STATISTICAL ANALYSIS PLAN

Protocol Number:	SGN35-015
Version:	13; 05-May-2020
Protocol Title:	A phase 2 open-label study of brentuximab vedotin in front-line therapy of Hodgkin lymphoma (HL) and CD30-expressing peripheral T-cell lymphoma (PTCL) in older patients or patients with significant comorbidities ineligible for standard chemotherapy
Sponsor:	Seagen, Inc. 21823 30th Drive SE Bothell, WA 98021, USA

APPROVAL SIGNATURES

Product:	Brentuximab vedotin
Protocol Number:	SGN35-015
SAP Version:	3
Version Date:	5-May-2023

The individuals signing below have reviewed and approve this statistical analysis plan.

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ABVD	doxorubicin, bleomycin, vinblastine, and dacarbazine
ADC	antibody-drug conjugate
ADI	absolute dose intensity
AE	adverse event
ALCL	anaplastic large cell lymphoma
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATA	antitherapeutic antibodies
AUC	area under the concentration-time curve
BA/BE	bioavailability/bioequivalence
BEACOPP	bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
BICR	blinded independent central review
C_{eoi}	concentration at the end of infusion
C_{max}	maximum concentration
C_{trough}	trough concentration
CBC	complete blood count
ChlVPP	chlorambucil, vinblastine, procarbazine, and prednisone
ChlVPP/ABV	chlorambucil, vinblastine, procarbazine, and prednisone plus doxorubicin, bleomycin, and vincristine
CHOP	cyclophosphamide, adriamycin, vincristine, and prednisone
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
CR	complete remission
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DNA	deoxyribonucleic acid
DOR	duration of response
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFTF	freedom from treatment failure
G-CSF	granulocyte colony stimulating factor
GHSG	German Hodgkin Study Group
GM-CSF	granulocyte macrophage colony stimulating factor
HEENT	head, eyes, ears, nose, and throat
HIPAA	Health Information Portability and Accountability Act
HL	Hodgkin lymphoma
HRS	Hodgkin Reed-Sternberg
iADL	instrumental activity of daily living

ICH	International Conference on Harmonization
IDI	Intended dose intensity
IEC	Independent Ethics Committee
IND	Investigational New Drug
INN	International Nonproprietary Name
IPS	International Prognostic score
IR	indeterminate response
IRB	Institutional Review Board
IV	intravenous
JCV	John Cunningham virus
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MTD	maximum-tolerated dose
MUGA	multigated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NLPHL	nodular lymphocyte-predominant Hodgkin lymphoma
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PK	pharmacokinetic
PFS	progression-free survival
PML	progressive multifocal leukoencephalopathy
PR	partial remission
PTCL	peripheral T-cell lymphoma
PVAG	prednisone, vinblastine, doxorubicin, and gemcitabine
RDI	relative dose intensity
RT	radiotherapy
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SLD	sum of the longest diameters
SMQ	standardized MedDRA query
SOC	system organ class
SPD	sum of the products of the largest diameter
TAb	total antibody
TEAE	treatment-emergent adverse event
T_{max}	time at which the maximum concentration occurs
ULN	upper limit of normal
USAN	United States adopted name
USP	United States Pharmacopeia
WHO	World Health Organization

1 INTRODUCTION

This document outlines the statistical methods to be implemented within the scope of Protocol SGN35-015 amendment 13, entitled "A phase 2 open-label study of brentuximab vedotin in front-line therapy of Hodgkin lymphoma (HL) and CD30-expressing peripheral T-cell lymphoma (PTCL) in older patients or patients with significant comorbidities ineligible for standard chemotherapy". Results of the proposed analyses will become the basis of the clinical study report (CSR) for this protocol.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. All planned analyses specified in this document will be performed. Any changes to this plan in the form of "post hoc" or "data driven" analyses will be identified as such in the final clinical study report. Any changes will either be reflected in amendments to this plan before the database lock or specifically documented in the clinical study report.

2 STUDY OBJECTIVES

All objectives and endpoints are applicable to all parts of the study unless otherwise specified.

2.1 Primary Objective

- To assess the objective response rate (ORR) of single-agent brentuximab vedotin and brentuximab vedotin in combination with other agents as frontline therapy in subjects age ≥60 years and in subjects ineligible for conventional combination chemotherapy due to comorbidities

2.2 Secondary Objectives

- To evaluate safety and tolerability of single-agent brentuximab vedotin and the safety of brentuximab vedotin when given in combination with other agents
- To assess duration of response
- To assess complete remission (CR) rate
- To assess progression-free survival (PFS)
- To assess resolution of B symptoms
- To assess pharmacokinetics (PK) and immunogenicity of brentuximab vedotin (all parts) and nivolumab (Part D only)
- To assess overall survival (OS) (Parts E and F only)

2.3 Additional Objectives

- To assess event-free survival (EFS)
- To assess OS (Parts A, B, C and D)
- To assess biomarkers in serum and tumor biopsies
- To assess the relationship between PK and disease response
- To assess immunomodulatory effects of the combination of brentuximab vedotin and nivolumab in peripheral blood (Part D only)
- To assess indeterminate response (IR) rate and subsequent response (Part D only)

3 STUDY ENDPOINTS

3.1 Primary Endpoint

- ORR according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007) (Parts A, B, and C)
- ORR according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Lugano criteria) and the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Cheson 2014; Cheson 2016) (Part D)
- ORR according to modified Lugano criteria. The assessment will be per blinded independent central review (BICR) (Parts E and F)

3.2 Secondary Endpoints

- Type, incidence, severity, seriousness, and relatedness of adverse events (AE) and laboratory abnormalities
- CR rate, disease control rate, duration of ORR, duration of CR, and PFS
- ORR according to Lugano criteria per BICR (Parts E and F)
- B symptom resolution rate
- Estimates of selected PK parameters
- Incidence of antitherapeutic antibodies (ATA) to brentuximab vedotin (all parts) and nivolumab (Part D only)
- OS (Parts E and F only)

3.3 Additional Endpoints

- ORR according to the Response Evaluation Criteria in Lymphoma (RECIL) (Younes 2017), per BICR (Parts E and F)
- EFS
- OS (Parts A, B, C and D)
- Co-expression of CD30 and PD-L1/PD-L2 by HRS cells; accompanying T-cell, macrophage, and myeloid cell populations in diagnostic tumor specimens; and correlation with response rates (Part D only)
- Immune status changes, including immunophenotyping of blood immune cells, in response to treatment (Part D only)
- IR rate and subsequent response of CR, PR, or PD (Part D only)

4 STUDY DESIGN

Part A of this phase 2 open-label study is designed to evaluate the efficacy and tolerability of brentuximab vedotin as front-line monotherapy in adults age 60 and above with HL. Brentuximab vedotin, 1.8 mg/kg, will be administered intravenously (IV) every 3 weeks. Subjects enrolling on study with estimated creatinine clearance <30 mL/min will receive 1.2 mg/kg brentuximab vedotin. Subjects achieving a CR, partial remission (PR), or stable disease (SD) will be allowed to continue on treatment for up to 16 cycles. After discussion with the medical monitor, subjects who experience clinical benefit per the investigator will be eligible to receive continued brentuximab vedotin treatment until disease progression, unacceptable toxicity, or study closure.

