal pain, disease progression (recurrent sALCL), pulmonary embolism, and septic shock. A higher proportion of sALCL patients experienced SAEs, including deaths within 30 days of last dose, relative to HL patients, likely due to the older age and more aggressive nature of the malignancy in this patient population.

A total of 9 deaths were reported within the safety evaluation period (within 30 days of the last dose of brentuximab vedotin) in 357 patients across the 6 phase 1 and phase 2 studies for which data are available. Two patient deaths (0.6%) were considered related to study treatment. One patient in study SG035-0001 who received 3.6 mg/kg in phase 1 died due to febrile neutropenia and presumed septic shock. A second treatment-related death in study SG035-008A was attributed to pancytopenia, cytomegalovirus (CMV) infection, and intracranial hemorrhage. The remaining on-study deaths were primarily related to disease progression in sALCL patients.

Brentuximab vedotin has been shown to induce durable remissions in patients with HL both pre- and post-ASCT, and in patients with relapsed or refractory sALCL. Progression-free survival results comparing PFS with brentuximab vedotin to PFS from prior systemic therapy indicate that PFS is significantly prolonged with brentuximab vedotin for both HL and sALCL. A substantial number of HL and sALCL patients with B symptoms at baseline saw these symptoms resolve during treatment with brentuximab vedotin. In addition, the large majority of sALCL patients presenting with cutaneous lesions at baseline experienced resolution of these symptoms after receiving brentuximab vedotin.

Further details on clinical studies with brentuximab vedotin are provided in the brentuximab vedotin IB.

1.4 Study Rationale

1.4.1 Treatment Options in CTCL

There is no universally accepted single standard of care across first, second, and advanced lines of treatment of CTCL. Single-agent therapy has been used, including retinoids, interferons, HDAC inhibitors, and chemotherapy; these therapies include methotrexate, bexarotene, glucocorticoids, cyclophosphamide, cisplatin, etoposide, bleomycin, doxorubicin, vincristine, and vinblastine.[26] Single-agent therapy can yield complete response rates up to 30%, but remissions are generally of short duration. Chemotherapy combined with other agents may induce remissions of pcALCL. More potent chemotherapy is complicated by immune deficiency, and infectious complications. Both methotrexate and bexarotene are approved by the FDA and are widely used treatments for CTCL across the diagnoses.[27]

Denileukin diftitox (ONTAK®) is a recombinant fusion protein combining human IL-2 with the membrane translocation and catalytic domain of diphtheria toxin. It targets and induces

apoptosis of IL-2 receptor-bearing cells. FDA approved denileukin diftitox for CTCL in 1999, denileukin diftitox was initially reported to have a 30% ORR with one-third of responders experiencing CR. Two recent follow-up studies[28, 29, 30, 31] describe complete responders with exceptionally durable responses of at least 5 and 9 years. Patients experiencing a PR to denileukin diftitox may receive further combination therapy with IFN, oral bexarotene, and chemotherapy or phototherapy.

Histone deacetylase inhibitors (HDACi) are a novel class of compounds that inhibit the enzyme HDAC, and thus inhibit the deacetylation of histone proteins associated with DNA and nonhistone proteins. Vorinostat is the first FDA-approved, oral HDACi for refractory CTCL. Vorinostat has not yet received EMA approval for CTCL. In two phase 2 trials, vorinostat 400 mg daily was found to be well tolerated and effective with an ORR of 24% to 30% among highly refractory patients. Responses were observed at all disease stages, including those diagnosed with Sézary syndrome and large cell transformation. Improvement in pruritus, a major clinical symptom, was noted as well.[20, 32, 33]

A second HDACi, romidepsin, is an intravenously administered bicyclic peptide that inhibits classes I and II HDACs with activity in not only CTCL, but also peripheral T-cell lymphoma (PTCL). A single-arm, open-label, multicenter, pivotal, phase 2 study of romidepsin for the treatment of refractory CTCL (stages IB–IVA) was recently completed. After 6 cycles of treatment, a response rate (RR) of 34% was observed in 96 evaluable patients (including 6 clinical CRs), and pruritus improved in 43%. Median time to response was 2 months. Romidepsin was granted approval by the FDA for treatment of patients with CTCL.[21]

Chemotherapy is reserved for relapsed and refractory disease and yields moderate to high response rates; however, response durations are short. Agents with notable activity include gemcitabine and liposomal doxorubicin. In a phase 2 study, gemcitabine showed a response rate of 53% and a CR rate of 22%. In a retrospective analysis of pegylated liposomal doxorubicin, the response rate was 88% (30 out of 34 patients) and approximately 43% had CR.[22, 34, 35]

1.4.2 Choice of Comparator

1.4.2.1 Bexarotene

Bexarotene (Targretin®) is approved in the United States and European Union for the treatment of patients who are refractory to at least 1 prior systemic therapy for cutaneous T-

cell lymphoma. In clinical trials, bexarotene was administered for up to 97 weeks. In patients with advanced CTCL, 49% of patients achieved an objective response (complete and partial responses) to treatment with any dose of bexarotene. Patient response rates were 45% at a dose of 300 mg/m^2/day PO and 55% at doses > 300 mg/m^2/day PO. Responses were seen in patients with erythrodermic CTCL (mycosis fungoides) and Sézary syndrome. Median time to best response was 180 days and these responses were durable for a median of 299 days at bexarotene doses of 300 mg/m^2/day PO. Median time to response was shorter and the duration of response was longer with doses > 300 mg/m^2/day PO but the incidence of side effects increased substantially at the higher doses.[36]

1.4.2.2 Methotrexate

Methotrexate (MTX, amethopterin) is a folate antimetabolite. It is an analog of aminopterin, which is also derived from folic acid, and is approved for the treatment of patients with CTCL. Methotrexate is a standard of care in early and advanced CTCL. Although low-dose methotrexate has been used to treat mycosis fungoides for many years, documentation is very limited. In a retrospective study of 69 patients with patch/plaque and tumor stage mycosis fungoides patients were observed for up to 201 months. The greatest number of patients (60) had patch/plaque stage T2 disease (≥ 10% skin involved). Of these, 7 (12%) achieved complete remission and 13 (22%) achieved partial remission for a total response rate of 20 of 60 (33%). The median time to treatment failure was 15 months. Only 1 of 7 patients with tumor stage disease responded. Adverse events resulted in treatment failure in 6 (9%) of the total cohort of 69 patients.[37, 38]

1.4.3 Summary of Study Rationale

CTCL is a rare tumor that presents an unmet need; most therapies are associated with response rates of 30% to 49%. Though chemotherapy regimens tend to have higher response rates, the duration of response is often short lived. More effective therapeutic options, with improved toxicity profiles, are needed. The CTCL disease subtypes chosen for inclusion in this study constitute the majority of CD30-positive CTCL.[4] CD30 expression is a diagnostic criteria in lymphamatoid papulosis and primary cutaneous anaplastic lymphoma, and CD30 expression is reported in MF. Selected diseases have a similar clinical course of disease: they are indolent and incurable. They share a common treatment goal: reduction in tumor burden (CR and PR) and symptomatic relief. The treatment modalities are similar. In addition the number and types of prior systemic therapies is generally not considered to influence sensitivity to subsequent therapy, and patient can be retreated with the same agents.

Although a number of treatments have shown efficacy in the symptomatic management of CTCL, response durations are short and many patients with advanced disease rapidly become refractory to therapy, presumably because of drug resistance. Other intensive lymphoma salvage regimens likewise have demonstrated responses, albeit with significant immunosuppression-related toxicity.

Brentuximab vedotin is a novel ADC directed against the CD30 surface antigen expressed on hematologic malignancies including some types of CTCL. Preclinical studies of brentuximab vedotin demonstrated antitumor activity in both in vitro and in vivo models. Currently brentuximab vedotin as monotherapy in relapsed/ refractory patients with CD30+ systemic ALCL and Hodgkin lymphoma has been studied in two phase 1 studies and 2 pivotal phase 2 studies, for a total of more than 300 patients who have completed brentuximab vedotin therapy.

Building on these data as well as the robust results of a phase 2 study of the cAC10 antibody component alone in CD30+ CTCL, we propose a study designed to investigate if brentuximab vedotin, a novel targeted antibody-drug conjugate agent, could increase efficacy in patients with CD30+ MF or pcALCL.

1.5 Potential Risks and Benefits

Brentuximab vedotin had been shown to be therapeutically active in CD30+ hematological malignancies. A phase 1, single-arm, open-label, dose escalation study of brentuximab vedotin was conducted in patients with CD30+ hematologic malignancies (SG035-0001). Brentuximab vedotin was generally well tolerated at doses of up to 1.8 mg/kg in this study and induced multiple objective responses in these heavily pretreated patients. Complete and partial responses were achieved by 10 patients treated at the 1.2-, 1.8-, or 2.7-mg/kg dose level with the following diagnoses: HL (8 of 20 patients; 3 CR, 5 PR) and systemic ALCL (2 CR in 2 patients). In addition, clinical benefit (defined as CR, PR, or SD) was achieved in 86% of patients treated at 1.2, 1.8, and 2.7 mg/kg.

Study SG035-0003, a phase 2 trial of brentuximab vedotin evaluated 1.8 mg/kg administered intravenously every 3 weeks in a relatively homogeneous population of 102 adult HL patients whose lymphoma had relapsed or was refractory to multiple-agent, high-dose chemotherapy and autologous SCT. A 75% ORR (representing the predefined primary endpoint of the trial) with a durability of 6.7 months was observed. A substantial proportion (34%) of all treated patients obtained a complete remission as manifested by no evidence of lymphoma by clinical, laboratory, or radiographic measures. Observed CRs

were durable, with the median duration not reached and a lower 95% confidence interval bound of 8.8 months. Achievement of CR in lymphoma is highly correlated with prolonged survival after a subsequent alloSCT, and this potentially curative treatment option was enabled in a meaningful fraction of HL patients treated in the pivotal study.

In a preplanned analysis of PFS per investigator assessment in which each patient served as his or her own control, PFS with brentuximab vedotin was nearly twice that of the most recently delivered treatment. Analysis of transplant ineligible patients in phase 1 studies demonstrated clinical benefit in the pretransplant setting.

Study SG035-0004, a phase 2 study of brentuximab vedotin 1.8 mg/kg administered intravenously every 3 weeks in 58 patients 12 years of age or older with sALCL, an ORR of 86% was observed and 53% of patients obtained a CR as manifested by no evidence of lymphoma by clinical, laboratory, or radiographic measures. The ability to attain a second CR or achieve a first CR after the failure of frontline therapy enables an improved opportunity for SCT, an exploratory yet potentially curative treatment.

The recommended dose of brentuximab vedotin is 1.8 mg/kg administered intravenously every 3 weeks for a minimum of 8 treatment cycles for those patients who achieve stable disease or better; there is clinical experience with treating patients through 16 cycles. At this dose and schedule, the most common adverse events observed were peripheral sensory neuropathy, fatigue, nausea, diarrhea, pyrexia, upper respiratory tract infection, neutropenia, and vomiting. These events were primarily mild to moderate in severity.

The most notable adverse event associated with brentuximab vedotin was peripheral neuropathy, which tended to increase in severity with longer duration of therapy, consistent with what is observed with other antimicrotubule agents such as vinca alkyloids or taxanes. The majority of peripheral neuropathy events were Grade 1 to 2 and were manageable by dose delay and reduction. Further information on the management of peripheral neuropathy events is provided in Table 6-3.

Severe and prolonged (≥ 1 week) neutropenia can occur with brentuximab vedotin, which may increase the risk of patients developing serious infections. The median duration of Grade 3 or 4 neutropenia was limited (1 week); 2% of patients had Grade 4 neutropenia that lasted ≥ 7 days. Less than half of the patients in the phase 2 population with Grade 3 or 4 neutropenia had temporally associated infections, and the majority of temporally associated infections were Grade 1 or 2. Complete blood counts should be monitored prior to

administration of each dose of brentuximab vedotin. Events of Grade 3 or 4 neutropenia should be managed according to best medical practice.

Infusion-related reactions are possible with brentuximab vedotin, especially related to the development of clinically significant titers of antitherapeutic antibodies (ATA). Premedication prior to the infusion of brentuximab vedotin will not be required in Cycle 1, but is allowed in subsequent cycles, if indicated. Patients must be monitored for the possibility of an acute reaction during brentuximab vedotin administration.[39]

Progressive multifocal leukoencephalopathy (PML) has been reported with brentuximab vedotin use. PML is a rare demyelinating disease of the brain that is caused by the John Cunningham virus (JCV). It typically occurs in immunocompromised individuals and can be fatal. Presenting features may include altered mental status, motor deficits such as hemiparesis or ataxia, visual disturbances, or higher cortical dysfunction such as dysphasia or agnosia. Seizures have also been reported in PML patients (approximately 20%). The onset of neurological deficits may occur over weeks to months.[40] Cognitive decline without accompanying deficits in motor or sensory function is uncommon. Optic nerve involvement, fever, and spinal cord disease are not typically associated with PML. In addition, peripheral neuropathy, which has been reported with brentuximab vedotin treatment, is not commonly reported with PML. If PML is suspected, a diagnostic work-up should be performed, as described in Section 6.8.5.

