Title: A Phase 2, Single-Arm, Open-label Study of Brentuximab Vedotin in Chinese Patients With Relapsed/Refractory CD30-Positive Hodgkin Lymphoma (HL) or Systemic Anaplastic Large Cell Lymphoma (sALCL)

NCT Number: NCT02939014

SAP Approve Date: 30 August 2018

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C25010

A Phase 2, Single-Arm, Open-label Study of Brentuximab Vedotin in Chinese Patients With Relapsed/Refractory CD30-Positive Hodgkin Lymphoma (HL) or Systemic Anaplastic Large Cell Lymphoma (sALCL)

PHASE 2

Version**:** Final

Date**:** 30 August 2018

Prepared by:

PPD

Based on:

Protocol Version: Original

Protocol Date: 20 April 2016

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

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3.0 LIST OF ABBREVIATIONS

ADC	antibody-drug conjugate
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
ATC	Anatomical Therapeutic Chemical classification
AUC	area under the concentration-time curve
CI	confidence interval
CL	clearance
C_{max}	maximum observed concentration
CR	complete response
CSR	clinical study report
CT	computed tomography
CTMS	clinical trial management system
CV	coefficient of variation
DCR	Disease control rate
DOR	duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOT	end of treatment
HL	Hodgkin lymphoma
IRF	independent review facility
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MMAE	monomethylauristatin E
nATA	neutralizing antitherapeutic antibodies
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OS	overall survival
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
RDI	relative dose intensity
SAE	serious adverse event
sALCL	systemic anaplastic large cell lymphoma
SAP	statistical analysis plan

SD	stable disease
SPD	sum of products of diameters
StdDev	standard deviation
SMQ	standardised MedDRA queries
TAb	total antibody
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of C_{max}
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective is to evaluate the efficacy and the safety of brentuximab vedotin in Chinese patients with relapsed/refractory CD30+ HL or sALCL.

4.2 Secondary Objectives

The secondary objective is to evaluate the PK and immunogenicity of brentuximab vedotin in Chinese patients with relapsed/refractory CD30+ HL or sALCL.

4.3 Additional Objectives

Not applicable.

4.4 Study Design

This is a single-arm, open-label, multicenter, phase 2 study designed to evaluate the efficacy, safety, and PK of brentuximab vedotin as a single agent in Chinese patients with relapsed/refractory CD30+ HL or sALCL. Brentuximab vedotin will be administered as a single, 1.8 mg/kg IV infusion on Day 1 of each 3-week cycle.

Patients will receive a maximum of 16 cycles if they do not meet the criteria for removal from the study. Patients will be assessed for overall response using the Revised Response Criteria for Malignant Lymphoma [1]. Dedicated computed tomography (CT) scans (neck, chest, abdomen, and pelvis) will be performed at Baseline and at Cycles 2, 4, 7, 10, 13, and 16, and positron emission tomography (PET) scans will be performed at Baseline and at Cycles 4 and 7. No additional PET scanning is required beyond Cycle 7 unless clinically indicated. B symptoms will be assessed at Baseline and on Day 1 of each cycle.

Patients may continue on study treatment until the sooner of disease progression, unacceptable toxicity, or completion of 16 cycles. Patients, including those who discontinue study treatment for any reason other than withdrawal of consent, will have safety follow-up assessments through 30 days after the last dose of study drug until end of treatment (EOT). Patients who discontinue study treatment with stable disease (SD) or better will be followed for PFS until disease progression, death, withdrawal of consent, or initiation of a new treatment other than the stem cell transplantation (SCT), whichever occurs first. A CT scan will be performed every 12 weeks for the first 12 months and at 18 months after EOT. Patients will be followed for OS every 12 weeks until death, withdrawal of consent, or study closure, whichever occurs first. All patients will have the opportunity to be followed for 18 months after EOT. The study will be closed when all patients enrolled have completed the required follow-up.

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective 14 June 2010 [2]. Laboratory values, vital signs, and electrocardiograms (ECGs) will be obtained to evaluate the safety and tolerability of brentuximab vedotin. Serial blood samples for determination of the serum/plasma

concentration and immunogenicity of brentuximab vedotin will be obtained at prespecified time points as described in Table B in Appendix A of the Study Protocol.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

- ORR.
- Safety: AEs, assessments of clinical laboratory values, and vital sign measurements.