Part B of the study is designed to evaluate the efficacy and tolerability of brentuximab vedotin in combination with dacarbazine as frontline therapy in adults age 60 and above with HL. Treatment with brentuximab vedotin 1.8 mg/kg in combination with dacarbazine 375 mg/m^2 will be given on Day 1 of Cycles 1 through 12, followed by single-agent brentuximab vedotin 1.8 mg/kg on Day 1 of Cycles 13 through 16. Subjects enrolling on study with estimated creatinine clearance <30 mL/min will receive 1.2 mg/kg brentuximab vedotin in combination with a reduced dose of dacarbazine (262 mg/m^2; ~30% reduced) every 3 weeks. Subjects who have progressive disease must discontinue treatment with both investigational agents. Subjects who have unacceptable toxicity to dacarbazine prior to completion of 12 cycles may continue to receive brentuximab vedotin as a single agent on Day 1 of each cycle for a total of 16 cycles or more of treatment. After discussion with the medical monitor, subjects who complete 16 cycles of treatment and experience clinical benefit per the investigator will be eligible to continue to receive single-agent brentuximab vedotin treatment until disease progression, unacceptable toxicity, or study closure.

Part C of this study is designed to evaluate the efficacy and tolerability of brentuximab vedotin in combination with bendamustine as frontline therapy in adults age 60 and above with HL. Treatment with bendamustine 70 mg/m^2 will be given in combination with brentuximab vedotin 1.8 mg/kg on Day 1 and then as a single agent on Day 2 of each cycle for up to 6 cycles, followed by single-agent brentuximab vedotin 1.8 mg/kg on Day 1 of the remaining cycles for up to 16 cycles. Subjects who have unacceptable toxicity to bendamustine, including developing estimated creatinine clearance <40 mL/min, prior to completion of up to 6 cycles may continue to receive brentuximab vedotin as a single agent on Day 1 of each cycle for a total of 16 cycles or more of treatment. After discussion with the medical monitor, subjects who complete 16 cycles of treatment and experience clinical benefit per the investigator will be eligible to receive continued single-agent brentuximab vedotin treatment until disease progression, unacceptable toxicity, or study closure.

In Parts A, B, and C, disease response and progression will be assessed using the Revised Response Criteria for Malignant Lymphoma (Cheson 2007).

Part D of the study is designed to evaluate the tolerability and efficacy of brentuximab vedotin in combination with nivolumab as frontline therapy in adults age 60 and above with

HL. Treatment with brentuximab vedotin 1.8 mg/kg in combination with nivolumab 3 mg/kg will be given on Day 1 of each 3-week cycle. Brentuximab vedotin will be administered at least 30 minutes prior to nivolumab. Subjects with PD or subjects with unacceptable toxicity at any time will not continue on treatment. Subjects with a response of IR will continue on treatment until demonstration of PD via radiographic imaging or biopsy. If subjects have unacceptable toxicity that is attributable to only one agent, as determined by the investigator, they will be eligible to continue on treatment with the tolerated drug as a single agent. Subjects may be treated for up to 16 cycles. Additional cycles may be allowed following approval from the sponsor medical monitor. Disease response will be assessed using the Lugano criteria (Cheson 2014) and LYRIC (Cheson 2016).

Part E and F of the study are designed to evaluate the safety, efficacy, and tolerability of brentuximab vedotin as frontline monotherapy in subjects with classical HL or CD30-expressing PTCL, respectively, who are unsuitable or unfit for combination chemotherapy. Unsuitability or unfitness for conventional combination chemotherapy will be justified by the presence of comorbidity-related factors, as documented by either a) a Cumulative Illness Rating Scale (CIRS) score ≥10 (according to the criteria specified by Salvi and colleagues (Salvi 2008) excluding current active lymphoma) or b) requiring assistance with or dependence on others for any instrumental Activities of Daily Living (IADL). Brentuximab vedotin, 1.8mg/kg, will be administered IV every 3 weeks. Subjects achieving a CR, PR, or SD will be allowed to continue treatment for up to 16 cycles. Disease response will be assessed according to modified Lugano criteria, according to the original Lugano criteria, and according to RECIL. The assessment will be per BICR.

Computed tomography (CT) and positron emission tomography (PET) scans are required for all subjects at baseline. Radiographic imaging for response assessment will be performed as follows:

- Parts A, B, and C: Response assessments with CT will be performed at Cycles 2, 4, 8, 12, and at End of Treatment (EOT). Imaging with PET will be performed at Cycles 2, 8, and at EOT. CT will be performed at Cycle 16 for subjects eligible for continued brentuximab treatment beyond 16 cycles. Response assessments performed after 16 cycles of treatment will include CT scans per institutional standard of care or at least every 6 cycles and PET scans per institutional standard of care.
- Part D: Response assessments will be performed with CT at Cycle 2 and with CT and PET at Cycles 4, 8, 12, and EOT. CT and PET are required at Cycle 16 for subjects eligible for continued treatment with brentuximab vedotin and/or nivolumab beyond 16 cycles. For subjects with a response determination of IR, radiographic assessment (CT/PET) of disease must be performed 12 weeks following IR or earlier if clinically indicated. If a subject has a second determination of IR, then subsequent repeat imaging must be performed between 4 and 8 weeks. Follow-up radiographic assessment for subjects with IR is not required if a follow-up biopsy has been performed that confirms response.

- Parts E and F: Response assessments with CT and PET will be performed at Cycles 2, 6, 11, and at EOT approximately 1 month after completion of therapy. Following the EOT visit, subjects discontinuing study treatment without progression will be followed until progression or initiation of further anti-cancer therapy. Follow-up CT scans will be performed every 4 months for 2 years and then per institutional standard of care, and follow-up PET scans will be performed per institutional standard of care.

CT/PET of diagnostic quality may be utilized for CT and PET scanning. Once a subject achieves a CR, PET scans are no longer required. PET scans performed as part of institutional standard of care may be collected at any time during the study, as available.

Subjects who receive any amount of brentuximab vedotin will be followed for survival every 3 months (Parts A to D) or 4 months (Parts E and F) until withdrawal of consent, death, or study closure, whichever comes first. Subjects who have not progressed will have response assessments until disease progression. Initiation of alternative treatment for lymphoma will also be collected.

Safety assessments will include the subject incidence and severity of adverse events and changes in clinical laboratory values, and physical examination findings. Serum concentrations of ATA to brentuximab vedotin and ATA against nivolumab will also be measured.

A detailed study assessment schedule can be found in the protocol.

5 ANALYSIS SETS

This section defines each of the analysis sets that will be utilized. The use of each analysis set will be discussed in Section 7.

5.1 Full Analysis Set

The full analysis set includes all subjects who receive any amount of brentuximab vedotin. The full analysis set will be used for efficacy analyses and all safety analyses.

