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

NCT Number: NCT02979522

Protocol Approve Date: 11 June 2021

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This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
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PROTOCOL

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

Brentuximab Vedotin+Adriamycin, Vinblastine, and Dacarbazine in Pediatric patients with Advanced Stage Newly Diagnosed Hodgkin Lymphoma

Sponsor:	Takeda Development Center (TDC) Americas, Inc. 95 Hayden Avenue, Lexington, Massachusetts 02421 USA Please note: TDC Americas, Inc. may be referred to in this protocol as "sponsor" or "Takeda".		
Study Number:	C25004		
IND Number:	110,636	**EudraCT Number:**	2015-004112-38
Compound:	Brentuximab vedotin (ADCETRIS)		
Date:	11 June 2021	**Version/Amendment Number**	04

Amendment History

Date	Amendment Number	Amendment Type	Region
12 August 2016	Initial protocol		Global
27 July 2017	01	Nonsubstantial	Global
03 January 2019	02	Nonsubstantial	Global
10 December 2019	03	Substantial	Global
11 June 2021	04	Substantial	Global

1.0 ADMINISTRATIVE

1.1 Contacts

A separate contact information list will be provided to each site.

Serious adverse event (SAE) and pregnancy reporting information is presented in Section 10.0, as is information on reporting product complaints.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

The ethical principles that have their origin in the Declaration of Helsinki.

International Council on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.

All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

Electronic Signatures may be found on the last page of this document.

PPD

1.3 Protocol Amendment 04 Summary of Changes

This document describes the changes in reference to the protocol incorporating Amendment 04. The primary reasons for this amendment are to describe the modifications in study conduct because of the coronavirus disease 2019 (COVID-19) pandemic, clarify the time points for analysis of study data, provide additional guidance on long-term follow-up procedures, and provide an update to the sponsor's name. In addition, the protocol signatories are updated.

As all patients have completed the treatment period of the study, the protocol will confirm that study participation is not restricted by administration of the COVID-19 vaccine. Where permitted by local regulations, the study will allow remote monitoring due to COVID-19 impact. Guidance is also provided for handling of delayed or missed protocol visits due to the pandemic.

With the agreement of the European Medicines Agency (EMA) Paediatric Committee (PDCO), and as prespecified in the study's approved statistical analysis plan, the analyses for reporting the results of the study's primary endpoints in the clinical study report (CSR) were performed after all enrolled patients had the opportunity to be followed for 15 months after enrollment of the last patient in the main study. Efficacy analyses included all evaluable patients treated at the recommended dose.

All enrolled patients will continue to be followed for survival and disease status every 12 weeks (±1 week) for 12 months, and then every 24 weeks (±2 weeks) until death or study closure or for up to 2 years after enrollment of the last patient in the main study. An updated analysis of time-to-event efficacy endpoints and other selected endpoints will be performed after all enrolled patients have had the opportunity to be followed for up to 2 years after enrollment of the last patient, denoting the end of the main study. This updated analysis may include data from the long-term follow-up period. Results of the updated analysis performed at the end of the main study will be presented in an addendum to the CSR. A separate CSR addendum is planned to present the results for participating patients at the end of the 10-year optional long-term follow-up.

This protocol amendment provides an update to the sponsor name, now Takeda Development Center (TDC) Americas, Inc.

Minor grammatical, editorial, and formatting changes are included, if applicable for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see Appendix J.

Changes in Amendment 04

1. Modifications in study conduct instituted in response to the COVID-19 pandemic.
2. Clarification of time points for analysis and reporting of study results.
3. Additional guidance pertaining to the long-term follow-up procedures.
4. Updated sponsor name and protocol signatories.

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting SAEs defined in Section 10.0 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix B Responsibilities of the Investigator.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center (TDC) Americas, Inc.	**Compound:** Brentuximab vedotin (ADCETRIS)	
Title of Protocol: An Open-Label Study of Brentuximab Vedotin+Adriamycin, Vinblastine, and Dacarbazine in Pediatric Patients With Advanced Stage Newly Diagnosed Hodgkin Lymphoma	**IND No.:** 110,636	**EudraCT No.:** 2015-004112-38
Study Number: C25004	**Phase:** 1/2	

Study Design:

This phase 1/2, open-label, multiagent, multicenter study has the primary objectives of assessing the safety, tolerability, and recommended dose of brentuximab vedotin (A) in combination with a multiagent chemotherapy regimen, Adriamycin (doxorubicin), vinblastine, and dacarbazine, (referred to as AVD), in pediatric patients with advanced stage, newly diagnosed, classical CD30+ Hodgkin lymphoma (HL) and to evaluate the antitumor activity of this combination in pediatric patients.

