Title: An Open-Label Study of Brentuximab Vedotin+Adriamycin, Vinblastine, and Dacarbazine in Pediatric Patients With Advanced Stage Newly Diagnosed Hodgkin Lymphoma

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: C25004

An Open-Label Study of Brentuximab Vedotin + Adriamycin, Vinblastine, and Dacarbazine in Pediatric Patients with Advanced Stage Newly Diagnosed Hodgkin Lymphoma

PHASE 1/2

Version: 2.0

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Prepared by:

PPD

Based on:

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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

A	brentuximab vedotin
A+AVD	brentuximab vedotin +Adriamycin (doxorubicin) vinblastine, and dacarbazine
ABVD	Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine
ADA	antidrug antibody
ADC	antibody-drug conjugate
AE	adverse event
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
ATA	antitherapeutic antibody
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
C_{max}	maximum observed concentration
CR	complete remission
CRF	case report form
CT	computed tomography
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
EFS	Event-free survival
EMA	European Medicines Agency
EOT	End of Treatment (visit)
HL	Hodgkin lymphoma
CCI	[redacted]
IA	Interim analysis
ICH	International Council on Harmonisation
IFRT	involved-field radiation therapy
IRF	independent review facility
ISRT	involved site radiotherapy
IWG	International Working Group
LLN	lower limit of normal
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
MTD	maximum tolerated dose

nATA	neutralizing antitherapeutic antibody
Nab	neutralizing antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall response rate
OS	Overall survival
PD	progressive disease
PDCO	Pediatric Committee
PET	positron emission tomography
PFS	Progression-free survival
PIP	Pediatric investigation plan
PK	pharmacokinetics
PR	Partial response
CCI [redacted]	
QOL	quality-of-life
CCI [redacted]	
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SOC	standard of care
SOE	Schedule of Events
TAb	total (free and conjugated) therapeutic antibody
TEAE	treatment-emergent adverse event
T_{max}	time of first time of occurrence of Cmax
ULN	upper limit of normal
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 Primary Objectives

Phase 1 Primary Objective

- To assess the safety and tolerability, and to identify the recommended dose of brentuximab vedotin (Adcetris [A]) when combined with multiagent chemotherapy regimen (Adriamycin [doxorubicin], vinblastine, and dacarbazine [AVD]) for first-line treatment of advanced stage Hodgkin lymphoma (HL) in pediatric patients.

Phase 2 Primary Objectives

- To evaluate the complete remission (CR) rate of pediatric patients with advanced stage HL at the end of protocol therapy.
- To determine the percentage of patients who are positron emission tomography negative (PET-) after 2 cycles of protocol therapy.
- To evaluate the partial remission (PR) rate of pediatric patients with advanced stage HL at the end of protocol therapy.
- To evaluate the overall response rate (ORR) of pediatric patients with advanced stage HL at the end of protocol therapy.
- To determine the percentage of patients who are able to complete 6 cycles of protocol therapy at the recommended dose.

4.2 Secondary Objectives

Phase 1 Secondary Objectives

- To describe the maximum observed concentration (C_{max}), area under the concentration-time curve from time 0 to 15 days (AUC_{0-15}), and time of first time of occurrence of Cmax (T_{max}) of brentuximab vedotin, monomethyl auristatin E (MMAE), and total (free and conjugated) therapeutic antibody (TAb).
- To evaluate the CR rate of pediatric patients with advanced stage HL at the end of protocol therapy.
- To evaluate the PR rate of pediatric patients with advanced stage HL at the end of protocol therapy.
- To evaluate the ORR of pediatric patients with advanced stage HL at the end of protocol therapy.
- To determine the percentage of patients who are PET- after 2 cycles of protocol therapy.
- To determine the percentage of patients who are PET+ after 6 cycles of protocol therapy.

- To determine the immunogenicity of brentuximab vedotin.

Phase 2 Secondary Objectives

- To evaluate the progression-free survival (PFS), event-free survival (EFS), overall survival (OS), and duration of response (DOR) in pediatric patients with advanced stage HL treated with protocol therapy.
- To determine the percentage of patients receiving irradiation for HL following study treatment.
- To assess the safety and tolerability of brentuximab vedotin when combined with multiagent chemotherapy regimen AVD for first-line treatment of advanced stage HL in pediatric patients.
- To determine the immunogenicity of brentuximab vedotin.
- To evaluate the effect of antitherapeutic antibody (ATA) status on the safety, efficacy, and pharmacokinetics (PK) of brentuximab vedotin.
- To describe the C_{max}, AUC_{0-15}, and T_{max} of brentuximab vedotin, MMAE, and TAb.
- To describe the frequency, severity, and time to resolution of peripheral neuropathy events.
- To assess immune reconstitution.