5.2 Efficacy Evaluable (EE) Analysis Set

The efficacy evaluable analysis set includes all subjects with the histology of classical HL (Parts, A, B, C, D and E) and CD30-expressing PTCL (Part F) who receive any amount of brentuximab vedotin and who had both a baseline and at least one post-baseline disease assessment any time after receiving any amount of brentuximab vedotin.

5.3 Per-Protocol Analysis Set

The per-protocol analysis set includes all subjects who receive any amount of brentuximab vedotin and who had both a baseline and at least one post-baseline disease assessment and no important protocol deviations that could potentially affect tumor response.

The per-protocol analysis set may be used for secondary analyses of selected efficacy endpoints.

6 STATISTICAL CONSIDERATIONS

6.1 General Principles

This is a phase 2 open-label study to evaluate the overall clinical benefit of brentuximab vedotin as a monotherapy (in Part A, E, and F) and in combinations (with dacarbazine in Part B, with bendamustine in Part C, and with nivolumab for Part D).

Unless otherwise specified, analyses and summaries will be provided by part. For each part, descriptive statistics (mean, median, standard deviation, minimum and maximum) will be used to summarize continuous variables. Frequencies and percentages will be used to summarize categorical variables.

All confidence intervals will be calculated at two-sided 95% level. Any analysis not described in this plan will be considered exploratory, and will be documented in the clinical study report as a post hoc analysis or a change to the planned analysis.

To comply with regulatory electronic submission guidelines, listings of all clinical data will be submitted as electronic data sets. To facilitate data review for the study report, only pertinent data listings will be created and attached to the appendix of the CSR.

All statistical Tables, Listings and Figures will be produced using SAS®, version 9.2 or higher. Other statistical software used will be described in the CSR.

6.2 Determination of Sample Size

Parts A, B, C, and D will evaluate whether the ORR (CR + PR) for single-agent brentuximab vedotin or brentuximab vedotin in combination with dacarbazine, bendamustine, or nivolumab is greater than 25% using a single-arm study design. The objective of this study is to be able to detect an ORR of at least 25%, which is considered to show minimal clinical benefit given that the subject population may not have other options for initial conventional chemotherapy.

With a sample size of 30 subjects for Part A and an overall significance level of 0.1, observing 13 or more objective responses (43% ORR [lower limit of exact 90% CI, 27.87%]) would allow us to reject the null hypothesis and claim that the true ORR is greater than 25%. Similarly, with a sample size of 20 subjects for Part B and an overall significance level of 0.1, observing 9 or more objective responses (45% ORR [lower limit of exact 90% CI, 25.87%]) would allow us to reject the null hypothesis and claim that the true ORR is greater than 25%. For Part C, approximately 30 subjects will be enrolled, with at least 20 subjects treated using the lower starting dose of bendamustine (70 mg/m^2) combined with 1.8 mg/kg brentuximab vedotin. Using this sample size of 20 subjects included in the analysis for Part C and an overall significance level of 0.1, observing 9 or more objective responses (45% ORR [lower limit of exact 90% CI, 25.87%]) in this group would allow us to reject the null hypothesis and claim that the true ORR is greater than 25%. An analysis will also be performed for all 30 subjects in Part C. With the assumption of a true ORR of 75%, Parts A, B, and C of the study will have over 90% power (nQuery). For Part D, with a sample size of

20 subjects and an overall significance level of 0.1, observing 9 or more objective responses (45% ORR [lower limit of exact 90% CI, 25.87%]) would allow us to reject the null hypothesis and claim that the true ORR is greater than 25%.

Part E (the classical HL cohort) is designed to estimate the ORR at a reasonable level of precision. Approximately 50 subjects will be enrolled to ensure adequate data for safety and efficacy evaluation. If 35 responses are observed, the estimated ORR and the associated 2-sided 95% CI using the Clopper-Pearson method is 70% (95% CI: 55.4%, 82.1%) (Clopper 1934).

Part F (the PTCL cohort) is designed to estimate the ORR at a reasonable level of precision. Approximately 50 subjects will be enrolled to ensure adequate data for safety and efficacy evaluation. Enrollment of subjects with sALCL will be capped at 50% of the total enrollment in Part F (approximately 25 subjects out of 50). If 25 responses are observed, the estimated ORR and the associated 2-sided 95% CI using the Clopper-Pearson method is 50% (95% CI: 35.5%, 64.4%) (Clopper 1934).

6.3 Randomization and Blinding

This is a phase 2, open-label study. No randomization or blinding will be utilized.

6.4 Data Transformations and Derivations

Age in years will be calculated with SAS INTCK function using first dose date and birth date.

Study Day will be calculated as Date – First Dose Date + 1 for dates on or after the first dose date. For dates prior to the first dose date, Study Day will be calculated as Date – First Dose Date. For all calculations of Study Day, the First Dose Date will be the earliest date of treatment administration of any study drug.

Other time variables based on two dates, e.g., Start Date and End Date, will be calculated as (End Date – Start Date + 1) (in days) unless otherwise specified in the planned analysis section.

The following unit conversion will be implemented unless otherwise specified:

Months = Days / 30.4375
Years =Days / 365.25

Baseline values used in all analyses will be the most recent measurement prior to the first dose of study drug.

The end-of-treatment (EOT) date will be the date the EOT visit is performed; if an EOT visit is not performed, the EOT date will be either the EOS date or 30 days after the last dose of any study drug, whichever is earlier.

The change from baseline is the post-baseline value minus the baseline value:

(Post-baseline Value – Baseline Value)

If the baseline or post-baseline is missing, then the change from baseline is set to missing. The percent change from baseline is the change from baseline divided by baseline and multiplied by 100:

(Post-baseline – Baseline)/Baseline*100

If the baseline value is 0 and the postbaseline value is also 0, then the percentage change from baseline is set to 0. If the baseline value is 0 and the post-baseline value is non-zero, then the percent change from baseline is set to missing.

For efficacy assessments for all parts, the date of response will be the latest of all radiologic scan dates for the given response assessment. The date of progression will be the earliest of all radiologic scan dates for the given response assessment.

The investigator claim of clinical progression is also collected in Part D, E and F. A sensitivity analysis to incorporate investigator claim of clinical progression, in addition to the radiologic scan information will be provided for Part D, E and F. In the sensitivity analysis, subjects in Part D-F who have a response of stable disease or better per response assessment at the same visit as investigator claim of clinical progression will be counted as disease progression. The date of progression will be the earliest of all radiologic scan dates for the given response assessment, or date of investigator claim of clinical progression.

6.5 Handling of Dropouts and Missing Data

Missing data will not be imputed with the exception of AE start dates while calculating duration of events (see Appendix A for AE partial date imputation details) and treatment-emergent status (see Appendix B for treatment-emergent definition). Subjects with missing values of a variable other than the time-to-event endpoints (e.g. duration of response, PFS and OS) will be excluded from the analysis of that endpoint. Censoring rules will be applied to the estimation of the distribution of the time-to-event endpoints (Section 7.5). Subjects whose disease response cannot be assessed will be scored as non-responders for calculating the CR rate and ORR.

