Title: A Phase 1/2 Study of brentuximab vedotin (SGN-35) in Pediatric Patients with Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma or Hodgkin Lymphoma

NCT Number: NCT01492088

SAP Approve Date: 01 December 2016

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C25002

A Phase 1/2 Study of brentuximab vedotin (SGN-35) in Pediatric Patients with Relapsed or Refractory Systemic Anaplastic Large-Cell Lymphoma or Hodgkin Lymphoma

PHASE 1/2

Version**:** Final

Date**:** 01 December 2016

Prepared by:

PPD

Based on:

Protocol Version: Amendment 4

Protocol Date: 12 June 2014

1.1 Approval Signatures

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

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

3.0 LIST OF ABBREVIATIONS

AE	adverse event
ALCL	anaplastic large cell lymphoma
alloSCT	allogeneic stem cell transplant
ATA	antitherapeutic antibodies
CI	confidence interval
CR	complete remission
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival
HL	Hodgkin lymphoma
IRF	independent review facility
IV	intravenous; intravenously
IWG	International Working Group
MedDRA	medical dictionary for regulatory activities
MMAE	monomethyl auristatin E
MTD	maximum tolerated dose
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 remission
RDI	relative dose intensity
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
sALCL	systemic anaplastic large-cell lymphoma
SCT	stem cell transplant
SD	stable disease
StdDev	standard deviation
TTP	time to progression
WHO	World Health Organization

4.0 OBJECTIVES

4.1 Primary Objectives

Phase 1 primary objectives are:

- To assess the safety profile and determine the pediatric maximum tolerated dose (MTD) and/or RP2D of brentuximab vedotin
- To assess the pharmacokinetics (PK) of brentuximab vedotin

Phase 2 primary objective is:

- To determine the best overall response rate (CR, PR) with brentuximab vedotin at RP2D

4.2 Secondary Objectives

Phase 1 secondary objectives are:

- To determine the immunogenicity of brentuximab vedotin
- To determine the best overall response rate (CR, PR) with brentuximab vedotin
- To determine the time to progression, time to response, duration of response, and event-free, progression-free, and overall survival with brentuximab vedotin

Phase 2 secondary objectives are:

- To determine the time to progression, time to response, duration of response, and event-free, progression-free, and overall survival with brentuximab vedotin
- To assess the PK and safety profile of brentuximab vedotin
- To determine the immunogenicity of brentuximab vedotin

4.3 Exploratory Objectives

Phase 1 exploratory objective is:

CCI [redacted]

Phase 2 exploratory objective is:

CCI [redacted]

4.4 Study Design

This is a phase 1/2, open-label, single-agent, multicenter, dose-escalation study of brentuximab vedotin in pediatric patients with relapsed or refractory sALCL or HL for which standard, curative, life-prolonging or palliative treatment does not exist or is no longer effective. The primary objectives of the study are to assess the safety and pharmacokinetics, determine the pediatric MTD and/or RP2D of brentuximab vedotin in pediatric patients, and evaluate the antitumor activity of brentuximab vedotin in eligible patients.

Approximately 42 evaluable patients will be enrolled in this study. In the phase 1 portion of the study, up to 12 patients with relapsed or refractory CD30+ malignancies (including HL and sALCL) will be enrolled in 2 planned dose cohorts (3 to 6 patients per cohort) according to the standard 3 + 3 dose escalation scheme.

Once the MTD and/or RP2D have been reached, patients will be enrolled by diagnosis into two phase 2 study arms: relapsed or refractory sALCL, or relapsed or refractory HL. A sufficient number of patients will be enrolled in the phase 2 portion of the study to have at least 15 evaluable patients with sALCL (including patients treated at the RP2D during phase 1), of whom at least 10 patients are in first relapse, and at least 15 evaluable patients with HL (including patients treated at RP2D during phase 1).

Brentuximab vedotin will be administered by IV infusion once every 21 days. Each 21-day treatment cycle is composed of 1 day of study drug treatment, followed by a monitoring period of 20 days. The starting dose in phase 1 will be 1.4 mg/kg, and escalation will proceed using a traditional 3 + 3 design to a maximum dose of 1.8 mg/kg.