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 (48 and 36 mg/m^2, 3-6 patients per cohort) to determine the recommended dose according to a modified 3+3 design. Once the recommended dose is identified, additional patients will be enrolled into phase 2 so that the total number of evaluable patients will be approximately 55, including the patients treated at the recommended dose in phase 1.

A+AVD will be administered on Days 1 and 15 of each 28-day cycle for up to 6 cycles.

In phase 1, the study will enroll up to 6 dose-limiting toxicity (DLT)-evaluable patients at a brentuximab vedotin dose of 48 mg/m^2 to determine the recommended dose. The first 3 patients enrolled in the study will be monitored for DLTs during the DLT observation period (Cycle 1+28 days [from 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 period 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 receive the protocol therapy in phase 2 to further assess safety and efficacy, for a total of at least 55 evaluable patients at the recommended dose in the study. Available pharmacokinetics (PK) data will be reviewed together with the safety data to guide the final decision on the recommended dose.

Given the known safety profile of this regimen in adult patients and the importance of dose intensity in the first-line treatment of HL, this study will begin with a dose that is expected to deliver equivalent brentuximab vedotin exposure to that in the adult regimen (see Section 4.5). If at any time more than 1 patient out of a maximum of 6 DLT-evaluable patients treated with the protocol therapy experiences 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). If more than 1 patient experiences 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.

Response to treatment and disease status assessments will be evaluated according to the International Working Group (IWG) Revised Criteria for Response Assessment for Malignant Lymphoma [1]. These disease assessments will be performed by investigators and an independent review facility (IRF) at times specified in the Schedule of Events (SOE). Evaluations will be performed per the SOE until progressive disease 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 and at End of Treatment (EOT). Involved site radiotherapy (ISRT) should be employed (at EOT) in patients who are positron emission tomography (PET) positive (PET+) at the end of Cycle 2 at the node sites that were PET+ at

diagnosis with a boost to sites that are still PET+ at EOT.

Survival will be assessed until the sooner of death, study closure, or up to 2 years after enrollment of the last patient. The main study will be considered to be complete when all study patients have had the opportunity to be followed for up to 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 their date of enrollment in the main study.

Phase 1 Primary Objective:

To assess the safety and tolerability, and to identify the recommended dose of brentuximab vedotin when combined with multiagent chemotherapy regimen AVD for first-line treatment of advanced stage HL in pediatric patients.

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 C_{max} (T_{max}) of brentuximab vedotin, monomethyl auristatin E (MMAE), and total (free and conjugated) therapeutic antibody (TAb).
- To evaluate the complete remission (CR) rate of pediatric patients with advanced stage HL at the end 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 PET negative (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 Primary Objectives:

- To evaluate the CR rate 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 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 able to complete 6 cycles of protocol therapy at the recommended dose.

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 antibodies (ATA) and ATA status on the safety, efficacy, and 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.

Subject Population: Male or female patients aged 5 to <18 years with newly diagnosed classical CD30+ advanced (Ann Arbor Stage III or Stage IV) HL who are treatment naïve with Karnofsky Performance Status or Lansky Play-Performance ≥50.