Acute pancreatitis has been reported in patients treated with brentuximab vedotin and has contributed to fatal outcomes in some cases. Onset typically occurred after 1 to 2 doses of brentuximab vedotin. Early symptoms included severe abdominal pain, nausea, and vomiting. Some of the pancreatitis cases were complicated by other possible contributory factors, including cholelithiasis and alternate etiologies (eg, pancreatic lymphoma progression, displacement of bile duct stent, etc).

Concomitant use of brentuximab vedotin and bleomycin is contraindicated due to pulmonary toxicity. In a clinical trial that studied brentuximab vedotin with bleomycin as part of a combination regimen, the rate of noninfectious pulmonary toxicity was higher than the historical incidence reported with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). Patients typically reported cough and dyspnea. Interstitial infiltration and/or inflammation were observed on radiographs and computed tomographic imaging of the chest. Most patients responded to corticosteroids.

The clinical laboratory parameters for which the most patients had new or worsening shifts to ≥ Grade 3 were low neutrophils (11%), lymphocytes (11%), platelets (6%), leukocytes (5%), and high glucose (6%). Only 1 patient in the phase 2 studies had Grade 3 ALT and AST.

Any treatment directed towards blocking immune function may contribute to malignancy and infections; patients are to be monitored for these events during the treatment period and up to and including 30 days after the last dose of study medication. Additional information on risk minimization and assessment strategies to be used in this study is provided in Section 6.8.

Preliminary population PK analyses of the effects of brentuximab vedotin on renal and hepatic function suggest that no dose adjustments are necessary for patients with renal or hepatic impairment. Additional analysis is planned to more fully characterize the pharmacokinetics in this patient population.

The effects of brentuximab vedotin on embryogenesis, reproduction, and spermatogenesis in humans are unknown. In addition, data about the effects of brentuximab vedotin in pregnant women are unavailable. Female patients of childbearing potential are advised to use adequate and effective contraception during brentuximab vedotin treatment and for a 30-day period thereafter. Male patients are advised to use adequate and effective contraception during treatment with brentuximab vedotin and for 6-months thereafter.

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements (including International Conference on Harmonisation [ICH] guidelines).

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective is:

- To determine ORR, lasting at least 4 months, with brentuximab vedotin in patients with CD30+ MF or pcALCL compared to that achieved with therapy in the control arm

2.2 Secondary Objectives

The key secondary objectives are:

- To determine complete response (CR) rate with brentuximab vedotin compared to that achieved with therapy in the control arm
- To determine progression-free survival (PFS) with brentuximab vedotin compared to that achieved with therapy in the control arm
- To determine burden of symptoms during treatment with brentuximab vedotin compared to that achieved with therapy in the control arm

Other secondary objectives include:

- To assess duration of response with brentuximab vedotin
- To assess duration of skin response with brentuximab vedotin
- To determine event-free survival (EFS) with brentuximab vedotin compared to that achieved with therapy in the control arm
- To describe the PK of brentuximab vedotin and monomethylauristatin E (MMAE) in blood
- To determine the immunogenicity of brentuximab vedotin
- To assess patient-reported quality of life outcomes
- To assess the safety of brentuximab vedotin

2.3 Exploratory Objectives

The exploratory objectives include:

CCI

CCI

[redacted]

3. STUDY ENDPOINTS

3.1 Primary Endpoint

- Proportion of patients achieving an objective response that lasts at least 4 months, as determined by an independent review of global response score consisting of skin evaluations (modified severity weighted assessment tool [mSWAT] assessment), nodal and visceral radiographic assessment, and detection of circulating Sézary cells.

3.2 Secondary Endpoints

The key secondary endpoints are:

- Proportion of patients achieving CR
- Progression-free survival
- Changes in symptom domain per Skindex-29 questionnaire

Other secondary endpoints include:

- Adverse events (AEs) according to National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) Common Terminology Criteria for AEs version 4.03, serious adverse events (SAEs), assessments of clinical laboratory values
- Duration of response
- Duration of response in skin

- Event-free survival
- Blood concentrations of brentuximab vedotin and MMAE
- Immunogenicity assessment
- Quality of life assessments per Skindex-29 and FACT-G questionnaire

3.3 Exploratory Endpoints

The exploratory endpoints include:

CCI

[redacted]

4. STUDY DESIGN

4.1 Overview of Study Design

This is an open-label, randomized, multicenter study. All patients must have a diagnosis of MF or pcALCL and histologically-confirmed CD30+ disease by central laboratory assessment and pathology review. Patients are to be stratified by diagnosis: pcALCL or MF. Patients will enter 1 of 2 treatment arms:

- **Arm 1**: brentuximab vedotin monotherapy

  Brentuximab vedotin (1.8 mg/kg) will be administered intravenously over approximately 30 minutes once every 21 days and may continue as monotherapy for up to a total of 16 cycles (48 weeks).

- **Arm 2**: methotrexate (MTX) or bexarotene per physician's choice, up to a total of 48 weeks treatment.

  Methotrexate will be administered orally (5 to 50 mg) once weekly. Dose adjustment is guided by patient response and toxicity.

  OR

  Bexarotene will be administered orally (300 mg/m^2 recommended total dose per guidelines in Figure 6-1) once daily with meals.

Investigators are advised to consider a patient's prior treatment with reference therapy. It is recommended that patients who were last treated with methotrexate be treated with bexarotene, and patients who last received bexarotene be treated with methotrexate.

Objective response, lasting at least 4 months (ORR4), per independent review facility (IRF), will be assessed by global response score (GRS), which consists of skin evaluation (mSWAT assessment), 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 end of treatment (EOT). All treated patients without disease progression at EOT/ET will then be followed for objective response every 12 weeks for a minimum of 24 months, and then every 6 months; or until disease progression or study closure. CR or PR per GRS will be confirmed by sustained response in skin per mSWAT assessment at the subsequent cycle. Additional unscheduled GRS determinations may occur following a change in response in skin or at the time of a CT scan.

All randomized patients will also be followed for survival every 12 weeks for a minimum of 24 months after the EOT visit, and then every 6 months until patient withdrawal, death, or study closure. Safety will be evaluated by the incidence of treatment-emergent adverse events (TEAEs), severity and type of AEs, and by changes from baseline in the patient's vital signs, ECOG performance status, and clinical laboratory results using the safety population.

Patients with documented PR or CR at the end of Cycle 3 and at any disease assessment thereafter, may continue treatment with study drug for up to 16 cycles with brentuximab vedotin or 48 weeks with bexarotene or methotrexate; patients with stable disease may continue therapy at the discretion of the investigator. Patients with progressive disease at any time during the study will be discontinued from study treatment (Section 7.7). Patients with increasing mSWAT prior to 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 disease progression.

Disease progression will be assessed using the response criteria included in Olsen et al, 2011, and Kempf et al, 2011[11, 41]. As described in Section 7.4.16, efficacy will be assessed per IRF, using a global response score, which consists of skin evaluation (modified severity weighted assessment tool [mSWAT] assessment), nodal and visceral radiographic assessment, and detection of circulating Sézary cells.

FDG-PET scans and CT scans of the neck, chest, abdomen, and pelvis will be performed at screening. FDG-PET scans taken within 8 weeks before signing the informed consent form (ICF) may be used as the screening FDG-PET. FDG-PET scans will not be taken after screening unless clinically indicated. CT scans taken within 4 weeks before signing the ICF may be used as the screening CT scan if all of the following conditions are met:

- There is no nodal or visceral disease involvement noted
- There is no clinically evident lymphadenopathy or splenomegaly by physical exam at the time of screening
- The scan meets all quality criteria as outlined in the Imaging Manual

For patients without nodal or visceral involvement as determined by baseline CT scans, CT scans will be performed during the cycle following the first skin response, ideally corresponding to the confirmation of the skin response, and 6 cycles (a minimum of 4 months) after that confirmed skin response. Repeat CT scans will be performed if there is a question of new or progressive disease in the lymph node or viscera. For patients with baseline nodal/visceral disease, CT scans will be performed 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 per the follow-up schedule until disease progression, or if there is a question of new or progressive disease in the lymph node or viscera. CT scans will be performed at EOT for all patients with baseline nodal/visceral disease if the previous scan was performed more than 8 weeks before EOT.

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. In addition, lymphoma response and progression will be assessed by an independent review facility (IRF).

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[redacted]

Toxicity will be evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective date 14 June 2010.[42]

AEs will be assessed, and laboratory values and vital signs will be obtained to evaluate the safety and tolerability of brentuximab vedotin.

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4.2 Number of Patients

Approximately 124 patients (approximately 62 per treatment arm) will be enrolled in this study from approximately 50 study centers globally. A minimum of 30 patients (15 per treatment arm) with pcALCL will be enrolled. Enrollment is defined as randomization to a treatment arm. Patients will be stratified by diagnosis in each treatment arm (pcALCL or MF).

4.3 Duration of Study

Patients who achieve a response (CR or PR) may receive brentuximab vedotin up to 16 cycles (48 weeks) or reference therapy for up to 48 weeks. Patients with stable disease may continue therapy (maximum 16 cycles brentuximab vedotin or 48 weeks reference therapy) at the discretion of the investigator. For all patients who complete either 48 weeks of dosing in the control arm or 16 cycles of brentuximab vedotin, an attempt to discontinue therapy should be made following EOT. For patients who complete 48 weeks of reference therapy, initiation of subsequent standard-of-care therapy should be discussed with the study sponsor. For patients who complete 16 cycles of brentuximab vedotin, access to brentuximab vedotin may be permitted in accordance with local regulatory requirements and at the joint discretion of the sponsor and investigator.

To permit the detection of any delayed treatment-related AEs, patients will be followed for 30 days after the last dose of study medication. Posttreatment assessments of disease response will be conducted every 12 weeks for a minimum of 24 months after EOT, and then every 6 months; or until progressive disease or study closure. All randomized patients will also be followed for survival every 12 weeks for a minimum of 24 months after the

EOT visit, then every 6 months until patient withdrawal, death, or study closure. Information may be collected by phone for patients with progressive disease.

The final analyses for the clinical study report will be performed 10 months after the last patient is enrolled (ie, approximately 34 months from the start of study). The updated analyses on the efficacy endpoints will be conducted after all patients enrolled in the study have had the opportunity to complete 16 cycles of treatment with brentuximab vedotin or 48 weeks of treatment with reference therapy and 24 months of posttreatment follow up, and will be included in an addendum to the clinical study report.

The total study duration will be approximately 5 years, including an anticipated enrollment duration of 24 months.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be randomized to treatment:

1. Male or female patients 18 years or older with diagnosis of MF or pcALCL.

2. Histologically-confirmed CD30+ disease by central laboratory assessment and pathology review. Tissue from at least 2 lesion biopsies for MF and 1 lesion biopsy for pcALCL performed at screening must be available for confirmation of CD30 positivity, 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; patients with MF who have received at least 1 prior systemic therapy.

4. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (refer to Section 15.1).

5. Female patients 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 30 days 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 subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

   Male patients, 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 subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)

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, including PK sampling.

8. Clinical laboratory values as specified below within 4 days before randomization (laboratory values may be performed locally.):

   - Total bilirubin must be $< 1.5 \times$ the upper limit of normal (ULN).
   - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) must be $< 3 \times$ the upper limit of the normal range. AST and ALT may be elevated up to

5 times the ULN if their elevation can be reasonably ascribed to the presence of metastatic disease in liver.

- Creatinine clearance or calculated creatinine clearance > 40 mL/minute.

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.

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not eligible for participation:

1. A concurrent diagnosis of systemic ALCL, or other non Hodgkin lymphoma (excluding lymphomatoid papulosis [LyP]).

2. A concurrent diagnosis of Sézary syndrome or B_2 disease.

3. 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 Section 15.2).

   - Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure (CHF), angina, or electrocardiographic evidence of acute ischemia or clinically significant conduction system abnormalities.

4. 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.

5. Known active cerebral/meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy (PML).

6. Known HIV infection.

7. Known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection.

8. Any severe active systemic viral, bacterial, or fungal infection within 1 week prior to first study drug dose requiring systemic antimicrobial therapy. (Oral antibiotics for prophylaxis are allowed.)