5.2 Secondary Endpoints

- CR rate.
- DOR.
- PFS.
- OS.
- B symptom resolution rate.
- Maximum observed plasma concentration (C_{max}).
- Time to reach C_{max} (T_{max}).
- Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞}).
- Presence of antitherapeutic antibodies (ATA) and neutralizing antitherapeutic antibodies (nATA) to brentuximab vedotin.

6.0 DETERMINATION OF SAMPLE SIZE

The study will enroll approximately 30 evaluable patients, including approximately 22 patients with HL and approximately 8 patients with sALCL. For information purposes, the ORRs achieved in previous studies in relapsed/refractory HL and sALCL are referenced below.

Table 6.a ORRs in the Global Pivotal Studies and the Japan Study

	ORR (CR+PR) by IRF (95% CI)
Global Study SGN035-0003 (HL: n=102)	74.5 (64.9, 82.6)
Global Study SGN035-0004 (sALCL: n=58)	86.2 (74.6, 93.9)
Japan Study TB-BC010088 (HL: n=9)	66.7 (29.9, 92.5)
Japan Study TB-BC010088 (sALCL: n=5)	100 (54.9, 100)

Some observed response rates and the 95% exact CIs for 22 patients with HL and 8 patients with sALCL are summarized as follows.

Table 6.b ORRs and the 95% Exact CIs for Various Number of Responses

HL (n=22)				sALCL (n=8)			
Responses	**ORR (%)**	**95% Exact CI**		**Responses**	**ORR (%)**	**95% Exact CI**	
8	36.4	(17.2	59.3)	4	50.0	(15.7	84.3)
9	**40.9**	**(20.7**	**63.6)**	**5**	**62.5**	**(24.5**	**91.5)**
10	45.5	(24.4	67.8)	6	75.0	(34.9	96.8)
11	50.0	(28.2	71.8)	7	87.5	(47.3	99.7)
12	54.5	(32.2	75.6)	8	100	(63.1	100.0)
13	59.1	(36.4	79.3)				

Based on the exact binomial CI calculations, a minimum of 9 responses observed from 22 evaluable patients with HL (ORR of 40.9%) will provide a 95% CI (20.7%, 63.6%); 5 responses observed from 8 evaluable patients with sALCL (ORR of 62.5%) will yield a 95% CI (24.5%, 91.5%). In both cases, the lower limits of the 95% CIs are greater than the threshold response rate of 20% obtained from the results of alternative therapies for the same indications.

Assume similar ORR results to those in the Japan Study TB-BC010088 will be obtained, eg, the expected response rates are 65% for HL and 80% for sALCL. With 22 patients with HL and 8 patients with sALCL, the study will have >99% and >94% probability, respectively, to observe an ORR such that the lower limit of its 95% exact CI is still greater than the 20% threshold (ie, observe ≥9 responses for HL and ≥5 responses for sALCL).

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

In general, descriptive statistics (number of observations, mean, standard deviation [StdDev], median, minimum, and maximum) will be used to summarize continuous variables. Frequency and percentage will be used to summarize categorical variables. Time-to-event data will be analyzed using the Kaplan-Meier method and results will be summarized by the 25th, 50th (median), and 75th percentiles, if estimable, with associated 2-sided 95% confidence intervals, as well as the percentage of censored observations.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (StdDev) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

Unless otherwise specified, safety and efficacy data will be summarized in the following 3 groups: patients with r/r HL only, patients with r/r sALCL only, all patients. Analyses pertaining to pharmacokinetics and immunogenicity will be summarized by treatment cycle at the prespecified time points.

The baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration, unless otherwise specified. A windowing convention may be used to determine the analysis value for a given study visit for observed data analyses.

All available efficacy and safety data will be included in data listings and tabulations. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures. In general, there will be no imputation of missing data. For time-related endpoints, subjects who have no specified events will be censored as specified for each respective endpoint in Section 7.8. Imputation rules for missing dates of AEs and concomitant medications are detailed in Sections 7.1.3 and 7.1.4.