Number of Subjects: A total of at least 55 evaluable patients will be enrolled. 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. Once the recommended dose is 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.	**Number of Sites:** There are 14 study centers globally.
Dose Level(s): Brentuximab vedotin 48 or 36 mg/m^2, plus doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2.	**Route of Administration:** All protocol therapy will be administered by intravenous infusion on Days 1 and 15 of each 28-day cycle. Brentuximab vedotin infusion is to start approximately 1 hour after the conclusion of the dacarbazine administration.
Duration of Treatment: Patients will be treated for a maximum of six 28-day cycles.	**Period of Evaluation:** Patients will have an EOT assessment visit 30±7 days after receiving their final dose of protocol therapy. Survival will be assessed until the sooner of death, study closure, or up to 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 from their date of enrollment in the main study.
Main Criteria for Inclusion: Male or female patients aged 5 to <18 years with newly diagnosed classical CD30+ advanced stage (Stage III and Stage IV) HL who are treatment naïve with Karnofsky Performance Status or Lansky Play-Performance ≥50.	
Main Criteria for Exclusion: Patients may not have nodular lymphocyte-predominant HL, known active cerebral meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy (PML) or any history of PML, sensory or motor peripheral neuropathy, or known hypersensitivity to brentuximab vedotin or any component of AVD.	
Main Criteria for Evaluation and Analyses: Phase 1 primary endpoints for this study are: • Determination of the recommended dose of brentuximab vedotin in combination with AVD in a pediatric population. • Percentage of patients who experience adverse events (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 adverse events (SAEs) from the first dose of protocol therapy through 30 days after administration of the last dose of protocol therapy.	

Phase 1 secondary endpoints for this study are:

- Mean C_{max} and mean AUC_{0-15} of brentuximab vedotin (serum), TAb (serum), and MMAE (plasma).
- Median T_{max} of brentuximab vedotin (serum), TAb (serum), and MMAE (plasma).
- Percentage of patients who achieve a CR per IRF assessment at EOT per IWG criteria [1].
- Percentage of patients who achieve a PR per IRF assessment at EOT per IWG criteria [1].
- Percentage of patients who achieve an overall response (OR) per IRF assessment at EOT per IWG criteria [1].
- 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 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 primary safety, secondary efficacy, and PK endpoints.

Phase 2 primary endpoints for this study are:

- Percentage of patients who achieve a CR per IRF assessment at EOT per IWG criteria [1].
- 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 [1].
- Percentage of patients who achieve an OR per IRF assessment at EOT per IWG criteria [1].
- Percentage of patients who are able to complete 6 cycles of protocol therapy at the recommended dose.

Phase 2 secondary endpoints for this study are:

- PFS, EFS, OS, DOR.
- Percentage of patients receiving irradiation for HL following study treatment.
- Percentage of patients who experience AEs from first dose of protocol therapy through 30 days after administration of the last dose of protocol therapy.
- Percentage of patients who experience SAEs from first dose of protocol therapy through 30 days after administration of the last dose of protocol therapy.
- Percentage of patients who are ATA 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 primary safety, secondary efficacy, and PK endpoints.
- Mean C_{max} and mean AUC_{0-15} of brentuximab vedotin (serum), TAb (serum), and MMAE (plasma).
- Median T_{max} of brentuximab vedotin (serum), TAb (serum), and MMAE (plasma).
- 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 immunoglobulin [Ig] and IgG, IgM, and IgA levels; and levels of the antibodies to tetanus, hemophilus influenza type B [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).

Statistical Considerations:

Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, neuropathy assessment, and clinical laboratory results using the Safety Population. Exposure to protocol therapy, including percentage of patients who are able to complete 6 cycles of treatment and reasons for discontinuation, will be tabulated. Treatment-emergent AEs (TEAEs) that occur after administration of the first dose of protocol therapy and through 30 days after the last dose of protocol therapy will be tabulated. AEs will be tabulated according to the Medical Dictionary for Regulatory Activities and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- SAEs.

A listing of TEAEs resulting in protocol therapy discontinuation will be provided. The individual patient's information on the DLTs will also be presented in a listing.

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 also be plotted for key laboratory parameters. Shift tables for laboratory parameters will be generated based on changes in National Cancer Institute Common Terminology Criteria for Adverse Events grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the brentuximab vedotin safety profile.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs, weight, and development assessment results over time will be tabulated by scheduled time point. The results of lymphoma assessment and Lansky Play-Performance/Karnofsky Performance Status over time will also be tabulated.

All concomitant medications collected from Screening throughout the study period will be classified to generic terms according to the World Health Organization Drug Dictionary.