9. Receiving antibody-directed or immunoglobulin-based immune therapy (eg, immunoglobulin replacement, other monoclonal antibody therapies) within 12 weeks of first study drug dose.

10. Corticosteroid therapy for the treatment of CTCL within 3 weeks of first dose of study drug.

11. Known hypersensitivity to recombinant proteins, murine proteins, or any excipient contained in the drug formulation.

12. Female 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 of any cycle.

13. Treatment with radiotherapy or other skin-directed therapy or any investigational products within 3 weeks before the first dose of study drug.

14. Progressed on prior therapy with both bexarotene and methotrexate.

15. Oral retinoid therapy for any indication within 3 weeks of the first dose of study drug.

16. Systemic therapy with Vitamin A in doses of greater than 15,000 IU (5,000 mcg) per day (equivalent to approximately 3 times RDA) within 3 weeks before the first dose of study drug.

17. 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), or elevated lipase value ≥ 3 × ULN with an amylase level > ULN at screening.

18. 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.

19. Previous receipt of brentuximab vedotin.

6. STUDY DRUG

Patients will be randomized in a 1:1 ratio to receive study treatment with either Arm 1: brentuximab vedotin, or Arm 2: bexarotene or methotrexate (for bexarotene-treated patients, study treatment will include pretherapy with fenofibrate, per Section 6.2.2). All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

6.1 Brentuximab vedotin Administration

Study treatment will be administered by 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 treatment 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.

6.2 Reference/Control Therapy

6.2.1 Methotrexate

Methotrexate will be given once weekly as a single dose of 5 to 50 mg orally. Dosages may be gradually adjusted to achieve optimal clinical response but must not exceed 50 mg/week. Once optimal clinical response is achieved, the methotrexate dosage should be decreased to the lowest effective dose. For patients deriving benefit, methotrexate dosing should be continued up to 48 weeks. For further dose modification guidelines, refer to the methotrexate product label.

Further Guidelines for Methotrexate Use

Methotrexate cytotoxicity is highly dependent on the absolute drug concentration and the duration of drug exposure. MTX is actively transported across cell membranes. At serum methotrexate concentrations exceeding 0.1 μmol/mL, passive diffusion becomes a major means of intracellular transport of MTX. The drug is widely distributed throughout the body with the highest concentration in the kidney, liver, spleen, gallbladder, and skin. After oral administration, approximately 60% of a 30-mg/m^2 dose is rapidly absorbed from the GI tract, with peak blood levels at 1 hour. Even at low doses absorption may be very erratic, varying between 23% and 95%. MTX is excreted primarily by the kidneys via glomerular filtration and active secretion into the proximal tubules. Renal clearance usually equals or exceeds creatinine clearance. Small amounts are excreted in the feces.

Methotrexate Toxicity

When MTX toxicity occurs, the dosage should be modified.

- A 50% dose reduction of MTX is indicated when severe mouth ulcerations occur.

Dose modifications for hyperbilirubinemia are described in Table 6-1.

Table 6-1 Methotrexate Dose Modifications for Hyperbilirubinemia

Severity	Methotrexate Action
Total bilirubin > 1.5 - ≤ 3 mg/dL with an abnormal direct bilirubin	Reduce MTX to 50% of previous dose
Total bilirubin > 3 - ≤ 5 mg/dL	Reduce MTX to 25% of previous dose
Total bilirubin > 5 mg/dL	Discontinue MTX

Reported MTX-associated toxicities, categorized by frequency and onset time relative to MTX dosing, are presented in Table 6-2.

Table 6-2 Methotrexate-Associated Toxicities

	Common (> 10%)	Occasional (1%-10%)	Rare (< 1%)
Immediate: Within 1-2 days of receiving drug	Transaminase elevations	Nausea, vomiting, anorexia	Anaphylaxis, chills, fever, dizziness, malaise, drowsiness, blurred vision, acral erythema, urticaria, pruritus, toxic epidermal necrolysis, Stevens-Johnson Syndrome, tumor lysis syndrome, seizures, photosensitivity
Prompt: Within 2-3 weeks, prior to the next course		Myelosuppression, stomatitis, gingivitis, photosensitivity, fatigue	Alopecia, folliculitis, acne, renal toxicity (ATN, increased creatinine/BUN, hematuria), enteritis, GI ulceration and bleeding, acute neurotoxicity (headache, drowsiness, aphasia, paresis, blurred vision, transient blindness, dysarthria, hemiparesis, decreased reflexes) diarrhea, conjunctivitis
Delayed: Any time later during therapy, excluding the above conditions		Learning disability	Pneumonitis, pulmonary fibrosis, hepatic fibrosis, osteonecrosis, leukoencephalopathy, pericarditis, pericardial effusions, hyperpigmentation of the nails
Late: Any time after the completion of therapy			Progressive CNS deterioration
Unknown Frequency and Timing	Methotrexate crosses the placenta. Fetal toxicities and teratogenic effects of methotrexate have been noted in humans. The toxicities include: congenital defects, chromosomal abnormalities, severe newborn myelosuppression, low birth weight, abortion, and fetal death. Methotrexate is excreted into breast milk in low concentrations		

6.2.2 Bexarotene

The risks of bexarotene therapy should be considered by the investigator when selecting an appropriate Arm B treatment. The recommended total dose of bexarotene capsules is 300 mg/m^2/day. The Mosteller formula or the Dubois and Dubois formula should be used for all body surface area (BSA) determinations for each patient, and are provided in Section 15.2. Dosage should be rounded to the nearest 75 mg. Bexarotene capsules should be taken as a single oral daily dose with a meal. The dose of bexarotene may be reduced to 200 mg/m^2/day PO then to 100 mg/m^2/day PO, or temporarily suspended, if clinical toxicity occurs. When toxicity is controlled, doses may be restarted and carefully increased. Bexarotene capsules should be continued as long as the patient is deriving benefit, up to 48 weeks. For further dose modification guidelines, refer to the bexarotene product label.

Further Guidelines for Bexarotene Use

Hypertriglyceridemia of all grades has been recorded in 79% of patients who took bexarotene in a study in early-stage CTCL; hypercholesterolemia occurred in 48% of patients; and hypothyroidism in 40%. Similarly, in a study in advanced-stage CTCL, the incidence of hyperlipidemia of all grades (primarily hypertriglyceridemia) with bexarotene was 82%, hypercholesterolemia was 30%, and hypothyroidism was 29%. Before initiating bexarotene therapy, a patient history should be taken to identify those with familial hypertriglyceridemia, uncorrected hypothyroidism, an individual or family history of myocardial infarction or cardiovascular events, or a history of diabetes. A minority of patients with familial hypertriglyceridemia cannot tolerate bexarotene and should be considered for alternative therapy. A substantial proportion of patients will have pathology related to cardiovascular atherosclerosis or a history of cardiovascular disease and have hypertriglyceridemia that will need to be treated before bexarotene therapy. In addition, those with coronary heart disease are likely to have active atherosclerotic plaques that should be stabilized with low-dose statin therapy (eg, 10 mg daily) 3 days before beginning bexarotene. Diabetes can also contribute to the development of coronary heart disease and should be controlled. These groups of at-risk patients are identified by elevated plasma lipid levels and should be monitored particularly closely during treatment, with measurement of fasting lipid levels at weekly intervals for as long as necessary until it becomes apparent that these are stabilized reliably at the levels recommended.

Prior to dosing with bexarotene, attempts should be made to obtain triglyceride levels that meet the normalized lipid levels per the United States Prescribing Information (USPI)

guidelines. Baseline free T4, TSH and fasting levels of triglycerides, LDL-cholesterol, and HDL-cholesterol should be obtained in all patients being considered for bexarotene treatment and, if elevated, these should be normalized before the therapy is initiated. Ideally, normalization of lipid levels should be achieved through lifestyle changes: adopting a healthy diet low in calories, sugar, saturated fat, and alcohol, and high in fiber and unsaturated fat, along with increased exercise, and weight loss in obese patients. However, achieving compliance with lifestyle changes is difficult and, particularly in a patient with rapidly progressing CTCL, the physician may wish to begin bexarotene therapy as soon as possible. Many patients will therefore require therapy with lipid-lowering agents, such as a fibrate or high-dose omega-3 fatty acids for high triglycerides, a statin to normalize high LDL-cholesterol.[43]

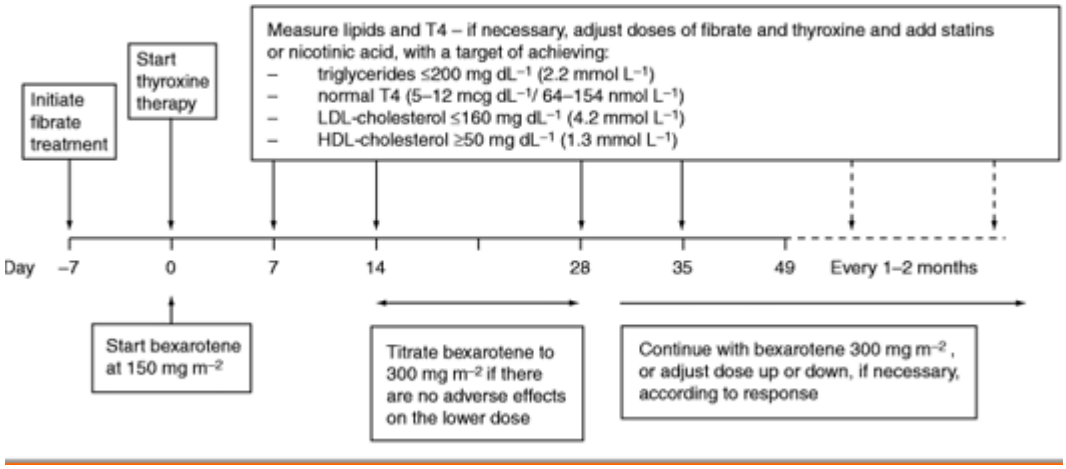
All patients (with normal or normalized triglyceride levels) who are to be given bexarotene should receive 7 days of pretherapy with fenofibrate 145 to 200 mg daily (the dose should be reduced to 100 mg or even 50 mg daily if creatinine is > 1.5 mg dL-1/0·133 μmol L-1, or in nephrotic syndrome). The fibrate gemfibrozil is not recommended for administration with oral bexarotene, as it results in higher plasma levels of bexarotene and an elevation of triglycerides. Fibrates are contraindicated in patients with liver and kidney failure and in pregnancy, and they potentiate the action of warfarin. They are also associated with a number of reversible adverse effects, including increased liver transaminases and muscular creatine kinase, which may lead to muscle pain. Should these events occur, fibrate treatment should be discontinued.

Most patients do not require a statin at this stage, as the increase in triglycerides with bexarotene therapy is generally more problematic than the increase in LDL-cholesterol level. In addition, patients should be advised on dietary and lifestyle changes that may help to reduce the need for lipid-lowering drugs during treatment.

Bexarotene therapy results in a dose-related reduction in thyroid hormone levels through an initial, rapid suppression of TSH gene expression, which leads to central hypothyroidism. This effect is reversible within several days of cessation of therapy. While measurement of TSH levels can provide a useful tool to assess patient compliance, it is essential to monitor free T4 and to keep this hormone within the normal range. At the recommended dose of 300 mg/m^2 daily, most patients experience a decrease in free T4 concentration to ≥ 25% below the normal range, and TSH decreases to the low-normal or even subnormal levels. In anticipation of this, low-dose thyroxine (levothyroxine 0.05 mg daily) should be initiated along with the bexarotene. Correcting hypothyroidism with hormone replacement during

bexarotene therapy will ease hypertriglyceridemia by increasing lipid clearance and can stabilize triglyceride levels. In addition, patients feel less fatigued if thyroxine is supplemented. Based on measurements of free T4, fasting cholesterol, and triglycerides at Days 7, 14, 28, 35, and 49 after initiation of bexarotene therapy, the doses of thyroxine and lipid-lowering therapy should be adjusted as necessary with the target of achieving normal levels of T4 5-12 µg dL^{-1} (64-154 nmol L^{-1}), triglycerides ≤ 200 mg dL^{-1} (2.2 mmol L^{-1}), LDL-cholesterol ≤ 160 mg dL^{-1} (4·2 mmol L^{-1}), and HDL-cholesterol ≥ 50 mg dL^{-1} (1·3 mmol L^{-1}). As patients on bexarotene may metabolize T4 more rapidly, the final daily dose of thyroxine required to keep free T4 within the normal range may be as high as 0.20 to 0.25 mg daily, depending on the patient's age and weight. Monitoring of lipids and free T4 should continue subsequently every 1 to 2 months during treatment. If the bexarotene dose is modified at any time, the doses of thyroxine and antilipid therapy will need to be adjusted accordingly.[36, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59]

Figure 6-1 Bexarotene Risk Mitigation



Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Suggested approach to minimize adverse events with bexarotene in patients with cutaneous T-cell lymphoma with normal (or normalized) free thyroxine (T4), fasting triglyceride and cholesterol levels at start of therapy.[43]

6.3 Dose Escalation Rules

No dose escalation of brentuximab vedotin (Arm 1) is permitted in this study. However, in Arm 2 (control arm), the dose of methotrexate or bexarotene may be escalated per treating physician as detailed in the methotrexate or bexarotene product label.