6.6 Multicenter Studies

There are multiple centers in this study, however it is not anticipated that any center will accrue enough subjects to warrant an analysis by center.

6.7 Multiple Comparison/Multiplicity

No multiple comparisons are planned. For retreatment subjects, the first treatment experience will be used in all analyses. Subsequent treatment experience/s will be summarized separately.

6.8 Examination of Subgroups

As exploratory analyses, subgroup analyses may be carried out for primary efficacy endpoint and selected secondary efficacy endpoints. The subgroups that may be examined include but are not limited to the following:

- Subjects who were ineligible versus subjects who had declined initial conventional chemotherapy for HL (Parts A-D only)
- Age at baseline (< median age, ≥ median age)
- Sex (Male, Female)
- Weight at baseline (<median, ≥ median weight)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status (grade 0, 1, and ≥2)
- Disease staging at initial diagnosis (stage I-II, stage III-IV)
- Instrumental Activities of Daily Living (IADL) score at baseline for Parts E and F only (<median, ≥ median)
- Cumulative Illness Rating Scale (CIRS) at baseline for Parts E and F only (<median, ≥ median)

6.9 Covariates

Covariates are not considered for adjustment in the analyses.

6.10 Timing of Analyses

The trial is not designed to allow for early stopping for futility or favorable efficacy results (see Section 8 for details).

The primary analysis for Parts A, B, C, and D will occur when the last subject in each part completes Cycle 8 restage. The primary analysis for Parts E and F will be conducted when all treated subjects have been followed for at least 6 months, discontinued from study, or had 30 days safety follow-up after PD, or study terminates, whichever comes first.

Preceding and subsequent cutoff dates may be defined and corresponding database snapshots/locks may occur to allow for more precise estimates of time-to-event endpoints.

Interim data from the study may be presented at scientific meetings such as the annual meetings of the American Society of Clinical Oncology and the American Society of Hematology.

7 PLANNED ANALYSES

All analyses will be presented by Part A, B, C, D, E and F separately. Analyses may be presented on further pooling (e.g. pooling of subjects in Parts A and E as BV monotherapy on cHL) as exploratory analyses where applicable. Analyses on selected efficacy endpoints may also be performed using the subgroups listed in Section 6.8.

7.1 Disposition

Subject enrollment and disposition will be summarized by part using the full analysis set. The table will present the number and percentage of subjects who were enrolled, received at least one dose of study drug, completed 16 and more than 16 treatment cycles, and participated in follow-up visits. The number and percentage of subjects who discontinued treatment will be summarized by the primary reason for treatment discontinuation. The number and percentage of subjects who discontinued the study will be summarized by the primary reason for study discontinuation. A listing of disposition data will be provided for the full analysis set.

Number of subjects who signed informed consent, the number of screen failures, and number of subjects in each analysis set will be summarized for all enrolled subjects. Screen failures will also be summarized by primary reason for screen failure.

A data listing will also be generated to include the primary end of treatment and end of study reasons for each subject.

7.2 Demographic and Baseline Characteristics

Demographics and baseline characteristics, including age, gender, ethnicity, race, baseline height, weight, BMI, electrocardiogram (ECG), and ECOG score will be summarized using the full analysis set. Disease specific characteristics, including time from disease diagnosis, disease staging at baseline, international prognostic index (IPI) score (for part F only), B symptom at baseline, geriatric assessment score (parts E and F only) will be summarized using the full analysis set.

Listings of demographics, and disease characteristics will be provided for the full analysis set.

7.3 Major Protocol Deviations

Major protocol deviations/violations, defined as a violation that is a divergence from the protocol that has a significant effect on subject's rights, safety, or welfare, or on the integrity of the resultant data, will be summarized by violation category (see Clinical SOP AA-000506 Handling Clinical Study Protocol Deviations). A list of subjects with major protocol deviations/violations will be presented. Protocol deviations that may affect the study results will be reviewed prior to the database lock.

7.4 Treatment Administration

Treatment administration will be summarized using the full analysis set and presented for each study drug. Summary statistics for duration of therapy (weeks) and the number of cycles per subject will be presented, as well as a frequency count for number of cycles received. Cumulative dose (mg), absolute dose intensity (ADI) and relative dose intensity (RDI) will be described. The number and percentage of subjects whose dose was ever modified will be summarized by modification type, cycle and overall (i.e., over all drug administrations for a subject). The number and percentage of doses that were modified may also be summarized by modification type, cycle and overall. Study drug administration and exposure information will be presented in a data listing by subject and visit.

The duration of treatment is defined as time from the first study dose to 21 days after the last study dose [(last dose date + 21) – first dose date]. If death occurs less than 21 days after the last study dose, duration of treatment is defined as [date of death – first dose date +1].

Intended Dose Intensity (IDI) is defined as is the intended dose of drug (e.g. mg/kg) per unit of time.

Absolute Dose Intensity (ADI) is defined as the actual dose (e.g. mg/kg) per unit of time that the subject received over the entire treatment period.

Relative Dose Intensity (RDI) is defined as the absolute dose intensity over the intended dose intensity.

RDI = ADI/IDI * 100.

Example 1:

For brentuximab vedotin, consider a subject treated for four cycles. The first intended dose was 1.2 mg/kg due to renal insufficiency and the later doses were increased to 1.8 mg/kg. The third dose was delayed for one week, and for the fourth cycle the infusion was not completed and the subject received less than the full dose, as represented in the following table:

Visit	Intended Dose Regimen (mg/kg)	Intended Dose (mg)	Actual Dose (mg)	Cycle Length
C1D1	1.2	60	60	3 weeks
C2D1	1.8	90	90	3 weeks + 1 week delay
C3D1	1.8	90	90	3 weeks
C4D1	1.8	90	45	3 weeks

ADI (per week):

= (1.2+1.8 + 1.8 + (1.8*[45/90])) / (3 wks +3 wks + 1 wk delay + 3 wks + 3 wks) mg/kg per week
= 0.44 mg/kg per week

IDI (per week)

= (1.2+1.8+1.8+1.8) / (3 weeks * 4) mg/kg per week
= 0.55 mg/kg per week

RDI:

=0.44/0.55 * 100
=80%

Example 2:

For dacarbazine, consider a subject treated for four cycles. The first intended dose was 262 mg/m^2. The third dose was delayed for one week, and for the fourth cycle the infusion was not completed and the subject received less than the full dose, as represented in the following table:

Visit	Intended Dose Regimen (mg/m^2)	Intended Dose (mg)	Actual Dose (mg)	Cycle Length
C1D1	262	420	420	3 weeks
C2D1	375	600	600	3 weeks + 1 week delay
C3D1	375	600	600	3 weeks
C4D1	375	600	300	3 weeks

ADI (per week):

= (262 + 375 + 375 + (375*[300/600])) / (3 wks + 3 wks + 1 wk delay + 3 wks + 3 wks) mg/m^2 per week
= 92.3 mg/m^2 per week

IDI (per week)

= (262 + 375 + 375 + 375) / (3 wks*4) mg/m^2 per week
= 115.6 mg/m^2 per week

RDI:

= 92.3/115.6 * 100
= 80%

7.5 Efficacy Analyses

All efficacy analyses may be presented using the EE analysis set, the full analysis set and the per-protocol (PP) analysis set. The EE analysis set and full analysis set will be used for the primary analysis of the efficacy endpoints. Additional analyses of efficacy endpoints using the PP set will be presented only when the analysis based on the EE analysis results in a different interpretation to that based on the PP set. Analyses may also be performed using the subgroups listed in Section 6.8.