Overall response will be evaluated beginning after 2 cycles of therapy. Objective response over the course of the study will be assessed by an IRF according to the IWG Revised Response Criteria for Malignant Lymphoma [1]. Patients, including those who achieve a CR, a PR, or stable disease (SD), may receive brentuximab vedotin for up to 16 cycles. Treatment with brentuximab vedotin beyond 16 cycles may be permitted at the joint discretion of the sponsor and the investigator for those patients experiencing continued clinical benefit. Following administration of the final dose of brentuximab vedotin, patients will be monitored for adverse events for a minimum of 30 days. Patients will be followed for PFS and OS every 12 weeks for 12 months after the EOT visit. Thereafter, assessment for OS will continue every 6 months until the sooner of death or study closure or a maximum of 2 years after enrollment of the last patient. Patients who remain on treatment after Cycle 16 will be followed according to the above schedule or until study closure.

Study drug will be discontinued due to occurrence of unacceptable AE, progressive disease, patient withdrawal, or study termination. Patients may discontinue therapy at any time. Additionally, those patients who experience a CR and are candidates for hematopoietic stem cell transplantation must discontinue brentuximab vedotin prior to chemotherapy and transplant; these patients will be followed for survival analyses until study closure.

AEs will be assessed, and 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 concentration of brentuximab vedotin, total therapeutic antibody, and MMAE will be obtained during Cycle 1 and subsequent cycles at prespecified time points as described in the Schedule of Events (SOE) in the protocol.

Radiological evaluations, (CT scan or magnetic resonance imaging [MRI], and PET as clinically indicated), will be employed to assess the status of the patient's underlying disease. An evaluation of disease response will be assessed by an IRF according to the IWG Revised Response Criteria for Malignant Lymphoma [1] evaluated at Cycles 2, 4, 7, 10, 13, and 16 and

then at the end of treatment. The scan frequency for patients who receive treatment past Cycle 16 is outlined in the Schedule of Events. Additional evaluations may be necessary when clinically indicated.

5.0 ANALYSIS ENDPOINTS

5.1 Phase 1 Primary Endpoints

- Adverse events (AEs), serious adverse events (SAEs), assessments of clinical laboratory values, and vital signs measurements
- Serum concentrations of brentuximab vedotin, total therapeutic antibody, and plasma concentrations of MMAE

5.2 Phase 1 Secondary Endpoints

- Antitherapeutic antibody (ATA), ATA titer, and neutralizing ATA
- Best overall response rate (CR, PR) as determined by an independent review facility (IRF) using positron emission tomography (PET), computed tomography (CT), magnetic resonance imaging (MRI), and clinical assessment, according to International Working Group (IWG) revised response criteria
- Time to progression
- Time to response
- Duration of response
- Event-free survival
- Progression-free survival
- Overall survival

5.3 Phase 1 Exploratory Endpoints

- CCI [redacted]

5.4 Phase 2 Primary Endpoints

- Best overall response rate (CR, PR) as determined by an IRF using PET, CT, MRI, and clinical assessment according to IWG revised response criteria

5.5 Phase 2 Secondary Endpoints

- Time to progression
- Time to response
- Duration of response
- Event-free survival

- Progression-free survival
- Overall survival
- Adverse events, serious adverse events, assessments of clinical laboratory values, and vital signs measurements
- Serum concentrations of brentuximab vedotin, total therapeutic antibody, and plasma concentrations of MMAE
- Antitherapeutic antibody (ATA), ATA titer, and neutralizing ATA

5.6 Phase 2 Exploratory Endpoints

- CCI [redacted]

6.0 DETERMINATION OF SAMPLE SIZE

Approximately 42 evaluable patients will be enrolled in this study. In the phase 1 portion of the study, up to 12 patients with relapsed or refractory CD30+ malignancies will be enrolled in 2 planned dose cohorts (3-6 patients per cohort), according to the standard 3 + 3 dose escalation scheme.

Once the MTD and/or RP2D have been reached, patients will be enrolled by diagnosis into two phase 2 study arms: relapsed or refractory sALCL or relapsed or refractory HL. A sufficient number of patients will be enrolled in the phase 2 portion of the study to have at least 15 evaluable patients with sALCL (including patients treated at the RP2D during phase 1), of whom at least 10 patients are in first relapse, and at least 15 evaluable patients with HL (including patients treated at the RP2D during phase 1).