6.4 Dose-Modification Guidelines

Dose modifications specific to peripheral neuropathy for patients receiving brentuximab vedotin are described in Table 6-4 in Section 6.4.2, Criteria for Dose Reduction.

6.4.1 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

Treatment with brentuximab vedotin or reference therapy will use a cycle length of 21 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be $\geq 1{,}000/mm^3$
- All other study drug-related toxicity must have resolved per the guidelines provided in Table 6-3 and Table 6-4.

If the patient fails to meet the criteria for retreatment cited previously, initiation of the next cycle of treatment should be delayed up to 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. The start of the next cycle may be delayed for up to 3 weeks if additional time is required for the patient to recover from study treatment-associated toxicity experienced during the current cycle. Delays of greater than 3 weeks are prohibited without approval of the sponsor.

6.4.2 Criteria for Dose Reduction

Brentuximab vedotin

Intrapatient dose reduction to 1.2 mg/kg brentuximab vedotin will be allowed depending on the type and severity of toxicity. Please refer to Table 6-3 and Table 6-4 for further information.

When a dose reduction of brentuximab vedotin is required, no re-escalation of dose will be permitted.

Reference Therapy

Please refer to Section 6.2 for drug-specific dose reduction guidelines for methotrexate and bexarotene, respectively.

Table 6-3 Recommended brentuximab vedotin Dose Modifications for Treatment-Associated Toxicity Excluding Neuropathy

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non-hematologic (excluding neuropathy)	Continue at same dose level.	Continue at same dose level.	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 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]
Hematologic	Continue at same dose level.	Continue at same dose level.	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 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]

Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03

a Patients who develop Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption. Brentuximab vedotin will be held for clinically meaningful Grade 3 or 4 electrolyte abnormalities.

b Patients who develop Grade 3 or 4 lymphopenia may continue study treatment without interruption.

Table 6-4 Recommended brentuximab vedotin Dose Modifications for Treatment-Emergent or Worsening Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Sensory or Motor Neuropathy (Signs and Symptoms [abbreviated description of CTCAE])	Modification of Dose and Schedule
Grade 1 (Asymptomatic; clinical or diagnostic observations only; intervention not indicated; paresthesia and/or loss of deep tendon reflexes)	Continue with the same dose and schedule
Grade 2 (Moderate symptoms; limiting instrumental activities of daily living) Grade 3 (Severe symptoms; limiting self care activities of daily living)	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 (life-threatening consequences; urgent intervention indicated)	Discontinue treatment
Grade 5 (Death)	

Grading based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v. 4.03; see neuropathy; peripheral motor neuropathy; peripheral sensory neuropathy.

6.4.3 Discontinuation of Study Drug Due to Toxicity

Brentuximab vedotin

Please refer to Table 6-3 and Table 6-4 for further information.

Reference Therapy

Methotrexate or bexarotene should be discontinued per institutional standards or local product label, as applicable.

6.5 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 disease progression)

- Systemic or topical corticosteroids for the treatment of CTCL

6.6 Permitted Concomitant Medications and Procedures

Patients may receive concomitant hormonal therapy provided they have been on a stable dosage for at least 1 month prior to 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.

6.7 Precautions and Restrictions

It is not known what effects brentuximab vedotin has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

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 informed consent form through 30 days after the last dose of study drug, or

- Practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

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

- Practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or

- Practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

6.8 Management of Clinical Events

6.8.1 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-HT_3 receptor antagonists should be tried first.

6.8.2 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.

6.8.3 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 prior to 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.

6.8.4 Management of Peripheral Neuropathy

Adverse events of peripheral neuropathy will be monitored closely throughout the study. These events may include, but are not limited to peripheral sensory neuropathy, peripheral motor neuropathy, pareaesthesia, hypoaesthesia, polyneuropathy, muscular weakness, and demyelinating polyneuropathy. Such events, 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. Events that are greater than Grade 1 in severity will result in dose interruption, reduction, or discontinuation. Guidelines for brentuximab vedotin dose modification in the event of peripheral neuropathy are shown in Table 6-4.

6.8.5 Management of Progressive Multifocal Leukoencephalopathy

Signs and symptoms of progressive multifocal leukoencephalopathy (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 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.

6.9 Blinding and Unblinding

This is an open-label study; investigators and patients will know the individual treatment assignments. However, aggregate efficacy results by treatment group will be blinded to the study team, investigators, patients, and IRF, throughout the study conduct.

6.10 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 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, USP, yields 11 mL of brentuximab vedotin solution (5 mg/mL).

6.11 Preparation, Reconstitution, and Dispensation

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

Study treatment 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 Study 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 treatment must be reconstituted with the appropriate amount of Sterile Water for Injection, USP (see Pharmacy Manual for details). GENTLY swirl the vial until the contents are completely dissolved. **The vial must not be shaken or vigorously swirled**; excess agitation may cause aggregate formation. Visually inspect the reconstituted drug product for any particulate matter and discoloration.

There are no known incompatibilities between study treatment and polyvinyl chloride (PVC), ethyl vinyl acetate (EVA), polyolefin, or polyethylene (PE) bags. The bag should be gently inverted to mix the solution. **The bag must not be shaken**; excess agitation may cause aggregate formation. Prior to administration, the reconstituted and diluted drug product should be inspected visually for any particulate matter and discoloration.

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.

6.12 Packaging and Labeling

Vials of study treatment 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.

6.13 Storage, Handling, and Accountability

Brentuximab vedotin

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

Study treatment does not contain preservatives; therefore, opened and reconstituted vials of study treatment must be used within 24 hours when stored under refrigeration at 2°C to 8°C. Reconstituted study treatment should not be stored at room temperature. It is recommended that study treatment 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.

Reference Therapy

Please refer to the methotrexate package insert for information regarding the proper storage and handling of methotrexate.

Please refer to the bexarotene package insert for information regarding the proper storage and handling of bexarotene.

Report all investigational product events, including complaints and issues, using the Investigational Product Complaints and reporting information listed in Section 11.11 in the protocol.

The drug supply must be kept in an appropriate, limited-access, secure place until it is dispensed to study enrollees, returned to the sponsor, or forwarded to the sponsor's designee for destruction. Drug supplies will be counted and reconciled at the site before being returned.

The investigator must maintain 100% accountability for all study medication received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if retest date is provided to the investigator
- Frequently verifying that actual inventory matches documented inventory
- Verifying that the drug accountability log is completed for the drug lot used to prepare each dose
- Verifying that all containers used are documented accurately on the log
- Verifying that required fields are completed accurately and legibly

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The investigator must maintain a current inventory (drug accountability log) of all study medication delivered to the site, inventory at the site, and patients' use records. This log must accurately reflect the drug accountability of the study medication at all times. The following information will be recorded at a minimum: protocol number and title, name of the investigator, site identifier and number, description of the study medication, expiry and/or retest date, date and amount dispensed, and the date and amount returned to the site by the patient, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each patient to whom study medication is dispensed.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform clinical study material accountability and reconciliation before

clinical study materials are returned to the sponsor or its designee for destruction. The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction, and copies will be sent to the sponsor.

The investigator will be notified of any expiry date or retest date extension of clinical study material during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical study materials for return to the sponsor or its designee for destruction. In the event of expiry date extension of supplies already at the study site, supplies will be relabeled with the new expiry date at the site. In such cases, the sponsor or its designee will prepare additional labels, certificates of analysis, and all necessary documentation for completion of the procedure at the sites.

Do not use or destroy the investigational product until you receive documented confirmation from Millennium stating the drug may be used or destroyed.

Drug accountability instructions are also provided in the Pharmacy Manual.

7. STUDY CONDUCT

This trial will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

7.1 Study Personnel and Organizations

The contact information for the Millennium project clinician for this study, the central laboratory and any additional clinical laboratories, the ICON CRO study team, and IVR vendor may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

7.2 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). It is not envisioned that prisoners (or other populations that might be subject to coercion or exploitation) will be enrolled into this study.

7.3 Treatment Group Assignments

Patients are to be stratified by diagnosis: pcALCL or MF. Patients will be randomized 1:1 to 1 of 2 treatment arms by interactive voice/web response system (IVRS/IWRS):

- Arm 1: brentuximab vedotin monotherapy: brentuximab vedotin will be administered intravenously over approximately 30 minutes once every 21 days, and may continue for up to 16 cycles.

- Arm 2: Patients receive either methotrexate PO (5-50 mg PO once weekly dose adjustment is guided by patient response and toxicity) or bexarotene (recommended total dose of 300 mg/m^2 PO once daily with meals) for up to a total of 48 weeks of treatment.

7.4 Study Procedures

Refer to the Schedule of Events for timing of assessments. Additional details are provided as necessary in the sections that follow.

7.4.1 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.

7.4.2 Patient Demographics

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

7.4.3 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 7.4.11.

7.4.4 Physical Examination

A physical examination will be completed per standard of care at the times specified in the Schedule of Events.

7.4.5 Patient Height

Height will be measured only during screening.

7.4.6 Patient Weight

Weight will be measured as specified in the Schedule of Events. Dosing with brentuximab vedotin 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 (Section 6.1).

7.4.7 Vital Signs

Vital sign measurements include blood pressure (determined with the patient in a seated position after the patient has been sitting quietly for 5 minutes), heart rate, and body temperature.

7.4.8 Pregnancy Test

A serum pregnancy test will be performed for women of childbearing potential at screening. Urine pregnancy tests will be performed prior to dosing on Day 1 of each cycle. Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations. The results of any pregnancy test must be negative before dosing on Day 1 of all cycles.

7.4.9 Skin Biopsy

Skin biopsies (at least 2 samples from separate lesions with a minimum of 2 mm diameter each for MF, and 1 sample for pcALCL) will be obtained at screening, following the mSWAT assessment, to confirm tumor-specific CD30+ expression, and again at the end of Cycle 3, and at time of disease progression (EOT or posttreatment follow-up visit).

7.4.10 Archived Tissue

If available and consistent with local regulations, tumor tissue collected at the time of original diagnosis (unstained slides or a paraffin-embedded block) will be obtained during screening after the patient has signed the informed consent form. The sample may be used in the evaluation of a diagnostic test to determine CD30 expression.

CCI

[redacted]

7.4.11 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will recorded in the eCRF from screening through 30 days after the last dose of study medication. See Section 6.5 and Section 6.6 for a list of medications and therapies that are prohibited and/or allowed during study treatment.

7.4.12 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the Schedule of Events. Refer to Section 10 for details regarding definitions, documentation, and reporting of pretreatment events, AEs, and SAEs. Changes in the severity of events relating to peripheral neuropathy will be recorded as described in Section 10.3.

7.4.13 Enrollment

A patient is considered to be enrolled in the study when randomized to a treatment arm.

Procedures for completion of the enrollment information are described in the Study Manual.

7.4.14 ECG

A 12-lead electrocardiogram (ECG) will be administered at the time points specified in the Schedule of Events.

7.4.15 Clinical Laboratory Evaluations

Clinical laboratory evaluations must be performed centrally at screening and per the Schedule of Events. For decisions regarding eligibility (values required within 4 days of randomization) and treatment, local hematology and chemistry results may be used. Sézary cell results must be available from the local lab to determine eligibility and treatment decisions. Handling and shipment of clinical laboratory samples will be outlined in the study manual.

Clinical Chemistry, Hematology, and Urinalysis

Blood samples for analysis of the following clinical chemistry and hematological parameters and urine samples for urinalysis will be obtained as specified in the Schedule of Events.