7.5.1 Primary Endpoint

7.5.1.1 Objective Response Rate (ORR)

Objective response rate (ORR) is defined as the proportion of subjects with CR or PR through the end of study or prior to the start of new anti-cancer treatment (including stem cell transplant, and excluding consolidative radiotherapy) other than the study treatment. The response will be assessed according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007) for Parts A, B and C, according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Lugano criteria) and the Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) (Cheson 2014; Cheson 2016) for Part D, and the modified Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson 2014) for Parts E and F. Details on response assessment according to the Modified Lugano criteria are provided in Appendix C. For part E and F, the assessment will be per BICR. Subjects whose disease response cannot be assessed will be scored as non-responders for calculating the ORR.

The ORR and its two-sided 95% exact confidence interval (Clopper 1934) will be calculated. This endpoint may also be tabulated by the subgroups defined in Section 6.8.

Best clinical response will be presented and may also be tabulated by the subgroups defined in Section 6.8.

Sensitivity analysis of ORR will be performed to include investigator claim of clinical disease progression for Parts D, E and F. Subjects in Parts D-F who have a response of stable disease or better per response assessment at the same visit as investigator claim of clinical progression will be counted as disease progression in the sensitivity analysis.

Up to 6 of the largest dominant nodes or nodal masses will be quantitatively identified at baseline based on the product of diameters (Cheson 2007). The nodes or nodal masses being followed for response assessment will also be quantitatively assessed at each pre-specified time point. SPD of these nodes or nodal masses is defined as the sum of the products of diameters from those nodes or nodal masses being followed for response assessment. The maximum SPD percent reduction (or minimum percent increase if there is no reduction) from baseline will be derived for each subject and will be graphically displayed (e.g. using a waterfall plot).

7.5.2 Secondary Endpoints

7.5.2.1 Complete Remission (CR) Rate

The CR rate is defined as the proportion of subjects with CR, according to the disease assessment criteria specified in Section 7.5.1.1 for each part. Subjects whose disease response cannot be evaluated will be scored as non-evaluable for calculating the CR.

CR rate will be summarized using descriptive statistics and an exact two-sided 95% confidence interval F distribution method given in (Collett 1991) will be calculated.

7.5.2.2 Disease Control Rate (DCR)

Disease control rate (DCR) is defined as the proportion of subjects with CR, PR or stable disease (SD), according to the disease assessment criteria specified in Section 7.5.1.1 for each part. Subjects whose disease response cannot be evaluated will be scored as non-evaluable for calculating the DCR.

DCR will be summarized using descriptive statistics and an exact two-sided 95% confidence interval F distribution method given in (Collett 1991) will be calculated.

7.5.2.3 Duration of Response

Duration of response is defined as the time from start of the first documentation of objective tumor response (CR or PR) to the first documentation of tumor progression (progressive disease, PD) based on radiographic evidence of progression or to death due to any cause, whichever comes first.

Duration of response data will be censored as described below:

- Subjects who do not have tumor progression and are still on study at the time of an analysis will be censored at the date of the last disease assessment documenting absence of progressive disease
- Subjects who have started an antitumor treatment (including stem cell transplant, and excluding consolidative radiotherapy) other than the study treatment prior to documented PD or death will be censored at the date of the last disease assessment prior to start of new therapy
- Subjects who are removed from study prior to documentation of tumor progression will be censored at the date of the last disease assessment documenting absence of progressive disease
- Subjects who have disease progression or death after missing two or more consecutive radiologic tumor assessments will be censored at the date of last visit with adequate tumor assessment prior to missed scans.

Duration of response will only be calculated for the subgroup of subjects achieving a CR or PR. Responses will be assessed according to the assessment criteria specified in Section 7.5.1.1 for each study part.

Duration of response will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median duration of response and its two-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated.

7.5.2.4 Duration of Complete Remission

Duration of complete remission is defined as the time from start of the first documentation of complete remission (CR) to the first documentation of tumor progression (PD) based on radiographic evidence of progression, or to death due to any cause, whichever comes first.

Duration of complete remission data will be censored as described in the section of duration of response.

Responses will be assessed according to the disease assessment criteria specified in Section 7.5.1.1.

Duration of complete remission will only be calculated for the subgroup of subjects achieving a CR. Duration of complete remission will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median duration of complete remission and its two-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated.

7.5.2.5 Progression-Free Survival (PFS)

Progression-free survival (PFS) is defined as the time from start of study treatment to first documentation of tumor progression based on radiographic evidence of progression, or to death due to any cause, whichever comes first.

Specifically,

PFS = Date of first documented PD or death – Date of first dose of study treatment + 1.

PFS will be censored as described in Table 1.

Table 1: Primary PFS censoring

Situation	Date of Progression or Censoring	Outcome
No adequate baseline tumor assessments	Date of first dose of study treatment	Censored
Progression documented at scheduled visit	Date of documented progression	Progressed
Progression documented between scheduled visits	Date of documented progression	Progressed
No progression through end of study or subject withdrawal	Date of the last disease assessment documenting absence of progressive disease.	Censored
No post-baseline tumor assessments	Date of first dose of study treatment	Censored
New anti-cancer treatment (including stem cell transplant, and excluding consolidative radiotherapy) other than the study treatment started before documented PD or death	Date of last visit with adequate assessment prior to start of anti-cancer treatment	Censored
Death before first tumor assessment	Date of death	Progressed
Death without prior progression	Date of death	Progressed
Death or progression documented after missing two or more consecutive radiologic tumor assessments	Date of last visit with adequate assessment prior to missed visits	Censored

Responses will be assessed according to the assessment criteria specified in Section 7.5.1.1 for each study part.

PFS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided. The median PFS and its two-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated.

Sensitivity analyses of CR, DCR, DOR, duration of CR, and PFS to incorporate investigator claim of clinical progression, in addition to the radiologic scan information will be provided for Part D, E and F. Sensitivity analysis of PFS and DOR by treating progression or death after missing two or more consecutive visits as an PFS event will also be provided for each part.

7.5.2.6 ORR per Lugano per BICR (Parts E and F only)

The ORR will be evaluated by BICR, according to the original Lugano criteria (Cheson 2014) as a secondary endpoint for parts E and F. The ORR will be summarized by parts and its two-sided 95% exact confidence interval (Clopper 1934) will be calculated.

7.5.2.7 B Symptom Resolution Rate

B symptom resolution rate is defined as the proportion of subjects with lymphoma-related B symptoms at baseline who achieve resolution of all B symptoms at any time during the treatment period.