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4.4 Study Design

This is a phase 1/2, open-label, multiagent, multicenter study of brentuximab vedotin in pediatric patients diagnosed with advanced stage, classical CD30+, first-line HL. The primary objectives of the study are to assess the safety and feasibility of combining brentuximab vedotin with a multiagent chemotherapy regimen that is based on a current SOC first-line treatment regimen for newly diagnosed HL, and to evaluate the antitumor activity of this combination in pediatric patients. The proposed regimen for this study is identical to the current SOC except that in this study B (bleomycin) will be replaced with A (brentuximab vedotin) for A+AVD multiagent therapy (protocol therapy).

The study will enroll at least 55 evaluable patients. In the phase 1 portion of the study, at least 6 patients will be enrolled into up to 2 planned dose cohorts dose cohorts (48 and 36 mg/m^2, 3-6 patients per cohort) to determine the recommended dose according to a modified 3+3 design. Patients will be administered A+AVD on Days 1 and 15 of every 28-day cycle for up to 6 cycles. The first 3 patients enrolled in the study will be monitored for DLTs during the DLT observation period (Cycle 1+28 days [from the first dose through Study Day 56]). If 0 or 1 DLT occurs in the first 3 patients, 3 additional patients will be enrolled and monitored for DLTs. If the first 6 patients complete the DLT observation with 0 or 1 patient experiencing a DLT, 48 mg/m^2 will be the recommended dose of brentuximab vedotin, and approximately 49 additional patients will be enrolled in the phase 2 portion of the study to receive the protocol therapy to further assess safety and efficacy for a total of at least 55 evaluable patients at the recommended dose in the study. If more than 1 patient out of a maximum of 6 DLT-evaluable patients treated with the protocol therapy experience a DLT, the brentuximab vedotin dose will be reduced to 36 mg/m^2. If 0 or 1 patient experiences a DLT among the 6 patients treated at 36 mg/m^2, approximately an additional 49 patients will be enrolled into the de-intensified dosing regimen to ensure a total of at least 55 evaluable patients at the recommended dose (36 mg/m^2), including the patients treated at the recommended dose in phase 1. If more than 1 patient experience a DLT in the first 6 patients treated at 36 mg/m^2, the study will be discontinued (pending review of available PK data to verify that exposures achieved at these doses are consistent with expectations), as both the 36 mg/m^2 dose and the 48 mg/m^2 dose will be deemed too toxic. Available PK data will be reviewed together with the safety data to guide the final decision on the recommended dose.

Study treatment will be discontinued due to completion of 6 cycles of protocol therapy, occurrence of unacceptable AE, progressive disease (PD), patient withdrawal, or study termination. Response to treatment and disease status assessments will be evaluated according to the IWG Revised Criteria for Response Assessment for Malignant Lymphoma (ref: Cheson 2007). These disease assessments will be performed by investigators and an IRF at times specified in the Schedule of Events (SOE). Evaluations will be performed per the SOE until PD is documented by the investigator, death occurs, or the study ends.

Restaging will be performed to assess the status of the patient's underlying disease after completion of Cycle 2 treatment. Involved site radiotherapy (ISRT) should be employed at EOT in those patients who are PET+ at the end of Cycle 2 at the node sites that were PET+ at diagnosis. Additionally, restaging to determine if there is a need for additional radiotherapy will

also be performed at the EOT disease assessment. Only residual lymph nodes >1 cm that are still PET+ at EOT should be considered for radiotherapy. Extranodal lesions should require radiotherapy only if they are PET+ at the end of Cycle 2 or EOT. Whenever possible, pericardial and liver irradiation should be avoided. The use of radiotherapy is not permitted until patients have completed their EOT disease assessment.

Patients will be followed for survival until the sooner of death, study closure, or for a maximum of 2 years after enrollment of the last patient. All patients will be offered the opportunity to participate in an optional long-term follow-up, for at least 10 years after patient enrollment.

5.0 ANALYSIS ENDPOINTS

5.1 Phase 1 Primary Endpoints

- Determination of the recommended dose of brentuximab vedotin in combination with AVD in a pediatric population.
- Percentage of patients who experience AEs from the first dose of protocol therapy through 30 days after administration of the last dose of protocol therapy.
- Percentage of patients who experience serious AEs (SAEs) from the first dose of protocol therapy through 30 days after administration of the last dose of protocol therapy.