Hematology

- Hemoglobin
- Hematocrit
- Platelet count
- Leukocytes with differential
- Neutrophils (absolute neutrophil count [ANC])

Serum Chemistry

- BUN
- Creatinine
- Bilirubin (total)
- Urate
- Lactate dehydrogenase (LDH)
- Phosphate
- Gamma glutamyl transferase (GGT)
- Albumin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Glucose
- Sodium
- Potassium
- Calcium
- Chloride
- Carbon dioxide (CO_2)
- Magnesium
- Amylase
- Lipase

Urinalysis

- Turbidity and Color
- pH
- Specific gravity
- Protein
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Glucose
- Leukocytes

Lipid Panel

- Total Cholesterol
- HDL
- LDL
- Triglycerides

Thyroid Panel

- TSH
- Free T3
- Free T4

Immune Reconstitution Assessments

- Lymphocytes counts
- Phenotypic T, B, and NK cell subsets:
  - $CD4^+$ T cells counts
  - $CD8^+$ T cells counts
  - CD8/CD4 ratio
  - $CD19^+$ B cells counts
- NK cells ($CD3^-$ CD56 CD16+ vs. $CD3^-$ CD56 CD16-)

Other

- Hemoglobin A1C

7.4.16 Disease Assessment

A GRS of complete response (CR), partial response (PR), stable disease (SD), progressive disease (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. For the purpose of disease assessment in the control arm, a period of 3 weeks (21 days) is equivalent to 1 cycle.

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

- Cutaneous disease (mSWAT) (Section 7.4.17.1)
- Lymph node involvement (Section 7.4.17.2)
- Visceral involvement (Section 7.4.17.2)
- Blood (MF patients only) (Section 7.4.17.3)
  - Sézary cells will be enumerated by morphology and immunophenotyping

7.4.17 Response Assessments

7.4.17.1 Cutaneous Disease Response Assessment

7.4.17.1.1 mSWAT

The mSWAT assessment tool 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 7-1.

Table 7-1 Modified Severity Weighted Assessment Tool

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				

mSWAT score equals summation of each column line.

Abbreviations: BSA = body surface area; mSWAT = modified Severity Weighted Assessment Tool.

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 of %TBSA from all body regions affected by patches x severity-weighting factor of 1

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

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

= Total mSWAT (maximum score = 400)

Figure 7-1 presents the mSWAT % of total body surface area for the 12 main body areas to assess disease burden in MF and pcALCL.[60, 61] The body is divided into 12 regions with preassigned % of total body surface area (TBSA) based on methodology used to assess burns.[62] The extent of skin disease is assessed for each region and quantified using the patient's palm as a "ruler" to measure the % 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 7-1 mSWAT % Total Body Surface Area (TBSA) for 12 Main Body Areas

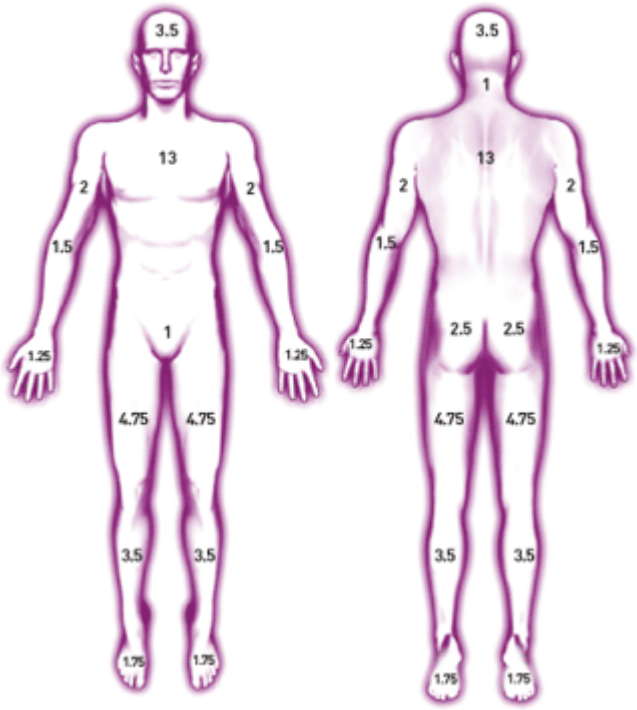


Table 7-2 Response in Skin

Response	Definition
Complete response (CR)	100% clearance of skin lesions[a]
Partial response (PR)	50%-99% clearance of skin disease from baseline No new tumors in patients without tumors at baseline (MF) No new tumors (pcALCL)
Stable disease (SD)	< 25% increase to < 50% clearance in skin disease from baseline No new tumors in patients without tumors at baseline (MF)
Progressive disease (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

Response criteria for MF are per Olsen 2011,[41] and for pcALCL per Kempf 2011.[11]

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

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 mycosis fungoides/Sézary syndrome, the response should be considered a partial response only.

b Whichever criterion occurs first.

7.4.17.1.2 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 prior to dosing on Day 1 of subsequent cycles); within 30 days after the last dose of study drug; and at the posttreatment follow-up visits. Full body global photographs, including head, trunk, legs, front, back, and side, will be taken at the same time points indicated above. Photographs will be uploaded for central review, per IRF.

7.4.17.2 Lymph Node and Visceral Evaluation

Lymph nodes and visceral involvement will be assessed by CT scan, and responses are defined in Table 7-3 and Table 7-4.

Table 7-3 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)

Response criteria are per Olsen 2011,[63] Kempf 2011,[11] and Cheson 2007.[64]

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

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-positive lymphoproliferative disorders,[11] an abnormal lymph node is considered ≥ 1.5cm 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 7-4 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 measureable 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

Table 7-4 Response in Viscera

Response	Definition
Relapse	New organ involvement in those with CR

Response criteria are per Olsen 2011[41] and Kempf 2011.[11]

Abbreviations: CR = complete response; PR = partial response; SPD = sum of the maximum linear dimension (major axis) X longest perpendicular dimension (minor axis); SD = stable disease; 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 and Section 4.1. 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. 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. 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. Radiographic studies will be reviewed by IRF.

7.4.17.3 Blood Assessment

MF involvement in blood is defined in Section 15.4. Sézary Syndrome (SS) is defined as meeting T4 plus B2 criteria, Section 15.4.[41]

Table 7-5 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

Abbreviations: CR = complete response; PR = partial response; SD = stable disease; PD = progressive 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.

7.4.17.4 Global Response Score

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 7-6.

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; and then every 12 weeks for a minimum of 24 months, and then every 6 months; or until disease progression or study closure. 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 prior to 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 7-6 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		

Abbreviations: CR = complete response; NI = noninvolved; PR = partial response; PD = progressive disease; 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.

7.4.17.5 Patient-Reported Outcomes and Health-Related Quality of Life Assessments

EQ-5D, FACT-G, and Skindex-29 questionnaires will be employed for health-related quality of life (HRQoL) assessment from the patient's perspective at 3 spectrums: comparability across the broadest health-related conditions, cancer-specific, and dermatology-specific, respectively. Patients will be requested to complete each of these 3 questionnaires at the time of clinical visits according to the Schedule of Events. If patients are not required to return for a visit, questionnaires (except for visual analog scales) will be completed over the telephone or by mail.

- **EQ-5D:** previously known as the EuroQol instrument, EQ-5D is a 5-item generic HRQoL measure developed by a group of largely European-based researchers. It is intended to be a simple, self-administered questionnaire that not only contains a

descriptive health state classification system but also is capable of generating a composite score or index reflecting the preference value associated with a given health state. EQ-5D consists of the EQ-5D descriptive system and the EQ visual analogue scale.

- **FACT-G:** the Functional Assessment of Cancer Therapy General Questionnaire is a 27-item general cancer quality-of-life instrument for evaluating patients receiving cancer treatment. FACT-G (now in version 4) incorporates a 7-day recall period and contains 4 primary subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being. It is considered appropriate for use with patients with any form of cancer and demonstrated validity, reliability, and sensitivity to change.[65] The total FACT-G score is obtained by summing individual subscale scores. Higher scores for the total scales and subscales indicate better quality of life. Information on US population norms for the FACT-G is available at facit.org. FACT-G is chosen based on its prior successful use in pivotal and non-pivotal clinical trials (NCT00050999 and NCT00724061) in support of treatments for CTCL.

- **Skindex-29:** Skindex-29 is a 29-item dermatology-specific HRQoL questionnaire. Because the skin lesions presented among CTCL patients may impact their quality of life widely, there is a need to quantify the quality of life impact of brentuximab vedotin along with its effect on the lesions. Skindex-29 has been extensively studied in different populations who have skin diseases.[66, 67, 68, 69, 70] Skindex-29 has been used to assess HRQoL in patients with CTCL.[71] Good to excellent conceptual validity, construct validity, internal consistency, and retest reliability have been reported for this instrument.[72] A total of 29 items are combined to form 3 domains: symptoms, emotions, and functioning. The domain scores and an overall score are expressed on a 100-point scale, with higher scores indicating lower levels of HRQoL. Skindex-29 elects a 28-day recall period. Completion requires approximately 5 to 10 minutes.

7.4.18 Pharmacokinetic Measurements

Pharmacokinetic measurements will be made in all brentuximab vedotin-treated patients. Pharmacokinetic parameters to be estimated may include, but are not limited to, the maximum concentration for MMAE (C_{max}) and concentration at the end of infusion for brentuximab vedotin (C_{eoi}). Population pharmacokinetics methodologies will be used to

determine PK parameters and covariates in this population. Efficacy parameters will be related to brentuximab vedotin exposure in the patients.

The incidence of ATA to brentuximab vedotin will also be assessed (See Section 7.4.19).

Table 7-7 presents the sample collection time points. Refer to the Research Specimen Manual for information on collection, processing, storage, and shipment of samples.

Table 7-7 Pharmacokinetic Sampling Time Points

Cycle	Study Day	Time	Window	Relative Time	PK	ATA
Arm 1 (All patients randomized to receive brentuximab vedotin)						
1, 3, 5, 7, 9, 11, 13, 15	1	Predose	Within prior 4 hrs	Start of SGN-35 infusion	X	X
		30 mins Postdose	± 25 mins	End of SGN-35 infusion	X	
EOT Visit	n/a	n/a	n/a	n/a	X	X
Group A[a] (half of patients randomized to receive brentuximab vedotin)						
1 and 3	2	24 hr	± 4 hr	Start of SGN-35 infusion	X	
	4	72 hr	± 4 hr	Start of SGN-35 infusion	X	
Group B[a] (half of patients randomized to receive brentuximab vedotin)						
1 and 3	3	48 hr	± 4 hr	Start of SGN-35 infusion	X	
	5	96 hr	± 4 hr	Start of SGN-35 infusion	X	

Abbreviations: ATA = antitherapeutic antibodies; EOI = end of infusion; EOT = end of treatment; hr = hour; min = minutes; n/a = not applicable; PK = pharmacokinetic.

a Patients randomized to brentuximab vedotin will be assigned to Group A or B at the time of randomization for PK sampling.

7.4.19 Immunogenicity Measurements

Blood (5 mL) for serum samples will be collected as specified in the Schedule of Events to evaluate ATA and neutralizing ATA as a safety assessment in all patients receiving brentuximab vedotin. On dosing days, the blood samples for ATA and neutralizing ATA assessment must be collected before dosing. The maximum volume of blood collected for immunogenicity will be 5 mL per cycle. Neutralizing ATA assessment will be performed only for ATA-positive samples.

7.4.20 Pharmacodynamic Measurements

7.4.20.1 Serum Biomarker Measurements

CCI

[redacted]

7.4.21 Tumor Biopsy for Baseline CD30 Expression and Biomarker Measurements

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 prior to 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 positivity 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. In addition, biomarkers implicated in sensitivity or resistance to vinca alkyloids and taxanes such as p53, beta 3 tubulin, and ABCC transporters may be examined. In order to assess whether treatment with brentuximab vedotin affects the overall expression of CD30 leading to a decrease in response, patients will have a second biopsy at the Cycle 3 evaluation and again at the time of relapse (EOT or during the posttreatment follow-up period) and will be assayed for changes from baseline in CD30 expression. If possible, repeat skin biopsies should be taken from the same lesions as the samples obtained at screening.

Tissue samples from skin biopsies may be used in the evaluation of the Ventana CD30 (Ber-H2) assay. This assay will be used to determine CD30 expression in this study, and is also being evaluated as a diagnostic test by Ventana. Study results may be used to support the use of this assay as a diagnostic test for brentuximab vedotin therapy in CTCL. Additionally, tissue samples from skin biopsies may be tested for other biomarkers and genomic markers of brentuximab vedotin sensitivity and resistance.

7.4.22 Germline DNA Polymorphism Assessment

CCI

[redacted]

7.4.23 Utility Measurement

CCI

[redacted]

7.4.24 Healthcare Utilization Data Collection

CCI

[redacted]

7.4.25 Cost Assessment

The cost of treatment in each arm of the study will be assessed through the collection of HU in each arm in terms of healthcare utilization frequency. Valuation of the costs will be undertaken separately.

7.5 Completion of Treatment

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 (48 weeks)
- Complete up to 48 weeks of treatment with reference therapy

7.6 Completion of Study

Regardless of the duration of treatment, all patients will remain on study for follow-up following the last dose of study treatment until they withdraw consent for further follow-up, are lost to follow-up, or until study closure. The study is expected to close approximately 5 years after the first patient starts study treatment.