For those subjects with any B symptom(s) at baseline, the B symptom resolution rate and its two-sided 95% exact confidence interval will be derived using the F distribution method given in (Collett 1991).

Additionally, a cross-tabulation of best clinical responses (CR, PR, SD, PD , and SD or better) versus B-symptom resolution (dichotomized, “yes” or “no”) will be presented for those subjects with any B symptom(s) at baseline.

7.5.2.8 Overall Survival (OS)

Overall survival is defined as the time from start of study treatment to date of death due to any cause. Specifically,

OS=Date of death – Date of first dose of study treatment + 1.

In the absence of confirmation of death, overall survival time will be censored at the last date the subject is known to be alive (i.e., date of last contact). The last contact date will be derived based on data points including, but not limited to, start/end dates from subsequent cancer-related therapy, last date subject known to be alive from long-term follow-up assessment, and end of study date. Subjects lacking data beyond the date of first dose will have their overall survival time censored to 1 day.

OS will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided by each part. The median OS and its two-sided 95% CI using the log-log

transformation method (Collett 1994) will be calculated if median is reached. OS will be analyzed as secondary efficacy endpoints for Parts E and F, and as additional endpoints for Parts A-D.

7.5.3 Pharmacokinetics, pharmacodynamic, and Immunogenicity Endpoints

All pharmacokinetics and pharmacodynamics parameters, and immunogenicity endpoints will be presented using the full analysis set who have at least one sample tested for these parameters post the first dose of study drug.

7.5.3.1 Pharmacokinetics and Pharmacodynamic Analyses

PK parameters including area under the concentration-time curve (AUC), concentration at the end of infusion (C_{eoi}) and trough concentration (C_{trough}), maximum concentration (C_{max}) and time C_{max} occurred (T_{max}) will be summarized as appropriate by cycle for brentuximab vedotin and unconjugated MMAE (Details are provided in protocol amendment 13 Section 7.4).

Brentuximab vedotin and unconjugated MMAE concentrations and nivolumab concentrations (Part D only) will be listed at each PK sampling time point. All concentrations below the limit of quantification or missing data will be labeled as such in listing.

Pharmacodynamic biomarkers data will be reported descriptively.

Correlative analysis may be conducted to explore the relationships between PK and immunogenicity and any of the measured pharmacodynamic biomarkers.

7.5.3.2 Anti-therapeutic Antibody (ATA) Incidence Rate

The ATA incidence rate is defined as the proportion of subjects that develop ATA at any time during the study. The incidence of ATA to brentuximab vedotin (all parts) and nivolumab (Part D only) will be assessed.

7.5.4 Additional Endpoints

7.5.4.1 ORR per RECIL (Parts E and F only)

For Parts E and F, ORR will be assessed per BICR, according to the Response Evaluation Criteria in Lymphoma (RECIL) (Younes 2017) as additional endpoint. ORR will be summarized by part and its two-sided 95% exact confidence interval (Collett 1991) will be calculated.

Up to 3 target lesions will be quantitatively identified at baseline based on the longest diameters (Younes 2017). The maximum percent reduction (or minimum percent increase if there is no reduction) in the sum of the longest diameters (SLD) of these nodes or nodal masses will be summarized and graphically displaced (e.g. using a waterfall plot).

7.5.4.2 ORR per Lugano per investigator (Parts E and F only)

The ORR will be evaluated by investigator, according to the original Lugano criteria (Cheson 2014) as additional endpoint for parts E and F. The ORR will be summarized by part and its two-sided 95% exact confidence interval (Clopper 1934) will be calculated.

7.5.4.3 Event Free Survival (EFS)

EFS is defined as the time from start of study treatment until any cause of treatment failure: PD, discontinuation of treatment for any reason, or death due to any cause, whichever occurs first. Subjects who withdraw consent or start new anti-cancer treatment (including stem cell transplant, and excluding consolidative radiotherapy) other than the study treatment will be treated as an EFS event. Subjects without post baseline data for disease assessment and no treatment discontinuation or death recorded will be censored at the date of first dose of study treatment.

EFS will be analyzed similarly as the PFS as described in Section 7.5.2.5.

7.5.4.4 Exploratory Correlation Analysis of Biomarkers and Pharmacokinetics parameters with Tumor Response (part D only)

Pharmacodynamic biomarkers and exploratory correlative analyses will be defined in a separate analysis plan and presented in a separate report.

7.5.4.5 IR Rate and Subsequent Response (part D only)

The IR rate is defined as the proportion of subjects with IR according to the LYRIC (Cheson 2016).

For subjects in Part D with an indeterminate response, a listing of response assessments by cycle will be provided. The indeterminate response rate and its two-sided 95% exact confidence interval will be derived using the F distribution method given in (Collett 1991). Their subsequent response of CR, PR, or PD will also be summarized.

7.6 Safety Analyses

The full analysis set will be used to summarize all safety endpoints.

Adverse events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA, Version 23.0 or higher).

Laboratory values will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE version 4.03).

Concomitant medications will be coded using WHODrug (version: WHODrug Global B3 March 1, 2020 or more recent).

7.6.1 Adverse Events

Adverse events will be summarized by descending order of frequency and then of MedDRA preferred term unless otherwise specified. For incidence reporting, if a subject reports more than one AE that was coded to the same system organ class or preferred term, the subject will be counted only once for that specific system organ class or preferred term.

A treatment-emergent AE (TEAE) is defined as a newly occurring or worsening AE after the first dose of any study drug component. Unless documented as a pre-existing condition, adverse events with unknown start date will be counted as treatment-emergent (see Appendix B for treatment-emergent definition).

Treatment-related AEs are defined as treatment-emergent AEs that are determined by the investigator to be related to the treatment on study.

Summary of subject incidence of AEs by each part will be provided for the following:

- Pre-existing AEs
- All treatment-emergent AEs
- TEAEs related to brentuximab vedotin/dacarbazine/bendamustine/ nivolumab
- Treatment-emergent serious adverse events (SAEs)
- Treatment-emergent SAEs related to brentuximab vedotin/ dacarbazine/bendamustine/ nivolumab
- TEAEs leading to dose delay of brentuximab vedotin/dacarbazine/bendamustine/ nivolumab
- TEAEs leading to dose reduction of brentuximab vedotin/dacarbazine/bendamustine/ nivolumab
- TEAEs leading to dose interruption (full dose received) of brentuximab vedotin/dacarbazine/bendamustine/ nivolumab
- TEAEs leading to the dose being stopped early (full dose not received) of brentuximab vedotin/dacarbazine/bendamustine/ nivolumab
- TEAEs leading to dose discontinuation of brentuximab vedotin/dacarbazine/ bendamustine/nivolumab
- TEAEs leading to treatment discontinuation of brentuximab vedotin/dacarbazine/bendamustine/nivolumab
- Treatment-emergent AEs by system organ class (SOC), preferred term (PT) and maximum severity. At each system organ class or preferred term, multiple occurrences of events within a subject are counted only once at the highest severity
- Grade 3 – 5 treatment-emergent AEs
- Treatment-emergent AEs by system organ class and preferred term
- Treatment-emergent peripheral neuropathy (PN) SMQ (defined by the peripheral neuropathy SMQ broad search) by preferred term
- Grade 3 –5 treatment-emergent peripheral neuropathy (PN) SMQ by preferred term

- Infusion reactions related to brentuximab vedotin/dacarbazine/bendamustine/ nivolumab by preferred term and severity grade
- Infusion reactions related to brentuximab vedotin/ dacarbazine/ bendamustine/nivolumab by cycle and severity grade
- Treatment-emergent immune-mediated AEs for Part D

7.6.2 Clinical Laboratory Parameters

Clinical laboratory data (CBC with differential and serum chemistry) will be summarized as appropriate using the full analysis set.