5.2 Phase 1 Secondary Endpoints

- Mean C_{max} and mean AUC_{0-15} of brentuximab vedotin, TAb, and MMAE.
- Median T_{max} of brentuximab vedotin, TAb, and MMAE.
- Percentage of patients who achieve a CR per independent review facility (IRF) assessment at EOT per IWG criteria.
- Percentage of patients who achieve a PR per IRF assessment at EOT per IWG criteria.
- Percentage of patients who achieve an overall response (OR) per IRF assessment at EOT per IWG criteria.
- Percentage of patients whose disease is PET- after 2 cycles of protocol therapy per IRF assessment.
- Percentage of patients whose disease is PET+ after 6 cycles of protocol therapy per IRF assessment.
- Percentage of patients who are ATA negative, positive, persistently positive, or transiently positive, ATA titer and neutralizing ATA (nATA) positive at baseline, predose Cycle 2 Day 1, Cycle 4 Day 1, Cycle 6 Day 1, or at termination if treatment is terminated before Cycle 6, and at EOT.
- Impact of ATA and nATA on the safety, efficacy, and PK endpoints.

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5.4 Phase 2 Primary Endpoints

- Percentage of patients who achieve a CR per IRF assessment at EOT per IWG criteria.
- Percentage of patients whose disease is PET- after 2 cycles of protocol therapy per IRF assessment.
- Percentage of patients who achieve a PR per IRF assessment at EOT per IWG criteria.
- Percentage of patients who achieve an OR per IRF assessment at EOT per IWG criteria.
- Percentage of patients who are able to complete 6 cycles of protocol therapy at the recommended dose.

5.5 Phase 2 Secondary Endpoints

- PFS, EFS, OS, DOR.
- Percentage of patients receiving irradiation for HL following study treatment.
- Percentage of patients who experience AEs from the first dose of protocol therapy through 30 days after administration of the last dose of protocol therapy.
- Percentage of patients who experience SAEs from the first dose of protocol therapy through 30 days after administration of the last dose of protocol therapy.
- Percentage of patients who are ATA negative, positive, persistently positive, or transiently positive, ATA titer and nATA positive at baseline, predose Cycle 2 Day 1, Cycle 4 Day 1, Cycle 6 Day 1, or at termination if treatment is terminated before Cycle 6, and at EOT.
- Impact of ATA and nATA on the safety, efficacy, and PK endpoints.
- Mean C_{max} and mean AUC_{0-15} of brentuximab vedotin, TAb, and MMAE.
- Median T_{max} of brentuximab vedotin, TAb, and MMAE.

- Percentage of patients who experience peripheral neuropathy, regardless of seriousness, from the first dose of protocol therapy through study closure.
- Time to onset and time to resolution for all peripheral neuropathy events.
- Immune reconstitution (peripheral blood CD34+ count; enumeration of the total lymphocyte count and lymphocyte subsets; total Ig and IgG, IgM, and IgA levels; and levels of the antibodies to tetanus, HiB, and polio serotypes) at baseline, EOT, and at 6, 12, and 18 months (±1 month) after last dose, until the start of subsequent anticancer therapy (with the exception of radiotherapy administered as part of first-line therapy).

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6.0 DETERMINATION OF SAMPLE SIZE

A total of approximately 55 evaluable patients treated at the recommended dose will be enrolled in this study. In phase 1, up to 12 DLT-evaluable patients will be enrolled into up to 2 planned dose cohorts (48 and 36 mg/m^2, 3-6 patients per cohort) according to a modified 3+3 design. Once the recommended dose has been identified, additional patients will be enrolled into phase 2 so that the total number of evaluable patients will be at least 55, including the patients treated at the recommended dose in phase 1.

Assuming the true ORR at EOT for the A+AVD regimen is 90%, with 55 evaluable patients and a two-sided type I error of α=0.2 (equivalent to a one-sided α=0.1), the study would have approximately 78% power to state that the ORR is greater than 80%.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

The primary analysis for the clinical study report will be conducted 15 months after the enrollment of the last patient, as agreed in the 2020 PIP modification. An updated analysis will be conducted 2 years after the enrollment of the last patient and will be included in an addendum to the clinical study report. A subsequent 10-year report will be provided for patients continuing in the optional long-term follow-up.