The primary analysis for the clinical study report including the primary and the secondary endpoints will be conducted when all patients have had the opportunity to receive 16 cycles of treatment and have had EOT assessments. The results will be summarized in the primary CSR. The final analysis will be conducted when all patients have had the opportunity to be followed for 18 months after EOT. These results will be summarized in the CSR Addendum.

SAS Version 9.4 (or higher) will be used for all analyses.

7.1.1 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the study medication. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.2 Definition of Study Visit Windows

All data will be categorized based on the scheduled visit at which it was collected. These visit designators are predefined values that appear as part of the visit tab in the eCRF.

7.1.3 Conventions for Missing Adverse Event Dates

Missing or partial AE start dates will be imputed according to the following rules.

Table 7.a Imputation Rules for Missing AE Start Dates

Non- missing	Missing	Estimated
Month and Year	Day	Day of first dose date of STUDY DRUG, if month and year of onset date are the same as month and year of date of first dose. The last day of the month, if the month and year of onset date are before the month and year of date of first dose of STUDY DRUG. The first day of the month, if the month and year of onset date are after the month and year of date of first dose of STUDY DRUG.
Year	Day and Month	Day and month of first dose date of STUDY DRUG, if the year of onset date is the same as the year of date of first dose of STUDY DRUG. December 31st, if the year of onset date is prior to the year of date of first dose of STUDY DRUG. January 1st, if the year of onset date is after the year of date of first dose of STUDY DRUG.
	Day, Month and Year	Date of first dose of STUDY DRUG

Missing or partial AE stop dates will be imputed according to the following rules. If only the day is missing, use 15th of the month; if both month and day are missing, use June 30th. For a record with a complete start date and a partial stop date, if the estimated stop date would become earlier than the start date, the stop date will not be estimated.

If AE stop date is not missing and AE stop date < estimated start date, let estimated onset date = AE stop date.

All dates presented in listings are recorded dates without imputation.

7.1.4 Conventions for Missing Concomitant Medication Dates

If only the day is missing, use 15th of the month; if both month and day are missing, use June 30th. For a record with a complete start date and a partial stop date, if the imputed stop date would become earlier than the start date, the stop date will not be estimated.

All dates presented in listings are recorded dates without imputation.

7.2 Analysis Sets

7.2.1 Safety/Modified Intent-to-Treat Population

The safety/modified intent-to-treat (mITT) population consists of all subjects who have measurable lesions at Baseline and receive at least 1 dose of brentuximab vedotin. The safety/mITT population will be used for analyses of efficacy, safety, and patient demographics and baseline disease characteristics, unless otherwise stated.

7.2.2 Per-protocol Population

The per-protocol population consists of all subjects who have measurable lesions at Baseline and no significant protocol deviations determined by the project clinician. The per-protocol population will be used for sensitivity analyses of tumor response.

7.2.3 PK Population

The PK analysis population consists of patients with sufficient dosing and PK data to reliably estimate PK parameters as determined by the clinical pharmacologist. The PK population will be used for all PK analyses.

7.2.4 Immunogenicity Population

The Immunogenicity population consists of patients who receive at least 1 dose of brentuximab vedotin and have ATA status assessment at Baseline, and at least one postbaseline sample.

7.3 Disposition of Subjects

Disposition of patients will be tabulated with the number and percentage of patients for the following categories: patients in each of the study populations in Section 7.2, patients discontinued from the study drug treatment, primary reason to discontinue from the study drug treatment, patients discontinued from the study, and primary reason to discontinue from the study. All percentages will be based on the number of patients in the safety/mITT population.

A listing will be used to present data concerning patient disposition.

7.3.1 Protocol Deviations

Protocol deviation will be collected by clinical team and entered into clinical trial management system (CTMS). Important protocol deviation criteria will be established as “Major” in Protocol Deviation and patients with important protocol deviations will be identified and documented before database lock. Important protocol deviations and the number of subjects with important protocol deviations will be tabulated for enrolled patients with HL, with sALCL, and for the combined populations.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized for patients in the safety/mITT population by disease type. Baseline demographic data to be evaluated will include sex, age, race, ethnicity, body weight, height, and BMI. The formulation for BMI is:

$$\text{BMI} = \frac{weight(kg)}{height(m)^2}$$

The following baseline disease characteristics will be summarized for patients in the safety/mITT population by disease type.