A summary of the worst post baseline NCI CTCAE (Version 4.03) grade will be presented for each parameter.

Laboratory results and NCI CTCAE grades for hematology, serum chemistry and pregnancies tests results will be presented as appropriate in data listings.

7.6.3 ECOG Performance Status

Shifts from baseline to the best and worst post-baseline score will be tabulated.

7.6.4 Concomitant Medications

Concomitant medications will be summarized by the WHO Drug substance name and listed by subject. Transfusions, colony-stimulating factors, and erythropoietin stimulating agents will also be summarized by the WHO Drug substance name.

7.6.5 Subsequent therapies

The data for subsequent anti-cancer therapies will be summarized and listed. For all parts, subsequent anti-cancer therapies will be summarized by the WHO Drug substance name.

7.6.6 Deaths

The number of total deaths, deaths that occur within 30 days of last study treatment, deaths that occur more than 30 days after last study treatment and relationship to disease will be summarized for each part (except for part D) and by total. For part D, number of total deaths, deaths that occur within 30 days of last brentuximab vedotin or 100 days of last nivolumab, whichever is later, deaths that occur more than 30 days after last brentuximab vedotin dose or 100 days of last nivolumab and relationship to disease will be summarized. In addition, cause of death will be identified by descending MedDRA preferred term (unless otherwise specified) and summarized for each part and by total. Death information will be listed by subject.

8 INTERIM ANALYSIS

This study is not designed to allow for early stopping for futility or favorable efficacy results. A formal interim efficacy or futility analysis is not considered meaningful or practical for this study.

Interim data from the study may be presented at scientific meetings such as the annual meetings of the American Society of Clinical Oncology and the American Society of Hematology.

Cumulative safety reviews by the Medical Monitor will occur approximately monthly. An ongoing real-time review of SAEs will be conducted by the Seattle Genetics Drug Safety Department.

9 CHANGES FROM PLANNED ANALYSES

9.1 Changes from the Protocol amendment 13

- Analyses of efficacy endpoints using the PP set may be performed for a subset of efficacy endpoints. Results for PP set will be presented only when the analysis based on the EE analysis results in a different interpretation to that based on the PP set.
- Subgroup by International prognostic score (IPS) at initial disease diagnosis for Parts A – E is not to be performed because some components of IPS data were not collected on the study case report form.

9.2 Changes from the Original SAP

Study design, determination of sample size, study objectives and endpoints, and analysis were updated to incorporate the newly added cohorts based on protocol amendments. Changes from the original SAP include the followings:

- Parts B, C, D, E and F were added.
- Languages about formal statistical hypothesis for primary efficacy endpoints in part A were removed.
- Full analysis set was added in Section 5.1.
- Safety analysis set was replaced by full analysis set in Section 5.1.
- Updated confidence intervals (CIs) to 95% CI throughout the SAP for consistency.
- Section 6.8 and Section 7.5.1 removed the statement about the timing of primary analysis occurring when the last patient completes Cycle 8 restage for Part A.
- Timing of analysis was added for all parts in Section 6.10.
- Summary of subsequent anti-cancer therapies was added in Section 7.6.5.
- Minor editorial changes were made to improve consistency and clarification throughout the document.

9.3 Changes from the SAP Amendment 1

- Updated the start date for survival time calculation to first dose date in Section 7.5.2.8 and clarified censoring rule for unknown survival status.

- Timing of analysis was updated to take into consideration of possible study closed out in Section 6.10.

10 REFERENCES

Cheson BD, Ansell S, Schwartz L, et al. Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy. Blood. 2016;128(21):2489-96.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-68.

Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-86.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-13.

Collett D. Statistical inference for binary data. Modelling Binary Data. London, Chapman and Hall. 1991:23-6.

Collett D. Interval-censored survival data. Modelling survival data in medical research. London, Chapman & Hall. 1994:237-51.

Salvi F, Miller MD, Grilli A, et al. A manual of guidelines to score the modified cumulative illness rating scale and its validation in acute hospitalized elderly patients. J Am Geriatr Soc. 2008;56(10):1926-31.

Younes A, Hilden P, Coiffier B, et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Ann Oncol. 2017;28(7):1436-47.

APPENDIX A: IMPUTATION OF PARTIALLY UNKNOWN ADVERSE EVENT DATES

The algorithm below should be used to impute pre-existing condition and adverse event (AE) start dates for which only partial information is known. For ease of reading, both pre-existing conditions and AEs will be referred to as AE for the remainder of this document. The algorithm should be applied to every AE record on a record by record basis. AE start dates should be imputed before imputation of AE condition end date in all cases. The AE condition end date should only be used in the imputation of the AE start date if it a full known date.

AE day and month are missing

If the year is the same as the year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was pre-dose:

- AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of investigational agent)

If the year is the same as the year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was post-dose:

- AE start date will be imputed as the minimum of (AE condition end date*, first dose date of investigational agent)

If the year is before the year of first dose of investigational agent:

- AE start date will be imputed as the minimum of (AE condition end date*, December 31st see example 2 below)

If the year is after the year of first dose of investigational agent:

- AE start date will be imputed as the minimum of (AE condition end date*, January 31st see example 2 below)

AE month only is missing

Treat day as missing and replace both month and day according to the above procedure

AE day only is missing

If the month/year is the same as the month/year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was pre-dose:

- AE start date will be imputed as the minimum of (AE condition end date*, day prior to first dose of investigational agent)

If the month/year is the same as the month/year of first dose of investigational agent and the onset period and/or onset time indicate that the start of the AE was post-dose:

- AE start date will be imputed as the minimum of (AE condition end date*, first dose date of investigational agent)

If the month/year is before the month/year of first dose of investigational agent:

- AE start date will be imputed as the minimum of (AE condition end date*, last day of the month)

If the month/year is after the month/year of first dose of investigational agent:

- AE start date will be imputed as the minimum of (AE condition end date*, last day of the month)

* only use condition end date if known and full end date is available.