In general, descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum) will be used to summarize continuous variables. Unless otherwise noted, in addition to the analysis for a specific study Phase, all the endpoints will be presented for Phase 1 and Phase 2 combined. Frequencies and percentages will be used to summarize categorical variables. Exact confidence intervals (Clopper-Pearson Method) may be used when appropriate and will be clearly indicated. Time-to-event endpoints 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 events and censored observations. The maturity of time-to-event endpoints will be characterized by the median follow-up time using the reverse Kaplan-Meier method.

Unless otherwise specified, safety and efficacy data will be summarized in the following 5 groups when applicable: 48 mg/m^2 Phase 1 only; 36 mg/m^2 Phase 1 only; 48 mg/m^2 Phases 1&2; 36 mg/m^2 Phases 1&2; all patients enrolled. If the recommended phase 2 dose is 48 mg/m2 and no patients receive brentuximab vedotin at 36 mg/m^2, then the 36 mg/m^2 groups will be omitted from the summary. The analyses of the PK, immunogenicity, and immune reconstitution endpoints will be summarized by dose level (48 mg/m^2 and 36 mg/m^2, if applicable) 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.

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 7.1.4 and 7.1.5. CCI [redacted]

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

7.1.1 Study Definitions

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the medication, i.e., non-zero dose of any component of A+AVD. 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.

7.1.3 Definition of Study Visit Windows

All data will be categorized based on the scheduled visit at which it is collected. These visit designators are predefined values that appear as part of the visit tab on the electronic case report form (eCRF).

7.1.4 Conventions for Missing Adverse Event Dates

Every effort will be made to avoid missing/partial dates. First impute the end date of a resolved adverse event (AE) according to the following rules.

- If only the day is missing (eg, dd-Oct-2010), use min (last day of the month, death date if applicable);
- If both the day and month are missing (eg, dd-mmm-2010), use min (31-DEC, death date if applicable).

Next impute the start date of an AE according to the following rules.

- If only the day is missing (eg, dd-Oct-2010)
  - If AE year < TRTSDT(first dose) year, or AE year= TRTSDT year but AE month < TRTSDT month, use the 15th of the month;
  - If AE year > TRTSDT year, or AE year= TRTSDT year but AE month > TRTSDT month, use the 1st of the AE month;
  - If both AE year=TRTSDT year and AE month=TRTSDT month, then use min (TRTSDT, AE end date).
- If both the day and month are missing (eg, dd-mmm-2010)
  - If AE year > TRTSDT year, then use 01-Jan-(AE year) is used;
  - If AE year < TRTSDT year, then use min (01-Jul-[AE year], AE end date);
  - If AE year = TRTSDT year, then use min (TRTSDT, AE end date).
- If the year is missing, eg 20-Oct-yyyy or all three components are missing, then the AE start date will not be imputed.

All dates presented in listings are recorded dates without imputation.

7.1.5 Conventions for Missing Concomitant Medication and Subsequent Therapy Dates

The imputation of the concomitant medication (CM) start date will follow the same rules for the AE start date. Partial CM end dates will not be imputed.

For subsequent therapies (i.e., subsequent chemotherapy, radiotherapy, etc.) impute the start date as follows:

- If the date component is missing, use max (TRTEDT [last dose], first day of the month);
- If both date and month are missing, use max (TRTEDT, 01-Jan).

Partial subsequent therapy end dates will not be imputed.

7.2 Analysis Sets

7.2.1 Safety Population

The Safety Population will include patients who receive at least 1 dose of any drug in the A+AVD regimen.

All safety analyses will be performed using the safety population.

The primary analysis of the efficacy endpoints of PFS, EFS, OS, and percentage of patients receiving irradiation for HL following study treatment will also be performed based on the safety population.

7.2.2 Response-Evaluable Population

The Response-Evaluable Population will include patients who receive at least 1 dose of A+AVD, have measurable disease at baseline, and have 1 postbaseline disease assessment. The Response-Evaluable Population will be defined separately per IRF and per investigator (INV).

The Response-Evaluable Population will be used for the primary analysis of the efficacy endpoints of ORR, CR and PR rates, DOR, PET- after C2, and PET+ after C6.

7.2.3 PK Population

The PK Population will include patients with sufficient data to enable calculation of at least 1 PK parameter.

The PK population will be used for PK analyses.

7.2.4 Immunogenicity Population

The Immunogenicity Population will include patients who receive at least 1 dose of study drug and have the baseline sample and at least one post-baseline sample assessment.

The immunogenicity population will be used for immunogenicity analysis.

7.2.4 Immune Reconstitution Population

The Immune Reconstitution Population will include patients who receive at least 1 dose of study drug and have a sufficient immune reconstitution blood sampling to allow for immune reconstitution evaluation.