7.7 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 or 48 weeks of reference therapy
- Progressive disease

The reason justifying study treatment withdrawal should be documented in the eCRF.

Patients who discontinue from study treatment will remain on study for follow-up unless they withdraw consent for the follow-up phase of the study. All randomized patients will be followed until study closure (see Section 7.6).

Patients who are randomized to a treatment arm but do not receive study drug for any reason will not be replaced. Additional patients may be enrolled to ensure an adequate number of evaluable patients in the study, ie, approximately 124 patients in the ITT population.

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

- Adverse event
- Protocol violation
- Study terminated by sponsor
- Withdrawal by subject
- Lost to follow-up

- Other

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

A "real-time" independent review of disease status will be performed at the time of treatment discontinuation for all patients. In the event of suspected progressive disease, investigators will be encouraged to await the results of the independent review that may indicate or confirm progression in GRS before recommending to the patient any treatment or management options, such as discontinuation from study drug treatment to pursue alternative anticancer therapy.

Note that some patients may discontinue study drug for reasons other than progressive disease before completing the full treatment course; these patients will remain in the study for posttreatment assessments as outlined in the Schedule of Events.

7.8 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 subject
- 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.

Millennium or their designee must be notified if a patient is withdrawn from study treatment 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. If a patient withdraws from study treatment, every attempt should be made to follow the

patient until death or administrative study closure. 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 CRF.

7.9 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.

8. STATISTICAL AND QUANTITATIVE ANALYSES

8.1 Statistical Methods

The statistical methods are outlined below. Details will be provided in the statistical analysis plan (SAP).

8.1.1 Determination of Sample Size

Approximately 124 patients (approximately 62 patients per treatment arm) will be randomized to the study (124 patients are targeted for the ITT population). The sample size was calculated to provide 90% power to detect a 30% improvement in ORR, lasting at least 4 months, in the brentuximab vedotin treatment group, assuming ORRs lasting at least 4 months for brentuximab vedotin treatment group and for the MTX or bexarotene alone treatment group are 70% and 40%, respectively. This calculation is based on a two-sided $\chi 2$ test with significance level of $\alpha = 0.05$, and a 10% dropout rate using nQuery Advisor 7.0. A minimum of 30 patients (15 per treatment arm) with pcALCL will be included in the study. This is not based on statistical consideration.

8.1.2 Randomization and Stratification

The randomization scheme will be generated by Millennium. Prior to dosing, a randomization number will be assigned to each patient. The randomization schedule also includes the study specific identifiers (company name, protocol name, and protocol number) and the date and time the schedule was generated.

Patients will be randomized in an overall ratio 1:1 to Arm 1: brentuximab vedotin or Arm 2: physician's choice of methotrexate or bexarotene using an Interactive Voice

Response/Interactive Web Response System (IVRS/IWRS), stratified by baseline disease diagnosis (pcALCL or MF).

8.1.3 Populations for Analysis

The populations used for analysis will include the following:

- The Safety population will include randomized patients who receive at least 1 dose of study drug. All patients in the safety population will be analyzed according to the actual treatment received. Patients receiving any dose of brentuximab vedotin will be grouped into the study drug group for the purposes of safety reporting.

- The intent-to-treat (ITT) population will include all patients identified as CD30 positive by the Ventana CD30 (Ber-H2) assay and randomized to treatment. All patients in the ITT population will be analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different.

- The all-enrolled population will include all patients randomized to treatment. All patients in the all-enrolled population will be analyzed according to the treatment they were randomized to receive and not according to what they actually received, if different.

- The per-protocol (PP) population will include a subset of ITT patients who do not have major protocol violation as determined by the project clinician. All decisions to exclude patients from the PP population will be made prior to database lock

- The response-evaluable population will include a subset of the ITT patients with measurable disease at baseline and with at least 1 post-baseline response assessment. The response-evaluable population will be used for the supplemental analyses of CR rate, objective response rate, time to response, and duration of response, as needed.

- The PK population will include patients with sufficient dosing and PK data to reliably estimate PK parameters as determined by a clinical pharmacologist. The PK population will be used for PK analyses.

- The pharmacodynamics population will include patients with sufficient dosing and sufficient pharmacodynamics data to reliably measure pharmacodynamics parameters will be used for pharmacodynamics analyses.

8.1.4 Procedures for Handling Missing, Unused, and Spurious Data

All available efficacy and safety data will be included in data listings and tabulations. The relevance of missing sample data will be assessed. Details on any sensitivity analyses and data handling details regarding issues such as missing data will be discussed in the SAP.

Data that are potentially spurious or erroneous will be examined according to standard data management operating procedures.

8.1.5 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized, including gender, age, race, weight, height, primary diagnosis, and other parameters as appropriate. No inferential statistics will be carried out.

8.1.6 Efficacy Analysis

All primary efficacy evaluations for the primary and key secondary efficacy endpoints will be conducted using the ITT population. In addition, sensitivity analysis may be performed using the all-enrolled population, per-protocol population, or response-evaluable population.

8.1.6.1 Analysis of Primary Efficacy Endpoints

The primary endpoint, ORR4, proportion of patients achieving an objective response that lasts at least 4 months, per IRF, will be analyzed using a Cochran-Mantel-Haenszel test stratified by baseline disease diagnosis (pcALCL or MF) based on ITT population. Details are described in the SAP. The 95% confidence interval of the difference in ORR4 between the 2 treatments will be provided.

The primary analysis will be based on the ITT population. The same analysis for the primary endpoint will be performed using the all-enrolled population, and PP population. Sensitivity analyses will be performed for ORR per IRF and ORR per investigator's assessment as well as objective response that lasts at least 4 months defined by the response criteria used for romidespin approval and published by Whittaker 2010.[21]

8.1.6.2 Analyses of Secondary Efficacy Endpoints

CR rate, progression-free survival, and changes in symptom domain per Skindex-29 assessment tool are designated as key secondary endpoints. A fixed sequential testing procedure will be used to test between the primary endpoint and the key secondary

endpoints; that is, the key secondary endpoints will be tested only if the primary endpoint is statistically significant. To test the key secondary endpoints, a weighted Holm's procedure will be used. Details of the testing procedure will be fully described in the SAP.

Comparison of the CR rates between the 2 treatment groups will be conducted using the stratified Cochran-Mantel-Haenszel test. The 95% confidence interval of the difference of the response rates between the 2 treatments will also be provided.

PFS is defined as the time from randomization until disease progression or death due to any cause, whichever occurs first. Detailed rules of handling missing assessments and censoring for the analysis of PFS are described in the SAP. Stratified log-rank test statistics will be used to compare PFS between the 2 treatment arms. The hazard ratios along with the 95% CIs will be estimated using a stratified Cox regression model. The Kaplan-Meier method will be used to estimate the distribution of PFS for each treatment. Median times (if estimable), along with the 2-sided 95% CIs will be presented.

Comparison of symptom reductions between the 2 treatment arms will be conducted using the ANCOVA model controlling for baseline covariates. Symptom reduction is defined for each patient as the maximum reduction from baseline. A longitudinal model will be used for the sensitivity analysis. Missing data will be imputed with mean if there is no more than 1 missing item. Sensitivity analysis will be performed to evaluate impacts of missing data imputation.

Other secondary efficacy endpoints include EFS, duration of response, and duration of skin response. EFS is defined as the time from randomization until any cause of treatment failure: disease progression, discontinuation of treatment for any reason, or death due to any cause, whichever occurs first. Duration of response in subjects with confirmed response is the time between first documentation of response and disease progression. Duration of skin response is the time between the first skin response to progressive disease in skin. Stratified log-rank test statistics will be used to compare EFS between the 2 treatment arms. The hazard ratios along with the 95% CIs will be estimated using a stratified Cox regression model. The Kaplan-Meier method will be used to estimate the distribution of EFS for each treatment. Median times (if estimable), along with the 2-sided 95% CIs will be presented. Duration of response and duration of skin response will be summarized descriptively using the Kaplan-Meier method.

8.1.7 Analyses of Patient-Reported Outcomes and Health Economics

Analyses of patient reported outcomes and health economics will be performed using the ITT population.

8.1.7.1 Patient-Reported Outcomes Analysis

Patient-reported outcome assessments using the FACT-G and Skindex-29 subscale surveys will be analyzed to determine if response to therapy and side effects of therapy are accompanied by measurable changes in PROs. The analysis will be performed on summary scores as well as on subscales with specific analytical methods outlined in a formal statistical analysis plan developed prior to database lock.

The analysis of symptom reduction (Skindex-29) is described in Section 8.1.6.2.

Other subscales of the Skindex-29 questions will be summarized descriptively.

Global score and subscales of FACT-G will be summarized descriptively. Investigation of missing data patterns and imputation, if appropriate, will be discussed in statistical analysis plan.

8.1.7.2 Health Economics Analysis Using Healthcare Utilization and Utility

CCI [redacted]

8.1.8 Pharmacokinetics/Pharmacodynamics/Biomarkers

8.1.8.1 Pharmacokinetic Analysis

The pharmacokinetics of the antibody drug-conjugate (brentuximab vedotin) and unconjugated drug (MMAE) will be derived from serum and plasma concentrations (respectively) versus time data for all patients who met study inclusion criteria, received study drug, and provided evaluable PK data. Population PK parameters will be calculated with an appropriate method based on a validated pharmacokinetic analysis program. Exploratory efficacy PK, and if possible, PK-pharmacodynamic relationship, will be determined.

8.1.8.2 Immunogenicity Analysis

All patients who were administered at least 1 dose of brentuximab vedotin will be evaluated for antitherapeutic antibody (ATA) development. A list/table of ATA status will be

provided. Antibody neutralizing status (neutralizing or not neutralizing) will also be listed for patients who have positive antibody status.

Immunogenicity information, including ATA and neutralizing ATA, will be summarized in descriptive statistics as applicable.

8.1.8.3 Pharmacodynamic Analysis

CCI

8.1.8.4 Biomarker Analysis

CCI

8.1.9 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, ECOG performance status, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment-emergent 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. Adverse events will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- TEAEs
- Study drug-related TEAEs
- Grade 3 or higher TEAEs

- Grade 3 or higher study drug-related TEAEs
- The most commonly reported treatment-emergent AEs (ie, those events reported by ≥10% of all patients)
- SAEs

A listing of treatment-emergent AEs resulting in study drug discontinuation will be provided.

Descriptive statistics for both the actual values and change from the baseline assessment values of the clinical laboratory parameters (hematology and chemistry) 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 the baseline assessment to the worst postbaseline value.

Descriptive statistics for the actual values (and/or the changes from the baseline assessment) of vital signs over time will be tabulated by scheduled time point.

Eastern Cooperative Oncology Group performance status and change from baseline will be summarized. Shifts from baseline to the worst postbaseline score will be tabulated by treatment group. Patients who have ECOG performance scores that worsen postbaseline compared to baseline will be listed with other pertinent patient information.

Investigators' assessments of ECG monitoring (normal, abnormal and clinically significant, or abnormal and not clinically significant), including unscheduled or retested measurements, will be presented in a listing.

Additional safety analyses may be performed to most clearly enumerate rates of toxicities and further define the safety profile of study drug.

9. STUDY COMMITTEES

9.1 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to review safety data according to a pre-specified IDMC charter. The first formal safety review will occur

after approximately 30 patients have been randomized in total and received at least 1 cycle of study treatment, or 6 months after the first patient is randomized (whichever comes first). Thereafter, IDMC safety reviews will be performed periodically per the IDMC charter.

10. ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation.

10.1.2 Adverse Event Definition

Adverse event (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 should 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.

10.1.3 Serious Adverse Event Definition

Serious AE (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 below 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, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 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.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[42] Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of less than 1,000/mm^3 to 500/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting Adverse Events and Serious Adverse Events

All AEs spontaneously reported by the patient and/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 1 comprehensive event.

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Millennium Department of Pharmacovigilance or designee (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by the Millennium Department of Pharmacovigilance or designee. SAE report information must be consistent with the data provided on the eCRF.

SAE Reporting Contact Information

CCI

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 intensity of the event and the relationship of the event to study drug administration. For serious pretreatment events, the investigator must determine both the intensity of the event and the relationship of the event to study procedures.

Intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010.[74] The criteria are provided in the Study Manual and also are available online at http://ctep.cancer.gov/reporting/ctc.html.

Relationship to study drug administration will be determined by the investigator responding yes or no to this question: Is there a reasonable possibility that the AE is associated with the study drug?

10.3 Monitoring of Adverse Events 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 Millennium Department of Pharmacovigilance or designee from the time of the signing of the informed consent form (ICF) up to first dose of study drug, but will not be recorded in the eCRF.