At initial diagnosis

- Age at initial diagnosis.
- Evidence of Bone Marrow Involvement.
- Evidence of Extranodal Involvement.
- Ann Arbor Stage.

At Study Entry

- Time since initial diagnosis.
- History of Bone Marrow Involvement.
- Evidence of Extranodal Involvement.
- Ann Arbor Stage.
- B Symptoms.

7.5 Medical History and Concurrent Medical Conditions

A complete medical history will be compiled for each patient during the screening period prior to the first dose of brentuximab vedotin. General medical history of all patients will be presented in a by-patient listing in reported terms.

Concurrent medical conditions that will be assessed include B symptoms (persistent fever, drenching night sweats, and unexplained weight loss >10%) and clinical evaluations of palpable liver and spleen. These assessments will be presented over time in by-patient listings.
B symptom resolution rate is defined as the proportion of patients with lymphoma-related B symptom(s) at baseline who achieve resolution of all B symptoms at any time during the treatment period. For patients with any B symptom at Baseline, B symptom resolution rate and the 95% exact CI will be summarized.

7.6 Medication History and Concomitant Medications

Medication history including prior antineoplastic therapy, prior surgery, prior radiation, and prior transplant procedure information that have been received prior to the first dose of brentuximab vedotin, if available, will be presented in by-patient listings. The number and percentage of patients with any prior event will be tabulated by disease type based on the safety/mITT population. The best response to last prior therapy will also be tabulated by disease type. For ordering purposes, prior therapies with partial end date will have the date imputed as the last day of the month or December 31st if the month is also unknown, but no later than the date of first dose of study drug. All dates presented in listings are recorded dates without imputation.

Concomitant medication is defined as any medication administered between the first dose of the study drug and the EOT visit. Concomitant medications will be coded by preferred term using the World Health Organization (WHO) Drug Dictionary (March 2012 Version or higher). The number and percentage of patients taking concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug generic term. Patients are counted once for each ATC pharmacological subgroup and once for each WHO generic term.

Subsequent anticancer therapies received after EOT will be tabulated separately.

Concomitant procedures will not be coded, instead will be presented in a by-patient listing.

7.7 Study Drug Exposure and Compliance

The exposure to brentuximab vedotin will be characterized by total amount of dose taken (mg), number of treated cycles, duration of treatment (days), and relative dose intensity (RDI, %).

Total amount of dose taken (mg) is the summation of actual doses (prepared dose (mg) × (actual volume / prepared volume)). Total dose expected (mg) is the summation of expected doses (dose level initially assigned multiply by weight used for dosing calculation). Dose intensity (mg/kg/week) is total dose (mg/kg) / (duration of treatment in days /7). Relative dose intensity (RDI) is

$$\text{RDI (\%)} = \frac{Dose\ intensity\ (mg/kg/week)}{\frac{expected\ dose\ level\ (1.8\ mg/kg)}{Number\ of\ treated\ cycles \times 3}} \times 100\%$$

A treated cycle is defined as a 21-day period, during which the patient receives any amount of brentuximab vedotin (scheduled for single dose in 21-day period). The duration of treatment is defined as time from the first study dose to 21 days after the last study dose, or death date, whichever is earlier:

Duration of treatment = min(Last dose date + 21, death) - First dose date

Action on study drug (including dose reduced, increased, missed, delayed, interrupted, held, or discontinued permanently) will be summarized by Cycle 1 through 16. Percentage will be calculated based on the number of patients treated during each cycle.

Dosing data including dose modification and action on drug will also be presented in a by-patient, by-cycle listing.

7.8 Efficacy Analysis

ORR, CR and PR rates, DOR, PFS, and OS will primarily be conducted using the safety/mITT population. Sensitivity analyses of the efficacy endpoints including ORR, CR and PR rates, and DOR will also be evaluated using the Per-protocol population. All efficacy data will be summarized by disease type outlined in Section 7.1.