The immune reconstitution population will be used to analyze immune reconstitution-related endpoints.

7.2.5 DLT-Evaluable Population

The DLT-Evaluable Population will include both patients who receive at least 1 dose of protocol therapy and experience a DLT during the DLT observation period (Cycle 1+28 days [from first dose through Study Day 56]), and patients who receive all planned doses of protocol therapy in Cycle 1 and complete all relevant study procedures/assessments during the DLT observation period (Cycle 1+28 days [from first dose through Study Day 56]) without a DLT. Only patients used to determine the recommended dose will be included in the DLT-Evaluable Population. Patients who received G-CSF during the DLT observation period will be excluded from the DLT-Evaluable Population.

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, patients discontinued from treatment, the primary reason to discontinue from treatment, patients discontinued from study, and the primary reason to discontinue from study, patients in progression-free survival follow-up, patients in OS follow-up, as well as patients in 10-year follow-up. 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. Baseline demographic data to be evaluated will include sex, age, race, ethnicity, body weight, height, body surface area (BSA).

A separate table will summarize the number and percentage of the subjects by region, country and site.

7.4.2 Other Baseline Disease Characteristics

The following baseline characteristics will be summarized for patients in the safety population.

- Primary diagnosis (including subtype).
- Weeks since initial diagnosis.
- Ann Arbor Stage.
- Lansky/Karnofsky Performance Score.
- Evidence of Bone Marrow Involvement.
- Evidence of Extranodal Involvement.
- Presence of B symptoms, including fever, night sweats and weight loss.

Baseline disease characteristics will be presented in by-patient listings as well.

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, i.e., 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. B symptom resolution rate defined as resolution of all symptoms among patients with any B symptom at baseline will be calculated. B symptom resolution time will be presented in weeks as well.

7.6 Medication History and Concomitant Medications

The patients to be enrolled are treatment-naïve for HL. Medication history including prior antineoplastic therapy, prior surgery, prior radiation, and prior stem cell transplant, if any, will be presented in by-patient listings.

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 treatment. The number and percentage of patients taking concomitant medications from signing of informed consent form through 30 days after the last dose of A+AVD will be tabulated by Anatomical Therapeutic Chemical (ATC) classification pharmacological subgroup and WHO drug generic term.

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

7.7 Study Drug Exposure and Compliance

The protocol regimen is A+AVD comprising doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2, and brentuximab vedotin (ADCETRIS, A) 48 mg/m^2 or 36 mg/m^2. A+AVD will be administered by IV infusion on Days 1 and 15 of each 28-day cycle for a total of 6 cycles. Details of study treatments administration is described in the protocol.

7.7.1 Extent of Exposure

The exposure to each component of study treatments A+AVD will be characterized by total amount of dose received (mg), total number of doses received (1-12), number of treatment cycles (1-6), number of patients in each of the 6 treatment cycles, numbers and percentages of patients by maximum number of treatment cycles completed (1-6).

A treatment cycle is defined as a cycle in which the patient received any amount of individual drugs of the A+AVD regimen. Duration of treatment (weeks) is defined as (last dose date-first dose date+14)/7.

Relative dose intensity (%) is defined as: 100× (total dose received) / (total dose intended), where the total dose intended is the summation of the intended doses in all treatment cycles and intended dose = prescribed dose level at C1D1× actual BSA (m2) at each dosing visit.

Dosing data will also be presented in a by-patient listing.

7.7.2 Treatment Modifications

Action on each component of study treatments A+AVD will be summarized by cycle. Number of patients dosed in each cycle will be summarized. Patients will be counted once for each applicable action, including dose reduced, increased, held, interrupted, delayed, and discontinued permanently as recorded on the eCRFs. The number of patients with and without any action during each cycle and overall will also be summarized.

7.8 Efficacy Analysis

The efficacy analyses encompass two major classes of endpoints, binary and time-to-event. All efficacy data will be summarized for the groups listed in Section 7.1.

Table 7.a Efficacy Endpoints

	Primary Analysis Population	Phase 1	Phase 2
Binary			
ORR, CR and PR rates at EOT	Response-evaluable	2nd	1st
PET- after Cycle 2 defined by Deauville score (1 and 2, as well as 1, 2, and 3)	Response-evaluable	2nd	1st
PET+ after Cycle 6 defined by Deauville score (3, 4, and 5 as well as 4 and 5)	Response-evaluable	2nd	
Radiation for HL after EOT	Safety	3rd	2nd
Time-to-event			
PFS, EFS, OS	Safety	3rd	2nd
DOR	Response-evaluable population with a response	3rd	2nd

Abbreviations: 1st=primary; 2nd=secondary; 3rd=exploratory.