- Related and unrelated SAEs will be reported to the Millennium 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 Millennium 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 faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 10.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

11. ADMINISTRATIVE REQUIREMENTS

11.1 Good Clinical Practice

The study will be conducted in accordance with the ICH-GCP and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and the IB.

11.2 Data Quality Assurance

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study patient. Study data will be entered into an eCRF by site personnel using a secure, validated, web-based electronic data capture (EDC) application. Millennium will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the investigator for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

11.3 Electronic Case Report Form Completion

Millennium 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.

Millennium, 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.

11.4 Study Monitoring

Monitoring and auditing procedures developed or approved by Millennium will be followed to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the patient's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner that ensures that patient confidentiality is maintained.

11.5 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the patients. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or the sponsor, as allowed by local regulations.

11.6 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

11.7 Patient Confidentiality

To maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient by initials where permitted and/or by the assigned patient number. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

11.8 Investigator Compliance

The investigator will conduct the trial in compliance with the protocol provided by Millennium and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Modifications to the protocol are not to be made without agreement of both the investigator and Millennium. Changes to the protocol will require written IRB/IEC approval/favorable opinion before implementation, except when the modification is needed to eliminate an immediate hazard or hazards to patients. Millennium, or a designee, will submit all protocol modifications to the appropriate regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard or hazards to patients, the investigator will contact Millennium, or a designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

11.9 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

11.10 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at the trial site is the responsibility of the investigator. Drug accountability records indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium, or a designee (or disposal of the drug, if approved by Millennium) will be maintained by the clinical site. Millennium or its designee will review drug accountability at the site on an ongoing basis.

All material containing study drug will be treated and disposed of in accordance with governing regulations.

11.11 Product Complaints and Medication Errors

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 contact [redacted] [redacted] see below) and report the event. Whenever possible, the associated product

should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact [redacted] (see below) and report the event.

For Product Complaints or Medication Errors
[redacted]

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to the Millennium Department of Pharmacovigilance or designee (refer to Section 10.2).

11.12 Closure of the Study

Within 90 days of the end of the study, the sponsor will notify the competent authorities and the IECs in all member states where the study is being carried out that the study has ended.

Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IECs in all member states involved in the study.

Study participation by individual sites or the entire study may be prematurely terminated if, in the opinion of the investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data

- Plans to modify, suspend or discontinue the development of the study drug

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to Millennium once the site's participation in the study has concluded.

Within 15 days of premature closure, Millennium must notify the competent authorities and IECs of any member state where the study is being conducted, providing the reasons for study closure.

11.13 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 last marketing application 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 Millennium notified.

12. USE OF INFORMATION

All information regarding brentuximab vedotin supplied by Millennium to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium. It is understood that there is an obligation to provide Millennium with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of brentuximab vedotin and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Millennium, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Group comprising Millennium employees and study investigators will be formed to oversee the publication of the study results, which will reflect the experience of all participating study centers. Subsequently, individual investigators may publish results from the study in compliance with their agreements with Millennium.

A prepublication manuscript or abstract is to be provided to Millennium a minimum of 30 days before the intended submission date of the manuscript or abstract to a publisher. Within 30 days after receipt by Millennium of the notification, Millennium shall inform the study centers whether it has objections to the publication for reasons including, but not limited to, those defined below:

- If patentable subject matter is disclosed, the publication shall be delayed for a period not to exceed 90 days from Millennium's receipt of the proposed publication to allow time for the filing of patent applications covering patentable subject matter.

- If confidential information is contained in any proposed publication or public disclosure, such confidential information will be removed at Millennium's request.

The overall principal investigator will be the last author on abstracts and publications of the data generated from this study. Other authors will be listed according to number of patients enrolled to the study. If the principal investigator has the highest enrollment, he/she may choose to be either first or last author. This policy may be changed with the agreement of both the investigators and Millennium.

13. INVESTIGATOR AGREEMENT

I have read Protocol C25001 Amendment 5: A Randomized, Open-Label, Phase 3 Trial of brentuximab vedotin (SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma

I agree to conduct the study as detailed herein and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice and applicable regulatory requirements and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____
Principal investigator printed name

_____ _____
Principal investigator signature Date

_____

_____

_____
Investigational site or name of institution and location (printed)

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15. APPENDICES

15.1 Eastern Cooperative Oncology Group (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 self-care. Totally confined to bed or chair.
5	Dead.

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.[75]

15.2 Body Surface Area Nomograms

Body surface area should be calculated using the Mosteller formula or Dubois and Dubois formula standard nomogram.

The Mosteller Formula
$BSA\ (m^2) = ([Height(cm) \times Weight(kg)]/ 3600)^{1/2}$ eg, BSA = SQRT((cm*kg)/3600) or in inches and pounds: $BSA\ (m^2) = ([Height(in) \times Weight(lbs)]/ 3131)^{1/2}$

Adapted from: Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987;317(17):1098.[76]

The Dubois and Dubois Formula
$BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$ where the weight is in kilograms and the height is in centimeter

Adapted from: DuBois D, DuBois EF. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Medicine. 1916; 17:863-71.[77]

15.3 New York Heart Association 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. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.[78]

15.4 Tumor-Node-Metastasis-Blood Classification and Clinical Staging System for Mycosis Fungoides

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	One 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

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

TNMB Stages	Description of TNMB
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
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 EA et al. Clinical End Points and Response Criteria in Mycosis Fungoides and Sezary Syndrome: A Consensus Statement of the International Society for Cutaneous Lymphomas, the United States Cutaneous Lymphoma Consortium, and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer. J Clin Oncol 2011.[41]

Abbreviations: ISCL = International Society for Cutaneous Lymphomas; EORTC = European Organisation for Research and Treatment of Cancer; MF = mycosis fungoides; SS = Sézary syndrome; NCI = National Cancer Institute.

* 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[24] 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.

15.5 Amendment 4 Rationale and Purposes

Rationale for Amendment 4

This amendment incorporates FDA guidance received on Amendment 3, an amendment that was not implemented by study sites. Amendment 4 reverts to text that states that the sponsor will be notified in the event that a patient is withdrawn from study treatment or from the study, and re-establishes the use of a standard formula to calculate body surface area (BSA).

In order to strengthen safety reporting, this amendment requires all events of peripheral neuropathy to be followed for changes in severity until resolution to baseline or study closure, whichever occurs first, and removes the requirement to end safety monitoring when a patient receives a subsequent anticancer therapy.

Purposes for Amendment 4

- The purposes of this amendment are to:
- Revert to language that states that the sponsor will be notified of patient withdrawal from study treatment or from the study
- Specify that BSA is calculated using the Mosteller formula or the Dubois and Dubois formula and add a statement to consider the risks of dosing with bexarotene
- Remove requirement to end safety monitoring when a patient receives subsequent anticancer therapy
- Add language regarding the collection of events of peripheral neuropathy
- Correct errors in response tables to align with reference documents
- Correct typographical errors, punctuation, grammar, and formatting

15.6 Amendment 5 Detailed Summary of Changes

THE PRIMARY SECTION(S) OF THE PROTOCOL AFFECTED BY THE CHANGES IN AMENDMENT 5 ARE INDICATED. THE CORRESPONDING TEXT HAS BEEN REVISED THROUGHOUT THE PROTOCOL.

Purpose: Add safety language regarding the potential risk of pancreatitis

The primary change occurs in Section 1.5, Potential Risks and Benefits:

Added text: **Acute pancreatitis has been reported in patients treated with brentuximab vedotin and has contributed to fatal outcomes in some cases. Onset typically occurred after 1 to 2 doses of brentuximab vedotin. Early symptoms included severe abdominal pain, nausea, and vomiting. Some of the pancreatitis cases were complicated by other possible contributory factors, including cholelithiasis and alternate etiologies (eg, pancreatic lymphoma progression, displacement of bile duct stent, etc).**

Purpose: Add lipase values and amylase levels to pancreatitis exclusion criterion

The primary change occurs in Section 5.2, Exclusion Criteria:

Added text:

17. 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)**, or elevated lipase value ≥ 3 × ULN with an amylase level > ULN at screening**.

Purpose: Add lipase and amylase to the chemistry lab panel

The primary change occurs in Section 7.4.15, Clinical Laboratory Evaluations:

Added text:

Serum Chemistry

- BUN
- Creatinine
- Bilirubin (total)
- Urate
- Lactate dehydrogenase (LDH)
- Phosphate
- Gamma glutamyl
- Albumin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Calcium
- Chloride
- Carbon dioxide (CO2)
- Magnesium
- **Amylase**
- **Lipase**

transferase (GGT)	• Glucose • Sodium • Potassium

Footnote h in the Schedule of Events also contains this change.

Purpose: Revise text regarding timing of FDG-PET and CT scans

The primary change occurs in Section 4.1, Overview of Study Design:

Formerly read:	FDG-PET scans and CT scans of the neck, chest, abdomen, and pelvis will be performed at screening. FDG-PET scans will not be taken after screening unless clinically indicated. For patients without nodal or visceral involvement as determined by baseline CT scans, CT scans will be performed ~~at the beginning of~~ the cycle following the first skin response, ideally corresponding to the confirmation of the skin response, and 6 cycles (a minimum of 4 months) after that confirmed skin response.
Now reads:	FDG-PET scans and CT scans of the neck, chest, abdomen, and pelvis will be performed at screening. **FDG-PET scans taken within 8 weeks before signing the informed consent form (ICF) may be used as the screening FDG-PET.** FDG-PET scans will not be taken after screening unless clinically indicated. **CT scans taken within 4 weeks before signing the ICF may be used as the screening CT scan if all of the following conditions are met:** • **There is no nodal or visceral disease involvement noted** • **There is no clinically evident lymphadenopathy or splenomegaly by physical exam at the time of screening** • **The scan meets all quality criteria as outlined in the Imaging Manual** For patients without nodal or visceral involvement as determined by baseline CT scans, CT scans will be performed **during** the cycle following the first skin response, ideally corresponding to the confirmation of the skin response, and 6 cycles (a minimum of 4 months) after that confirmed skin response.

Footnotes m and n in the Schedule of Events also contain this change.

Purpose: Clarify text regarding follow-up for objective response

The primary change occurs in Section 4.1, Overview of Study Design:

Formerly read:	Objective response, lasting at least 4 months (ORR4), per independent review facility (IRF), will be assessed by global response score (GRS), which consists of skin evaluation (mSWAT assessment), 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~~;~~

	at end of treatment (EOT)~~;~~ then every 12 weeks for a minimum of 24 months~~;~~ and then every 6 months~~,~~ until disease progression or study closure.
Now reads:	Objective response, lasting at least 4 months (ORR4), per independent review facility (IRF), will be assessed by global response score (GRS), which consists of skin evaluation (mSWAT assessment), 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 end of treatment (EOT)**. All treated patients without disease progression at EOT/ET will** then **be followed for objective response** every 12 weeks for a minimum of 24 months, and then every 6 months; **or** until disease progression or study closure.

Sections that also contain this change are:

- PROTOCOL SUMMARY
- Footnotes b, l, and r in the Schedule of Events
- Section 4.3, Duration of Study
- Section 7.4.17.4, Global Response Score

Purpose: Clarify text regarding timing of clinical laboratory assessments

The primary change occurs in Section 5.1, Inclusion Criteria:

Formerly read:	8. Clinical laboratory values as specified below within 4 days before ~~the first dose of study drug~~ (laboratory values may be performed locally.):
Now reads:	8. Clinical laboratory values as specified below within 4 days before **randomization** (laboratory values may be performed locally.):

Purpose: Revise timing for exclusion of oral retinoid therapy

The primary change occurs in Section Exclusion Criteria:

Formerly read:	15. Oral retinoid therapy for any indication within 3 weeks of ~~study entry~~.
Now reads:	15. Oral retinoid therapy for any indication within 3 weeks of **the first dose of study drug.**

Purpose: Add a statement regarding the scheduling of pregnancy tests

The primary change occurs in Section 7.4.8, Pregnancy Test:

Added text:	A serum pregnancy test will be performed for women of childbearing potential at screening. Urine pregnancy tests will be performed prior to dosing on Day 1 of each cycle. **Pregnancy tests may also be repeated during the study if requested by an IEC/IRB or if required by local regulations.** The results of any pregnancy test must be negative before dosing on Day 1 of all cycles.