The following algorithm should be used to impute AE condition end dates. The AE records for a condition/event should be sorted by the imputed start dates then record position (order of entry into the eCRF). After sorting the AE records, apply the following rules to partial or missing AE condition end dates:

For all records excluding the last chronological record for a condition/event

AE condition end date will be imputed as the start date of the subsequent record

For the last chronological record for a condition/event

If outcome is "recovered/resolved", "recovered/resolved with sequelae", or "fatal":

- AE condition end date will be imputed as the minimum of (last dose date + 30, death date, data extraction date)

If outcome is "recovering/resolving", "not recovered/resolved", "unknown", or blank:

- AE condition end date will not be imputed

Example 1

AESPID 1: Condition/Event HEADACHE
First dose date 01JAN2012

Prior to imputation:

Start date	Condition end date	Severity	Outcome	Onset
UNUNK2011	15APR2012	1	not recovered/resolved	pre-ICF
15APR2012	UNMAY2012	2	recovering/resolving	post 1st dose
UNMAY2012	UNJUN2012	1	not recovered/resolved	post 1st dose
UNJUN2012	UNJUN2012	3	recovering/resolving	post 1st dose
UNJUN2012	10JUL2012	2	recovering/resolving	post 1st dose
10JUL2012	--	1	not recovered/resolved	post 1st dose

Post imputation:

Start date	Condition end date	Severity	Outcome
31DEC2011	15APR2012	1	not recovered/resolved
15APR2012	31MAY2012	2	recovering/resolving
31MAY2012	30JUN2012	1	not recovered/resolved
30JUN2012	30JUN2012	3	recovering/resolving
30JUN2012	10JUL2012	2	recovering/resolving
10JUL2012	--	1	not recovered/resolved

Example 2 (highlights choice of last day of the month as opposed to the 1st or the 15th)

AESPID 4: Condition/Event NAUSEA
First dose date 01APR2012

Prior to imputation:

Start date	Condition end date	Severity	Outcome	Onset
UNUNK2011	25APR2012	1	not recovered/resolved	pre-ICF
25APR2012	UNAPR2012	2	recovering/resolving	post 1st dose
UNAPR2012	04MAY2012	1	recovered/resolved	post 1st dose

Post imputation:

Start date	Condition end date	Severity	Outcome
31DEC2011	25APR2012	1	not recovered/resolved
25APR2012	31APR2012	2	recovering/resolving
31APR2012	04MAY2012	1	recovered/resolved

APPENDIX B: DEFINITION OF THE TERM "TREATMENT-EMERGENT" WITH RESPECT TO AE CLASSIFICATION

The algorithm below should be used to determine whether an adverse event (AE) is classified as a treatment-emergent adverse event (TEAE). A TEAE is defined as any AE which worsens in severity during the safety reporting period or is newly occurring at any time, where newly occurring means that the AE was not present at baseline. For ease of reading, both pre-existing conditions and AEs will be referred to as AEs for the remainder of this document. AE dates should be imputed in accordance with the algorithm detailed in Appendix A prior to determination of TEAE classification. Details of the TEAE classification are as follows:

1. For each subject, determine the first dose date, which is the earliest date the subject receives any amount of study drug.
2. **Baseline AEs:** classify an AE record as baseline AE if it satisfies both criteria a and b below:
    a. AE onset satisfies either of i, ii or iii below:
        - Onset date is prior to the first dose date
        - Onset date is the same as the first dose date, and Onset Period is "started after consent but before the first dose of any study treatment" or Onset Time Relative to Study Treatment is "started before first infusion or before infusion on any dosing day"
        - Onset Period is "started before the signing of consent" or "started after consent but before the first dose of any study treatment"
    b. AE end date satisfies either of i or ii below:
        - End date is the same as or after the first dose date
        - End date is missing with outcome equal to
            - recovering/resolving, or
            - not recovered/not resolved, or
            - unknown or missing
3. **Post-baseline AEs:** classify an AE record as post-baseline AE if it meets either of criteria a, b or c below:
    a. Onset date is after the first dose date
    b. Onset date is the same as the first dose date, and Onset Period is "started after the first dose of any study treatment" or Onset Time Relative to Study Treatment is not "started before first infusion or before infusion on any dosing day"
    c. Onset Period is "started after the first dose of any study treatment"

4. **TEAE flag** will be derived as follows:

    a. For all AE records that have an end date prior to the first dose date, assign TEAE flag to 'N'
    b. For all baseline AEs, assign TEAE flag to 'N'
    c. For post-baseline AEs:
        - If the post-baseline AE is a continuing event of a baseline AE (i.e., events with the same AE identifier, where AE identifier is the number before the colon in SDTM AE.AESPID), then compare the post-baseline AE to the most recent baseline AE with the same AE identifier (to be referred to as "baseline AE" below). Assign TEAE flag to 'Y' for the applicable post-baseline AE records if a post-baseline AE record meets any of the following worsening criteria based on relatedness, seriousness or CTCAE grade:
            – If the post-baseline AE is related to treatment, or
            – If the post-baseline AE meets the criteria for an SAE and the most recent baseline AE was not an SAE, or
            – If the post-baseline AE has a higher CTCAE grade

            All subsequent episodes of the same AE should have TEAE flag = 'Y'.
        - Otherwise, assign TEAE flag to 'N'
        - If the post-baseline AE is not a continuing event of a baseline AE, then assign TEAE flag to 'Y'

NOTE: For summaries which include only treatment emergent AEs, include all AEs which have at least one record classified as a TEAE as well as those AEs for which TEAE status could not be determined (e.g., the value of the TEAE variable may be missing if the event cannot be identified as baseline or post-baseline – missing information on the AE CRF should be queried). Only exclude those AEs which were determined to not be treatment emergent for all records.

APPENDIX C: INTEGRATED PET AND CT RESPONSE ACCORDING TO MODIFIED LUGANO CRITERIA AND ORIGINAL LUGANO CRITERIA

The primary determination of antitumor efficacy will be ORR according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas modified to take into account CT response in the event of a PET partial response (PR) (modified Lugano criteria). The disease assessment on the basis of PET and CT response according to modified Lugano criteria is summarized in the table below:

PET Response	**CT Response**		**Integrated Response**
CR	Any		CR
PR	CR, PR		PR
	Non-CR, Non-PR		**SD**
SD	Any		SD
PD	Any		PD
	Prior PET response[a]	CT Response	
Not done or	CR	Non-PD	CR[b]
Not evaluable	non-CR	Non-PD	NE
	Any	PD	PD
No FDG-avid disease at baseline[c]	No disease present (NE)		NE
	PD		PD

NE=not evaluable.

a "Prior PET response" refers to the latest prior PET assessment that was evaluable. PET responses may be carried forward over multiple CT assessments.

b A CR according to PET will be carried forward irrespective of CT response, until CT shows PD or is assessed as NE.

c Per protocol all subjects must have FDG-avid disease at baseline.

Assessment of response, according to the original (unmodified) Lugano criteria (Cheson 2014), will be undertaken in the same manner as for modified Lugano, with the exception that if the PET response is PR the integrated response will be PR, irrespective of CT response.

Signature Page for SGN-CLIN-022892 v1.0

eSignature Approval	[redacted]23 18:33:37 GMT+0000
eSignature Approval	[redacted]23 18:54:01 GMT+0000
eSignature Approval	[redacted]6 GMT+0000
eSignature Approval	[redacted]23 22:51:48 GMT+0000
eSignature Approval	[redacted]9 GMT+0000

Signature Page for SGN-CLIN-022892 v1.0