7.8.1 Primary Efficacy Endpoint(s)

There is no primary efficacy endpoint in Phase 1. One of the primary endpoints in Phase 2 is overall response rate (ORR) of patients who achieve CR or PR at EOT, as determined by an independent review facility (IRF) using PET, CT, MRI, and clinical assessment according to IWG revised response criteria. Refer to the IRF Charter for greater detail of response assessment.

The primary efficacy endpoint of ORR at EOT per IRF, plus individual CR and PR rates at EOT per IRF, as well as PET- after Cycle 2 per IRF defined as a Deauville score of 1, 2 or 3 will be

summarized with 2-sided 80% exact CIs (Clopper-Pearson Method). The more conventional 95% CIs will also be shown for reference. A sensitivity analysis of PET- will be performed considering a Deauville score of 1, or 2 (a PIP Key Binding Element). These analyses will be summarized using the response-evaluable population per IRF.

The same analyses of ORR, CR and PR rates, PET- after Cycle 2 will be repeated based on the investigator assessment using the response-evaluable population per INV.

The ORR per IRF will also be compared to those in similar studies investigating treatment of children with advanced stage HL, namely, GPOH-HD-2002, AHOD0031, and CCG5942 (a PIP Key Binding Element).

7.8.2 Secondary Efficacy Endpoint(s)

The percentage of patients with PET+ after Cycle 6 per IRF defined as a Deauville score of above 3 will be summarized with 2-sided 95% exact CI using the response-evaluable population per IRF. A sensitivity analysis of PET+ will be performed considering a Deauville score of above 2 (a PIP Key Binding Element).

The percentage of patients receiving irradiation for HL following study treatment will be summarized with 2-sided 95% exact CI using the response-evaluable population per IRF.

PFS per IRF is defined as the time from the first dose until disease progression per IRF or death due to any cause, whichever occurs first. For patients who do not have an objective PD, did not die and are either still on study follow-up at the time of the analysis, or were removed from the study prior to documentation of PD, PFS will be censored on the date of last adequate disease assessment. In addition, for patients who were given antitumor treatment other than SCT or radiotherapy as part of the frontline treatment the censoring will be done at the last adequate disease assessment before initiation of such alternative treatment. It should be noted that if a patient experienced disease progression per IRF or died after the initiation of the antitumor treatment other than SCT or radiotherapy, such patient will be censored, and will not be considered having PFS. Patients lacking an evaluation of tumor response after their first dose will have their PFS censored at the day of first dose.

EFS per IRF is defined as the time from the first dose until any treatment failure: PD per IRF including progression events during follow-up period, failing to complete 6 cycles of treatment due to any reason, or death due to any cause, whichever occurs first. EFS per IRF will be censored on the last adequate disease assessment date per IRF if none of the above events occur during the study. In addition, for patients who were given antitumor treatment other than SCT or radiotherapy as part of the frontline treatment the censoring will be done at the last adequate disease assessment before initiation of such alternative treatment. It should be noted that if a patient experienced disease progression per IRF or died after the initiation of the antitumor treatment other than SCT or radiotherapy, such patient will be censored, and will not be considered having EFS.

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

DOR per IRF in subjects with a response (CR or PR per IRF) is defined as the time from start of the first objective tumor response (CR or PR per IRF) to the first subsequent PD or death due to any cause, whichever occurs first. For patients who do not have an objective PD, did not die and are either still on a study follow-up at the time of the analysis, or were removed from the study prior to documentation of PD, DOR will be censored on the date of last adequate disease assessment. In addition, for patients who were given antitumor treatment other than SCT or radiotherapy as part of the frontline treatment the censoring will be done at the last adequate disease assessment before initiation of such alternative treatment. It should be noted that if a patient experienced PD per IRF or died after the initiation of the antitumor treatment other than SCT or radiotherapy, such patient will be censored. A sensitivity analysis of DOR based on response using CR only will be done as well.

The same analyses of PET+ after Cycle 6, PFS, EFS, and DOR will be repeated based on the investigator assessment.

The percentage of patients receiving irradiation for HL following study treatment and OS will also be compared to those in Studies GPOH-HD-2002, AHOD0031, and CCG5942 (a PIP Key Binding Element).

The PFS, EFS and OS analysis will also be performed by PET negativity status at C2D25 and EOT. PET negativity will be defined as 1) Deauville score ≤2 or 2) Deauville score ≤3. The analyses will be conducted using IRF, as well as investigator assessment.