7.8.1 Primary Efficacy Endpoint(s)

The primary efficacy endpoint is the ORR of patients who achieve a CR or PR as determined by the investigator using PET scans, CT scans, and clinical assessment according to IWG revised response criteria.

ORR per investigator (CR+PR) will be summarized with 2-sided 95% exact confidence intervals using the safety/mITT population. A sensitivity analysis of ORR per investigator will also be summarized using the Per-protocol population.

The sum of products of diameters (SPD) for up to 6 of the largest dominant nodes or nodal masses will be quantitatively identified at baseline and subsequent response assessments. A waterfall plot will be used to characterize the best percent change of SPD from Baseline in target lesions for individual patients.

No formal hypothesis testing will be conducted with respect to ORR.

7.8.2 Secondary Efficacy Endpoint(s)

CR rate per investigator will be summarized with 2-sided 95% exact confidence intervals using the safety/mITT population. A sensitivity analysis of CR rate per investigator will also be summarized using the Per-protocol population

DOR and PFS will be estimated base on the investigator assessments using PET scans, CT scans, as well as clinical evaluations according to the IWG revised response criteria. DOR will primarily be summarized using the subset of patients with a CR or PR in the safety/mITT population; a sensitivity analysis of DOR will also be summarized using the subset of patients with a CR or PR in the Per-protocol population. PFS and OS will be summarized using the safety/mITT population.

DOR in subjects with a CR or PR is defined as the time from start of the first documentation of objective tumor response (CR or PR) to the first subsequent documentation of objective tumor progression or to death due to any cause, whichever comes first. DOR will be censored on the day of the last assessment of measured lesions documenting absence of PD for patients who do not have objective tumor progression and are still on study at the time of analysis, are given antitumor treatment other than the study treatment or SCT, or are removed from study prior to documentation of objective tumor progression.

PFS is defined as the time from the first dose until disease progression or death due to any cause, whichever occurs first. PFS will be censored on the day of the last assessment of measured lesions documenting absence of PD for patients who do not have objective tumor progression and are still on study at the time of analysis, are given antitumor treatment other than the study treatment or SCT, or are removed from study prior to documentation of objective tumor progression. Patients lacking an evaluation of tumor response after their first dose will have their event time censored at the day of first dose.

OS is defined as the time from the first dose until death due to any cause. In the absence of confirmation of death, survival time will be censored at the last date the patient is known to be alive. Patients lacking data beyond the day of first dose will have their survival time censored at the day of first dose.

DOR, PFS, and OS will be analyzed using the Kaplan-Meier method, the 25th, 50th (median), and 75th percentiles, if estimable, will be presented along with the associated 2-sided 95% confidence intervals. The results will also be presented in figures (Kaplan-Meier plots).

For patients with any B symptom at Baseline, B symptom resolution rate and the 95% exact CI will be summarized.

Efficacy data will also be listed by patient.

7.8.3 Additional Efficacy Endpoint(s)

Disease control rate (DCR) per investigator (CR+PR+SD) will be summarized with 2-sided 95% exact confidence intervals using the safety/mITT population. A sensitivity analysis of DCR per investigator will also be summarized using the Per-protocol population.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

Pharmacokinetic analysis will be conducted using the PK population.

Serum concentrations of brentuximab vedotin (ADC) and total therapeutic antibody (TAb), and plasma concentrations of monomethyl auristatin E (MMAE) will be determined using validated assays.

Descriptive statistics (eg, number of patients, arithmetic mean, geometric mean, StdDev, median, percentage of coefficient of variation (%CV), minimum, and maximum) will be used to summarize serum concentrations of ADC and TAb, and plasma concentrations of MMAE at each prespecified time point in Cycle 1 through 16. The mean concentrations-time profiles of ADC, TAb, and MMAE will be plotted over time and in greater detail for Cycles 1 and 2. The complete set of the same data (Cycles 1-16 or up to the cycle where N $\geq$3) will also be plotted for ADC on a single plot. Similar plots will be provided for TAb and MMAE. Individual patient concentration data will be listed and plotted over time by cycle.