The sample size is not based on statistical consideration. Based on the exact binomial confidence interval calculation, 10 responses observed out of the 15 evaluable patients (overall response rate of 66.7%) will provide a 95% confidence interval of (38%, 88%).

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. Frequencies and percentages 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.

Unless otherwise specified, safety and efficacy data will be summarized in the following 7 groups: 1.4 mg/kg phase 1 only; 1.8 mg/kg phase 1 only; 1.8 mg/kg phase 1&2 HL only; 1.8 mg/kg phase 1&2 sALCL only; 1.8 mg/kg phase 1&2 sALCL in first relapse only; 1.8 mg/kg all patients; all patients. Pharmacokinetic analyses will be summarized by dose and treatment cycle.

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 will 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.

SAS Version 9.2 (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 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 7.1 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 start date and a partial stop date, if the estimated stop date is before 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 start date and a partial stop date, if the imputed stop date is before 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 Population

The safety population will include patients who have received at least 1 dose of study drug. Safety population will be used for all safety, efficacy, and immunogenicity analyses, unless otherwise specified.

7.2.2 PK Population

The PK population will include patients with sufficient dosing and PK data to reliably estimate PK parameters.

The PK population will be used for PK analyses.

7.2.3 CCI

CCI

[redacted]

7.2.4 Response-Evaluable Population

The response-evaluable population will include patients who receive at least 1 dose of study drug, have measurable disease at baseline, and have 1 postbaseline disease assessment.

The response-evaluable population will be used for analyses of disease response, time to response and duration of response.

7.2.5 Dose-Limiting Toxicity (DLT)-Evaluable Population

The DLT-evaluable population will include patients who either experience a DLT during phase 1 or receive all scheduled doses and complete all study procedures in phase 1 without a DLT.

The DLT-evaluable population will be used for the analysis of DLTs.

7.3 Disposition of Subjects

Disposition of patients includes the number and percentage of patients for the following categories: patients in each of the study populations in Section 7.2, primary reason to discontinue from the 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 population.

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

7.4 Demographic and Other Baseline Characteristics

7.4.1 Demographics

Demographic and baseline characteristics will be summarized for patients in the safety population by dose level and disease type. Baseline demographic data to be evaluated will include sex, age, ethnicity, race, body weight, height, body surface area (BSA). The formulation for BSA is:

$$\text{BSA } (m^2) = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

7.4.2 Other Baseline Characteristics

The following baseline characteristics will be summarized for patients in the safety population by dose level and disease type.

At initial diagnosis

- Months since initial diagnosis
- Disease Type
- Ann Arbor Stage
- Evidence of Bone Marrow Involvement
- Evidence of Extranodal Involvement

At Study Entry

- Evidence of Bone Marrow Involvement
- B Symptoms

7.5 Medical History and Concurrent Medical Conditions

General medical history of all patients will be presented in a by-patient listing in reported terms, ie, not coded.

B symptom assessments (fever, night sweats, and weight loss) and clinical evaluation of palpable liver and spleen will be presented over time in by-patient listings.

7.6 Medication History and Concomitant Medications

Medication history including prior antineoplastic therapy, prior surgery, prior radiation, and prior transplant procedure information will be presented in by-patient listings. The number and percentage of patients with any prior event will be tabulated by dose and by disease type.

Concomitant medications will be coded by preferred term using the World Health Organization (WHO) Drug Dictionary (March 2012 Version). Concomitant medication is defined as any medication administered between the first and the last days (inclusive) of the study. The number and percentage of patients taking concomitant medications from signing of informed consent form through 30 days after the last dose of brentuximab vedotin 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 preferred term.

Concomitant procedures will not be coded, but 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 dose of drug received in mg, number of treated cycles, duration of treatment, and relative dose intensity (RDI, %).

RDI (%) =100% * (total dose administered (mg) / total dose expected (mg))

Total dose expected is the summation of expected dose (dose level initially assigned multiply by weight) in each cycle during treatment.

A treated cycle is defined as a 21-day period, during which the patient receive 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:

Duration of treatment = Last dose date + 21 - First dose date

Action on study drug (including dose reduction) will be summarized by Cycle 1 through 16.