The PFS analysis will also be performed by Ann Arbor disease stage at baseline. The analysis will be conducted using IRF, as well as investigator assessment.

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, ug/mL) and total therapeutic antibody (TAb, ug/mL), and plasma concentrations of monomethyl auristatin E (MMAE, ng/mL) will be determined using validated assays.

Noncompartmental analysis for the determination of PK parameters will be performed as data permits. Details of such analyses are specified in a separate standalone and according to the Clinical Pharmacology Analysis Plan (CPAP).

7.9.2 Pharmacodynamic Analysis

{Not applicable}

7.10 Other Outcomes

7.10.1 Immune Reconstitution Analysis

Effects of brentuximab vedotin on immune function will be assessed via serial measurement of the following parameters: total lymphocyte count and lymphocyte subsets, total Ig and IgG, IgM, and IgA levels; and levels of the antibodies to tetanus, HiB, and polio serotypes and peripheral blood CD34+ cell count.

Descriptive statistics will be presented for all scheduled measurements and their changes from baseline over time for each parameter.

7.10.2 Immunogenicity Analysis

Immunogenicity data will be summarized for patients in the immunogenicity population and will be presented using descriptive statistics into the following categories: ATA negative, transiently ATA positive, persistently ATA positive, low and high ATA titer, and neutralizing ATA (nATA) negative, and nATA positive.

- ATA Negative (subject-level) defined as patients who do not have a positive ATA in any postbaseline sample.
- Transiently ATA positive (subject-level) defined as patients who have positive ATA in 1 or 2 postbaseline samples.
- Persistently ATA positive (subject-level) defined as patients who have positive ATA in more than 2 postbaseline timepoints.

High/low titer is defined for the ATA positive (transiently or persistently) patients only

- High ATA Titer (subject-level) defined as patients who have at least one postbaseline ATA titer >25.
- Low ATA titer (subject-level) defined as patients whose postbaseline ATA titer are all ≤25.

nATA negative/positive is defined for the ATA positive (transiently or persistently) patients only

- nATA negative (subject-level) defined as patients who do not have positive nATA in any postbaseline ATA positive sample.
- nATA positive (subject-level) defined as patients who have at least one positive nATA in any postbaseline ATA positive sample.

ATA status, ATA titer and neutralizing ATA will be listed by patient. nATA status (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 at EOT will be summarized within each ATA response status (negative, transiently positive, persistently positive). The same analysis may be repeated based on ATA titer (high, >25; low, ≤25). In addition, patient-level ATA and efficacy data (ORR at EOT) will be listed together.

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

The relationship between immunogenicity responses to PK will be explored.

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[redacted]

7.11 Safety Analysis

Safety will be evaluated by the incidence of treatment-emergent AEs (TEAEs), severity and type of AEs, and by changes from baseline in the patient's vital signs, neurotoxicity, neuropathy assessment, ECGs, and clinical laboratory results. Exposure to protocol therapy, including the percentage of patients who are able to complete 6 cycles of treatment 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 20.0 or later by system organ class (SOC), high-level terms (HLTs), preferred terms (PTs) and intensity. AEs with missing start and/or end dates will be imputed according rules specified in Section 7.1.4. TEAE 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 treatment. Patients with the same AE more than once will have that event counted only once within each SOC, once within each HLT, and once within each PT. The summary of AEs will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- TEAEs resulting in study drug discontinuation.
- SAEs.
- Non-serious TEAEs (>5%).

TEAEs will be tabulated by SOC, HLT, and PT. The most commonly reported TEAEs (i.e., those events reported by ≥10% of all patients) will be tabulated by PT. Drug-related TEAEs as assessed by the investigator will be tabulated similarly. Both TEAEs and most commonly reported TEAEs tables will be repeated and presented by age (<=12 and >12).

Grade 3 or higher TEAEs (NCI CTCAE grades) and Grade 3 or higher drug-related TEAEs as assessed by the investigator will be tabulated by SOC, HLT, and PT.

A separate table for non-serious TEAE which occur in >5% of the patients will be tabulated by SOC, PT, and total. In addition to the number and percentage of the patients, a number of events will be presented in this table.

The individual patient's information on the Phase 1 DLT data, if any, will be presented in a by-patient listing.

7.11.1.1 Serious Adverse Events

The number and percentage of patients experiencing at least 1 treatment emergent SAEs will be summarized by MedDRA (Version 20.0 or later) primary SOC, HLT, and PT. The treatment emergent SAEs table will be repeated and presented by age (<=12 and >12). Drug-related SAE as assessed by the investigator will be summarized similarly.