Noncompartmental analysis for the determination of PK parameters such as t_{max}, C_{max}, AUC_{21D}, AUC_{∞}, $t_{1/2z}$, CL, and V_{ss} will be performed as data permit for ADC and TAb. The PK parameters of t_{max}, C_{max}, AUC_{21D}, AUC_{∞}, and $t_{1/2z}$ will be estimated for MMAE. These parameters will be summarized by cycle. The summary statistics will consist of N, mean, StdDev, %CV, median, min, max, and geometric mean. Individual patient values of the parameters will be listed by cycle.

More exploratory plots may be presented in the CSR as needed.

7.9.2 Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

7.10.1 Immunogenicity Analysis

Immunogenicity will be summarized using the Immunogenicity population (Section 7.2.4). Descriptive statistics will be used to summarize patients in the following categories: ATA negative, transiently ATA positive, persistently ATA positive, low or high ATA titer, and negative or positive nATA.

- ATA Negative – defined as patients who do not have a confirmed positive ATA status in any postbaseline assessment.
- Transiently ATA positive – defined as patients who have confirmed positive ATA status in 1 or 2 postbaseline assessments.
- Persistently ATA positive – defined as patients who have confirmed positive ATA status in more than 2 postbaseline assessments.
- High ATA titer – defined as patients who have at least one postbaseline ATA titer >25.
- Low ATA titer – defined as patients whose postbaseline ATA titer numbers are all ≤25.
- nATA negative – defined as patients who do not have positive nATA in any postbaseline ATA positive sample.
- nATA positive – defined as patients who have positive nATA in any postbaseline ATA positive sample.

ATA status, ATA titer and nATA will be listed by patient. ATA titer (high or low) and nATA status (nATA negative or positive) will also be tabulated for patients who are transiently or persistently ATA positive.

For effect of ATA and nATA on efficacy, the proportions of patients in CR and PR may be summarized within each ATA response status (negative, transiently positive, persistently positive) and nATA status by disease type. The same analysis may be repeated based on ATA titer (high, >25; low, ≤25). In addition, patient level ATA and efficacy (overall response) data may be listed together.

For effect of ATA and nATA on safety, patient incidence of AEs (preferred term) by ATA response status (negative, transiently positive, persistently positive) and nATA status may be provided for both HL and sALCL. The same analysis may be repeated based on ATA titer (high, >25; low, ≤25).

CCI [redacted]

7.11 Safety Analysis

Safety will be evaluated by the incidence of treatment-emergent AEs (TEAEs), severity and type of AEs, and by changes from baseline in the patient's vital signs, neurotoxicity assessment, ECGs, and clinical laboratory results. Exposure to study drug and reasons for discontinuation will also be tabulated.

These analyses will be performed using the safety/mITT population.

7.11.1 Adverse Events

AEs will be tabulated according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0 or higher by system organ class, high-level terms, preferred terms and severity. AEs with missing start and/or end dates will be imputed according to rules specified in Section 7.1.3. TEAEs are defined as any AEs that occur after administration of the first dose of brentuximab vedotin and up through 30 days after the last dose. Patients who experience the same AE more than once will have that event counted only once within each system organ class, once within each high-level term, and once for each preferred term. AEs will be summarized and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- TEAEs resulting in study drug discontinuation.
- SAEs.
- AEs of peripheral neuropathy identified by the broad search MedDRA SMQ "Peripheral neuropathy".

Treatment-emergent AEs will be tabulated by system organ class, high-level term and preferred term. The most commonly reported treatment-emergent AEs (ie, those events reported by ≥10% of all patients) will be tabulated by preferred term. Additional analyses of peripheral neuropathy may also be presented.

7.11.1.1 Serious Adverse Events

The number and percentage of patients experiencing at least 1 treatment-emergent SAE will be summarized by MedDRA (Version 19.0 or higher) primary system organ class, high-level term, and preferred term. Drug-related SAE assessed by the investigator will be summarized similarly.

In addition, a by-subject listing containing all SAEs will be presented, regardless of treatment-emergent AE status.