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

7.8 Efficacy Analysis

Response rates (OR, CR, PR), time to response, and duration of response will be conducted using the response-evaluable population. The other efficacy evaluations will be conducted using the safety population unless otherwise specified. All efficacy data will be summarized for the 7 groups listed in Section 7.1. If the sample size is too small to do a certain analysis in a group, no results will be presented for that group.

7.8.1 Primary Efficacy Endpoints

There is no primary efficacy endpoint in phase 1. The primary endpoint in phase 2 is overall response rate (ORR) of patients who achieve CR or PR as determined by an independent review facility (IRF) using PET, CT, MRI, and clinical assessment according to IWG revised response criteria.

The primary efficacy endpoint of ORR per IRF, along with CR rate, and PR rate will be summarized with 2-sided 95% exact confidence intervals. Response rates (OR, CR, and PR) will be summarized using the response-evaluable population.

7.8.2 Secondary Efficacy Endpoints

Besides response rates per IRF, response rates (ORR, CR, PR) per investigator assessments will also be summarized for all 7 groups listed in Section 7.1. Response rates will be summarized with 2-sided 95% exact confidence intervals.

The other secondary efficacy endpoints include time to progression (TTP), time to response, duration of response (DOR), event-free survival (EFS), progression-free survival (PFS), and overall survival (OS). TTP, DOR, EFS, and PFS will be estimated using independent review facility (IRF) assessment unless otherwise specified. Time to response and DOR will be

summarized using the response-evaluable population; TTP, EFS, PFS, and OS will be summarized using the safety population.

TTP is defined as the time from the first dose until the first subsequent documentation of objective tumor progression. TTP will be censored on the last radiological assessment of measured lesions documenting absence of PD for patients who do not have objective tumor progression.

Time to response is defined as the time from the first dose until the first documentation of objective tumor response (CR or PR). Time to response will be censored on the last radiological assessment of measured lesions documenting absence of CR or PR for patients who do not have a CR or PR.

Duration of response in subjects with response (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. Duration of response will be censored on the day following the date of the last radiological 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 stem cell transplant (SCT), or are removed from study prior to documentation of objective tumor progression.

EFS is defined as the time from the first dose until any cause of treatment failure: disease progression per IRF (including progression events during follow-up period), premature discontinuation of treatment for any reason (ie, not completing 16 cycles of treatment due to any reason), or death due to any cause, whichever occurs first. EFS will be censored on the last PFS assessment date if none of the above events occur during the study.

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 following the date of the last radiological 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.

TTP, time to response, DOR, EFS, 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).

A waterfall plot may be used to compare PFS per investigator from the current study versus PFS achieved with the last therapy received prior to study entry.

A waterfall plot will be used to summarize the greatest percent reduction in target lesions for individual patients.

Efficacy data will also be listed by patient.

7.8.3 Additional Efficacy Endpoint(s)

Not applicable

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic Analysis

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 ADC, serum TAb, and plasma MMAE concentrations at each time point in Cycles 1 and 8 at each dose level. The mean concentrations-time profiles of ADC, TAb, and MMAE will be plotted for cycles 1 and 8. The complete set of the same data (Cycles 1-16 or up to the cycle where N $\geq$3) will also be plotted for each dose level for ADC on a single plot. Similar plots will be provided for the TAb and the MMAE. Individual patient concentration data will be listed and plotted over time by cycle and by dose level.

Noncompartmental analysis for the determination of PK parameters such as t_{max}, C_{max}, $AUC_{0\text{-}21\ day}$, $AUC_{0\text{-}\infty}$, $t_{1/2}$, CL, and V_{ss} will be performed as data permits for ADC and TAb. The PK parameters of t_{max}, C_{max}, $AUC_{0\text{-}21\ day}$, $AUC_{0\text{-}\infty}$, and $t_{1/2}$ will be estimated for MMAE. These parameters will be summarized by dose level and cycle. The summary statistics will consist of N, mean, StdDev, %CV, median, min, max, and geometric mean. $AUC_{0\text{-}21\ day}$ or $AUC_{0\text{-}\infty}$ of ADC at 1.4 mg/kg will be scaled to 1.8 mg/kg (parameter to be scaled with multiplication of 1.29) for purposes of evaluating estimated exposures at the 1.8 mg/kg dose across the PK population. The individual CL of ADC and TAb will also be computed by normalizing for the baseline body weight and body surface area. Individual patient values of the parameters will be listed by cycle.