Purpose: Revise the definition of relapse in the text to align with the definition in the response tables

The primary change occurs in Section 7.4.17.4, Global Response Score:

Formerly read:	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 prior to 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 ~~as progressive disease~~ in the study endpoints definition.
Now reads:	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 prior to 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.**

Purpose: Add relapse to the list of GRS responses

The primary change occurs in Section 7.4.16, Disease Assessment:

Formerly read:	A GRS of complete response (CR), partial response (PR), stable disease (SD), ~~and~~ progressive disease (PD) will be determined based on sequential tumor burden assessments of body compartments (skin, lymph nodes, viscera, and blood for M~~R~~ patients) as further described below. For the purpose of disease assessment in the control arm, a period of 3 weeks (21 days) is equivalent to 1 cycle.
Now reads:	A GRS of complete response (CR), partial response (PR), stable disease (SD), progressive disease (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. For the purpose of disease assessment in the control arm, a period of 3 weeks (21 days) is equivalent to 1 cycle.

Section 7.4.17.4, Global Response Score also contains this change.

Purpose: Clarify text regarding the collection of pharmacokinetic parameters

The primary change occurs in Section 7.4.18, Pharmacokinetic Measurements:

Added text: Pharmacokinetic measurements will be made in all brentuximab vedotin-treated patients. Pharmacokinetic parameters to be estimated may include**, but are not limited to,** the maximum concentration for MMAE (Cmax) and concentration at the end of infusion for brentuximab vedotin (Ceoi).

Purpose: Clarify text regarding the amount of blood to be collected for germline DNA assessments

The primary change occurs in Section 7.4.22, Germline DNA Polymorphism Assessment:

Added text: CCI

Purpose: Clarify text regarding the discontinuation of study drug

The primary change occurs in Section 7.7, Discontinuation of Treatment With Study Drug, and Patient Replacement:

Formerly read: ~~At the time of~~ study drug ~~discontinuation~~, all study procedures outlined for the End of Treatment visit will be completed. The primary reason for study drug discontinuation will be recorded on the eCRF.

Now reads: **Once** study drug **has been discontinued**, all study procedures outlined for the End of Treatment visit will be completed **as specified in the Schedule of Events**. The primary reason for study drug discontinuation will be recorded on the eCRF.

Purpose: Revise text describing safety analysis

The primary change occurs in Section 8.1.9, Safety Analysis:

Formerly read:

Safety will be evaluated by the incidence of ~~TEAEs~~, severity and type of AEs, and by changes from baseline in the patient's vital signs, ECOG performance status, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment-emergent AEs ~~will be tabulated by primary system organ class (SOC), high-level term (HLT), and preferred term. A TEAE is defined as any AE~~ that occur~~s~~ after administration of the first dose of study drug and ~~up~~ through 30 days after the last dose of study ~~medication~~. Adverse events will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) ~~by system organ class (SOC), high-level terms, and preferred terms (PTs)~~ and will include the following categories:

- TEAEs
- Study drug-related TEAEs
- Grade 3 or higher TEAEs
- Grade 3 or higher study drug-related TEAEs
- ~~TEAEs resulting in study drug discontinuation~~
- ~~SAEs, including study drug-related SAEs~~

The most commonly reported ~~TEAEs~~ (ie, those events reported by ≥ 10% of all patients) will be ~~tabulated by high-level term and PT.~~

Now reads:

Safety will be evaluated by the incidence of **AEs**, severity and type of AEs, and by changes from baseline in the patient's vital signs, ECOG performance status, and clinical laboratory results using the safety population. Exposure to study drug and reasons for discontinuation will be tabulated.

Treatment-emergent 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**. Adverse events will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) and will include the following categories:

- TEAEs
- Study drug-related TEAEs
- Grade 3 or higher TEAEs
- Grade 3 or higher study drug-related TEAEs
- The most commonly reported **treatment-emergent AEs** (ie, those events reported by ≥10% of all patients)
- **SAEs**

A listing of treatment-emergent AEs resulting in study drug

discontinuation will be **provided.**

Purpose: Revise text describing monitoring of adverse events

The primary change occurs in Section 10.3, Monitoring of Adverse Events and Period of Observation:

Formerly read:

AEs, both nonserious and serious ~~(which include all deaths)~~, will be monitored throughout the study as follows:

...

- SAEs will be reported to Millennium 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. ~~All~~ 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). ~~Any SAE that occurs at any time after completion of the study and the designated follow-up period that the investigator considers to be related to study drug must be reported to PPD.~~

Now reads:

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

...

- **Related and unrelated** SAEs will be reported to **the** Millennium **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 Millennium 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).

Purpose: Revise text regarding the recording and reporting of adverse events and serious adverse events (SAEs)

The primary change occurs in Section 10.2, Procedures for Recording and Reporting Adverse Events and Serious Adverse Events:

Formerly read:

Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to Millennium ~~Pharmacovigilence's Designee PPDI~~ Pharmacovigilance ~~(PPD)~~ (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. ~~All SAEs and serious pretreatment events (which include all deaths) must be reported whether or not considered causally related to the study drug or study procedures.~~

Now reads:	Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to **the** Millennium **Department of** Pharmacovigilance **or designee** (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event.

Purpose: Replace references to PPD with Millennium Pharmacovigilance or designee

The primary change occurs in Section 10.2, Procedures for Recording and Reporting Adverse Events and Serious Adverse Events:

Formerly read:	Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to Millennium ~~Pharmacovigilence's Designee PPDI~~ Pharmacovigilance ~~(PPD)~~ (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. ~~All SAEs and serious pretreatment events (which include all deaths) must be reported whether or not considered causally related to the study drug or study procedures.~~ The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by ~~PPD or~~ Millennium. SAE report information must be consistent with the data provided on the eCRF.
Now reads:	Regardless of causality, SAEs and serious pretreatment events (as defined in Section 10.1) must be reported (see Section 10.3 for the period of observation) by the investigator to the Millennium **Department of** Pharmacovigilance **or designee** (contact information provided below). This should be done by faxing the SAE Form within 24 hours after becoming aware of the event. The SAE Form, created specifically by Millennium, will be provided to each clinical study site. A sample of the SAE Form may be found in the Study Manual. Follow-up information on the SAE or serious pretreatment event may be requested by **the** Millennium **Department of Pharmacovigilance or designee**. SAE report information must be consistent with the data provided on the eCRF.

Sections that also contain this change are:

- Section 10.3, Monitoring of Adverse Events and Period of Observation
- Section 10.4, Procedures for Reporting Drug Exposure During Pregnancy and Birth Events
- Section 11.11, Product Complaints and Medication Errors

Purpose: Update contact information for reporting SAEs

The primary change occurs in Section 10.2, Procedures for Recording and Reporting Adverse Events and Serious Adverse Events:

Formerly read:	~~For~~ SAE ~~and Pregnancy~~ Reporting Contact Information~~,~~ ~~please refer to Section 15.5.~~
Now reads:	SAE Reporting Contact Information [redacted]

Section 15.5, SAE and Pregnancy Reporting Contact Information, has been deleted.

Purpose: Correct errors in Background and Study Rationale text and in-text references

The primary change occurs in Section 1.4.1, Treatment Options in CTCL, and Section 1.4.2.1, Bexarotene:

Formerly read:

1.4.1 Treatment Options in CTCL

There is no universally accepted single standard of care across first, second, and advanced lines of treatment of CTCL. Single-agent therapy has been used, including retinoids, interferons, HDAC inhibitors, and chemotherapy; these therapies include methotrexate, bexarotene, glucocorticoids, cyclophosphamide, cisplatin, etoposide, bleomycin, doxorubicin, vincristine, and vinblastine.[27] Single-agent therapy can yield complete response rates up to 30%, but remissions are generally of short duration. Chemotherapy combined with other agents may induce remissions of pcALCL. More potent chemotherapy is complicated by immune deficiency, and infectious complications. Both methotrexate and bexarotene are approved by the FDA and ~~remain the most~~ widely used treatments for CTCL across the diagnoses.[5]

…

A second HDACi, romidepsin, is an intravenously administered bicyclic peptide that inhibits classes I and II HDACs with activity in not only CTCL, but also peripheral T-cell lymphoma (PTCL). A single-arm, open-label, multicenter, pivotal, phase 2 study of romidepsin for the treatment of refractory CTCL (stages IB–IVA) was recently completed. After 6 cycles of treatment, a response rate (RR) of ~~42%~~ was observed in ~~72~~ evaluable patients

(including 6 clinical CRs), and pruritus improved in 4~~8~~%. Median time to response was ~~1.9~~ months.[~~21~~] Romidepsin was granted approval by the FDA for treatment of patients with CTCL.[21, ~~35~~]

Chemotherapy is reserved for relapsed and refractory disease and yields moderate to high response rates; however, response durations are short. Agents with notable activity include gemcitabine and liposomal doxorubicin. In a phase 2 study, gemcitabine showed a response rate of 53% and a CR rate of 22%. In a retrospective analysis of pegylated liposomal doxorubicin, the response rate was approximately 85% (30 out of 34 patients) and approximately 43% had CR.[22, 23, 24]

1.4.2 Choice of Comparator

1.4.2.1 Bexarotene

Bexarotene (Targretin®) is approved in the United States and European Union for the treatment of patients who are refractory to at least 1 prior systemic therapy for cutaneous T-cell lymphoma. In clinical trials, bexarotene was administered for up to 97 weeks. In patients with advanced CTCL, 49% of patients achieved an objective response (complete and partial responses) to treatment with any dose of bexarotene. Patient response rates were 45% at a dose of 300 mg/m2/day PO and 55% at doses > 300 mg/m2/day PO. Responses were seen in patients with erythrodermic CTCL (mycosis fungoides) and Sézary syndrome. Median time to best response was 180 days and these responses were durable for a median of ~~159~~ days at bexarotene doses of 300 mg/m2/day PO. Median time to response was shorter and the duration of response was longer with doses > 300 mg/m2/day PO but the incidence of side effects increased substantially at the higher doses.[36]

Now reads:

1.4.1 Treatment Option in CTCL

There is no universally accepted single standard of care across first, second, and advanced lines of treatment of CTCL. Single-agent therapy has been used, including retinoids, interferons, HDAC inhibitors, and chemotherapy; these therapies include methotrexate, bexarotene, glucocorticoids, cyclophosphamide, cisplatin, etoposide, bleomycin, doxorubicin, vincristine, and vinblastine.[26] Single-agent therapy can yield complete response rates up to 30%, but remissions are generally of short duration. Chemotherapy combined with other agents may induce remissions of pcALCL. More potent chemotherapy is complicated by immune deficiency, and infectious complications. Both methotrexate and bexarotene are approved by the FDA and **are** widely used treatments for CTCL across the diagnoses.**[27]**

…

A second HDACi, romidepsin, is an intravenously administered bicyclic peptide that inhibits classes I and II HDACs with activity in not only CTCL, but also peripheral T-cell lymphoma (PTCL). A single-arm, open-label, multicenter, pivotal, phase 2 study of romidepsin for the treatment of refractory CTCL (stages IB–IVA) was recently completed. After 6 cycles of

treatment, a response rate (RR) of **34**% was observed in **96** evaluable patients (including 6 clinical CRs), and pruritus improved in **43**%. Median time to response was **2** months. Romidepsin was granted approval by the FDA for treatment of patients with CTCL.[21]

Chemotherapy is reserved for relapsed and refractory disease and yields moderate to high response rates; however, response durations are short. Agents with notable activity include gemcitabine and liposomal doxorubicin. In a phase 2 study, gemcitabine showed a response rate of 53% and a CR rate of 22%. In a retrospective analysis of pegylated liposomal doxorubicin, the response rate was **88**% (30 out of 34 patients) and approximately 43% had CR.[22, **34, 35**]

1.4.2 Choice of Comparator

1.4.2.1 Bexarotene

Bexarotene (Targretin®) is approved in the United States and European Union for the treatment of patients who are refractory to at least 1 prior systemic therapy for cutaneous T-cell lymphoma. In clinical trials, bexarotene was administered for up to 97 weeks. In patients with advanced CTCL, 49% of patients achieved an objective response (complete and partial responses) to treatment with any dose of bexarotene. Patient response rates were 45% at a dose of 300 mg/m^2/day PO and 55% at doses > 300 mg/m^2/day PO. Responses were seen in patients with erythrodermic CTCL (mycosis fungoides) and Sézary syndrome. Median time to best response was 180 days and these responses were durable for a median of **299** days at bexarotene doses of 300 mg/m^2/day PO. Median time to response was shorter and the duration of response was longer with doses > 300 mg/m^2/day PO but the incidence of side effects increased substantially at the higher doses.[36]

Section 1.1.2.1, Mycosis Fungoides Treatment and Staging, also contains this change.

Purpose: Correct typographical errors, punctuation, grammar, and formatting

These changes are not listed individually.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
PPD	Clinical Approval	03-Dec-2014 22:52
	Clinical VP Approval	05-Dec-2014 06:04