A separate table with a number of SAEs in addition to the number and percentage of patients experiencing SAEs will be summarized by SOC, PT, and total.

In addition, a by-subject listing of the SAEs will be presented (the subject listing will contain all SAEs regardless of TEAE status).

7.11.1.2 Peripheral Neuropathies

Peripheral Neuropathy (PN) is defined by the peripheral neuropathy standardised MedDRA query (SMQ) broad search. The incidence of treatment-emergent PN and treatment-emergent drug-related PN will, each, be summarized by PT and severity. Time-to-onset, time-to-resolution or improvement of PN events will be summarized using summary statistics (mean, median, range, etc). The number of patients with PN resolution or improvement at EOT and at last follow-up will be counted. Patients with ongoing PN events will be summarized by the maximum grade.

Treatment-emergent peripheral neuropathy (SMQ) events by PT will also be plotted to show grade changes where applicable. Treatment-emergent peripheral neuropathy will further be categorized by peripheral sensory neuropathy and peripheral motor neuropathy.

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 TEAE status). On-study death is defined as a death that occurs between the first dose of protocol treatment and 30 days after the last dose of protocol treatment. Follow-up death is defined as a death that occurs after 30 days of the last dose of protocol treatment.

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 in a summary table by system organ class, high-level term and preferred term. Drug or Dose discontinued permanently indicates at least one individual drug within the A+AVD regimen is discontinued permanently.

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 summarized are as follows:

- Hematology: hemoglobin, hematocrit, hemoglobin A1c, platelet count, total white blood cell (WBC) count, and differential WBC count (including ANC).
- Serum chemistry: blood urea nitrogen, creatinine, total bilirubin, urate, lactate dehydrogenase, gamma-glutamyl-transpeptidase (GGT), phosphate, albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), glucose, sodium, potassium, calcium, chloride, carbon dioxide, and magnesium.

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.

Tanner Scale data will be listed by patient.

7.11.4 12-Lead ECGs

Echocardiogram (ECHO) will be summarized as shift from baseline to the worst post-baseline value using NCI CTCAE grades. A by-patient listing will also be presented.

7.11.5 Other Observations Related to Safety

Performance Status, as measured by Lansky or Karnofsky Scale will be summarized as a shift table from baseline to the worst post-baseline value. A by-patient listing will also be presented.

7.12 Interim Analysis

An interim futility analysis (IA) will be conducted approximately half-way through the trial after approximately 25 patients have had the opportunity to receive 6 cycles of study treatment and had their EOT response assessments. The study may be terminated early in the case of inferior efficacy. However, the trial will not be terminated at this IA for overwhelming efficacy.

Study C25004 is largely descriptive in that no formal statistical hypothesis testing will be performed for the primary endpoint, i.e., ORR (CR+PR) at EOT per IRF assessment. As noted in Section 6.0 that the reported ORRs for standard of cares including ABVD have been consistently as high as 80%-90%, an observation of a lower ORR for A+AVD would suggest the protocol treatment is less efficacious. For example, if there are as few as 15 responders among the first 25 patients who have completed their EOT assessments (ORR: 60%; 80% exact CI: 45.2%, 73.5%; or conventionally 95% exact CI: 38.7%, 78.9%), the upper bound of CI would not reach the

desired minimum of 80% ORR. Moreover, with only 15 responders out of 25 patients at IA, the estimated posterior probability of observing 40 or more responders assuming a full enrollment of a total of 55 response-evaluable patients would become less than 4%, where the number of 40 is the minimum number of required responders to reach the 80% threshold (40/55=72.7%; 80% exact CI: 63.6%, 80.6%).We have assumed the number of responses to follow a beta-binominal distribution with parameters n, α, β, where α and β are the parameters estimated from a posterior beta distribution with non-informative prior, $\alpha_0=\beta_0=0.5$. In summary, given only 15 of the first 25 patients have responded it is highly unlikely (<4%) to still achieve an ORR that is not statistically less than 80% after full enrollment.

No p-values will be calculated at either IA or primary analysis for the ORR or CR rate. The point estimates of ORR, CR and PR rates will be presented together with the corresponding CIs.

7.13 Changes in the Statistical Analysis Plan

None.

8.0 REFERENCES

Koo, T. K., & Li, M. Y. (2016). A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *Journal of Chiropractic Medicine*, *15*(2), 155–163. http://doi.org/10.1016/j.jcm.2016.02.012

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