The 1.8 mg/kg and scaled 1.8 mg/kg $AUC_{0\text{-}21\ day}$ or $AUC_{0\text{-}\infty}$ of ADC will be plotted against age and/or body weight. 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 CCI

CCI [redacted]

7.10.2 Immunogenicity Analysis

Immunogenicity will be summarized using descriptive statistics into the following categories: ATA negative, transiently ATA positive, persistently ATA positive, low and high ATA titer, and neutralizing ATA (nATA).

- ATA Negative - defined as patients who do not have positive ATA in any postbaseline sample
- Transiently ATA positive - defined as patients who have positive ATA in 1 or 2 postbaseline samples
- Persistently ATA positive - defined as patients who have positive ATA in more than 2 postbaseline samples
- High ATA Titer: >25
- Low ATA titer: ≤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 neutralizing ATA will be listed by patient. Neutralizing ATA status (nATA negative and positive) will also be listed for patients who have positive antibody status.

For effect of ATA on efficacy, the proportion of patients in CR and PR will be summarized within each ATA response status (negative, transiently positive, persistently positive) 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 will be listed together by time.

For effect of ATA on safety, patient incidence of AEs (preferred term) by ATA response status (negative, transiently positive, persistently positive, high and low titer) will be provided for both HL and sALCL. Infusion-related reactions (preferred term) will also be summarized by ATA status, ATA titer and nATA status.

The relationship between immunogenicity status (ATA, ATA titer, nATA) and PK may be explored.

7.11 Safety Analysis

Safety will be evaluated by the incidence of treatment-emergent AEs, 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 be tabulated.

These analyses will be performed using the safety population.

7.11.1 Adverse Events

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

- Treatment-emergent AEs
- Drug-related treatment-emergent AEs
- Grade 3 or higher treatment-emergent AEs
- Grade 3 or higher drug-related treatment-emergent AEs
- Treatment-emergent AEs 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 (i.e., those events reported by ≥ 10% of all patients) will be tabulated by preferred term. The individual patient's information on the DLTs will be presented in a listing. 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 serious AE (SAE) will be summarized by MedDRA (Version 19.0) primary system organ class, high-level term, and preferred term. Drug-related SAE will be summarized similarly.

In addition, a by-subject listing of the SAEs will be presented (the subject listing will contain all SAEs 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 treatment-related PN will each be summarized by preferred term and severity. Time to onset, resolution and improvement of PN events will be summarized. Individual plot by preferred term for treatment-emergent peripheral neuropathy (SMQ) will also 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 study drug and 30 days after the last dose of study drug.

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 last evaluation will be used.

The parameters to be analyzed are as follows:

- Hematology: hemoglobin, hematocrit, platelet count, total white blood cell (WBC) count, and differential WBC count
- Serum chemistry: blood urea nitrogen, creatinine, total bilirubin, urate, lactate dehydrogenase, gamma-glutamyl-transpeptidase (GGT), phosphate, albumin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, sodium, potassium, calcium, chloride, carbon dioxide, magnesium and uric acid
- CCI [redacted]

Shift tables for laboratory parameters will be generated based on changes in National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grades from baseline to the worst postbaseline value.

7.11.3 Vital Signs and Development Assessment

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs and weight will be tabulated over time. A by-patient listing will also be presented.

Development assessment and Tanner Scale data will be listed by patient.

7.11.4 12-Lead ECGs

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

7.11.5 Other Observations Related to Safety

Performance Status, as measured by Lansky or Karnofsky Scale status over time will be listed by patient.

7.12 Interim Analysis

Not applicable

7.13 Changes in the Statistical Analysis Plan

None

8.0 REFERENCES

1. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579-586.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Biostatistics Approval	02-Dec-2016 15:54 UTC
	Biostatistics Approval	02-Dec-2016 16:04 UTC
	Pharmacovigilance Approval	02-Dec-2016 16:32 UTC
	Clinical Pharmacology Approval	02-Dec-2016 18:25 UTC
	Medical Monitor Approval	02-Dec-2016 20:32 UTC
	Biostatistics Approval	02-Dec-2016 21:03 UTC