7.11.1.2 Peripheral Neuropathies

Peripheral Neuropathy (PN) is defined by the peripheral neuropathy SMQ broad search. The incidence of treatment-emergent PN and treatment-emergent drug-related PN will each be summarized by preferred term and severity. The incidence of peripheral motor neuropathy will also be calculated. Time to onset, resolution and improvement of PN events will be summarized. Individual plot by preferred term for treatment-emergent peripheral neuropathy (SMQ) may be presented.

7.11.1.3 Deaths

A by-subject listing of the deaths will be presented. All deaths occurring on-study and during follow-up will be displayed (regardless of treatment-emergent AE status). On-study death is defined as a death that occurs between the first dose of brentuximab vedotin and 30 days after the last dose.

7.11.1.4 Adverse Events Resulting in Discontinuation of Study Drug

AEs resulting in discontinuation of study drug will be presented in a by-patient listing and also in a summary table by system organ class, high-level term and preferred term.

7.11.2 Clinical Laboratory Evaluations

Descriptive statistics for the actual values of clinical laboratory parameters (and/or change from baseline in clinical laboratory parameters) will be presented for all scheduled measurements over time. Mean laboratory values over time will be plotted for key laboratory parameters.

If a patient has repeated laboratory values for a given time point, the value from the latest evaluation will be used. If the report lab values contain a nonnumeric qualifier, eg, > or <, the given numeric portion will be used in summary statistics.

The parameters to be analyzed are as follows:

- Hematology: Red blood cells, hemoglobin content, hematocrit, white blood cells, platelets, differential white blood cells (neutrophils, eosinophils, basophils, lymphocytes, monocytes), reticulocyte.
- Serum chemistry: Sodium, potassium, chloride, albumin, calcium, phosphorus, glucose, BUN, uric acid, creatinine, total bilirubin, AST, ALT, ALP, LDH, GGT, HbA1c, total cholesterol, triglycerides, TSH, FT3, FT4.

- Coagulation: INR, PT, APTT.

Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grades from Baseline to the worst postbaseline value.

7.11.3 Vital Signs

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs (eg, blood pressure, pulse rate, and axillary temperatures) and weight will be tabulated over time. A by-patient listing will also be presented.

7.11.4 12-Lead ECGs

ECG (QT, corrected QT [QTcB and QTcF], PR,QRS, and RR) intervals, and ventricular rate will be summarized at each scheduled time point, along with mean change from baseline to posttreatment time point.

The corrected QT interval will be computed using Bazett's formula and Fridericia's formula. The Bazett and Fridericia corrected QT interval is calculated as

$QTcB$ (msec) $=QT/(RR)^{1/2}$ and $QTcF$ (msec) $=QT/(RR)^{1/3}$

respectively, where RR is presented in the unit of sec. No decimal place will be presented in the derived dataset and TLF outputs.

In addition, a categorical analysis of QTc intervals will be performed for each time point. The number and percentage of patients in each QTc interval (<450 msec, 450 to 480 msec, 480 to 500 msec, and ≥500msec) will be summarized at Baseline and each of the subsequent time points. Categories of changes from Baseline (≥30 msec and ≥60 msec) will be summarized as well.

In addition, Overall interpretation of ECG results (normal, not clinically significant abnormal, clinically significant abnormal) is collected by eCRF according to the scheduled measurements. Shifts in ECG interpretation will be presented as cross-tabulations of numbers of patients with normal, not clinically significant abnormal and clinically significant abnormal ECG interpretation results (and will include categories for missing and totals).

7.11.5 Other Observations Related to Safety

Pregnancy test results will be provided in a by-patient listing, if applicable.

ECOG performance status scores over time will also be tabulated. A by-patient listing of ECOG performance scores will be presented by time.

7.12 Interim Analysis

Not applicable.

7.13 Changes in the Statistical Analysis Plan

Disease control rate per investigator (CR+PR+SD) that was not included in the efficacy endpoint in the protocol will be summarized.

The Immunogenicity population that was not defined in the protocol has been clearly defined in this SAP.

8.0 REFERENCES

1. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25(5):579-86.
2. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. U.S. Department of Health and Human Services National Cancer Institute. 14 June 2010.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	04-Sep-2018 14:57 UTC
	Biostatistics Approval	04-Sep-2018 15:01 UTC
	Clinical Science Approval	05-Sep-2018 01:36 UTC