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

PK, Immune Reconstitution, and Immunogenicity Analysis

Descriptive statistics (eg, number of patients, arithmetic mean, geometric mean, standard deviation, median, percentage of coefficient of variation, minimum, and maximum) will be used to summarize brentuximab vedotin and TAb concentrations in serum, and concentrations of MMAE in plasma, by dose group. Mean plasma concentration data will be plotted over time by dose group. PK parameters (C_{max}, AUC_{0-15}, T_{max}) will be calculated from individual plasma (MMAE) or serum (brentuximab vedotin, TAb) concentration-time data using noncompartmental methods and summarized descriptively by analyte and dose group. Immune reconstitution (peripheral blood CD34+ count, enumeration of the total lymphocyte count and lymphocyte subsets, total Ig and IgG, IgM, and IgA levels, levels of antibodies to tetanus, HiB, and polio serotypes) over time will be summarized. Immunogenicity parameters (ATA titer and nATA titer in serum) will be summarized using descriptive statistics. The relationship of immunogenicity responses to efficacy and safety will be explored.

Efficacy Analysis

Analysis of efficacy measures will be descriptive. ORR, CR rate, and PR rate at EOT will be assessed by an IRF and by investigators per IWG criteria. The percentage of patients whose disease is PET- after 2 cycles of A+AVD chemotherapy and the percentage of patients whose disease is PET+ after 6 cycles will also be evaluated. Other efficacy endpoints including PFS, EFS, OS, and DOR will also be explored. The percentage of patients receiving irradiation for HL following study treatment will be summarized.

CCI

[redacted]

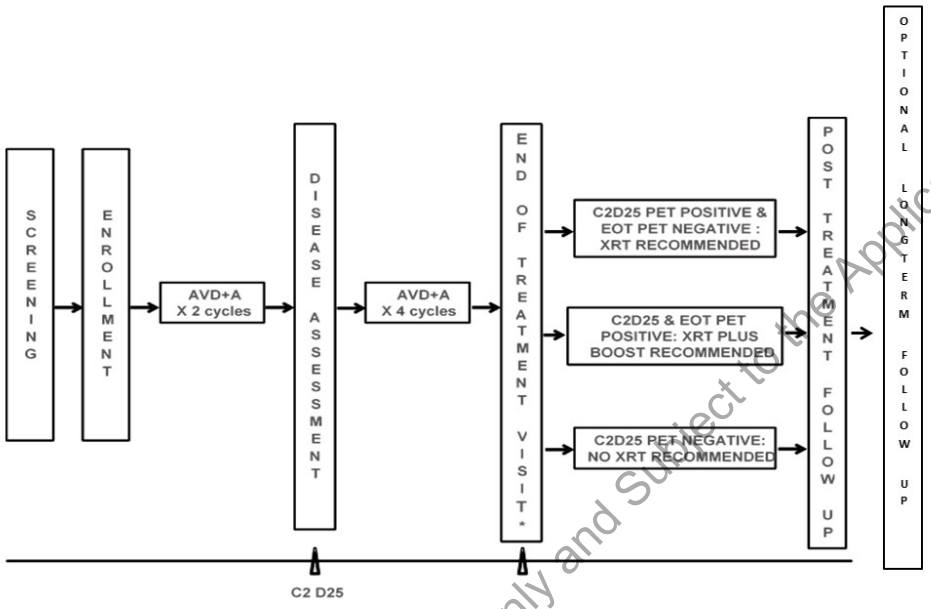
Sample Size Justification: A total of at least 55 evaluable patients treated at the recommended dose will be enrolled in this study. In phase 1, up to 12 DLT-evaluable patients will be enrolled into up to 2 planned dose cohorts (48 and 36 mg/m^2, 3-6 patients per cohort) according to a modified 3+3 design. Once the recommended dose is 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 that the true ORR for the A+AVD regimen is 90%, with 55 evaluable patients and a 2-sided type I error of α=0.2, the study would have approximately 78% power to state that the ORR is greater than 80%. An interim futility analysis will be conducted after 25 patients have completed 6 cycles of study therapy and had their EOT response assessment. The study may be terminated early in the case of inferior efficacy. Analyses will be primarily descriptive in nature. No formal statistical tests will be performed.

Planned Reporting: As prespecified in the approved SAP, the analyses for reporting the results of the study's primary endpoints in the clinical study report (CSR) were performed after all enrolled patients had the opportunity to be followed for 15 months after enrollment of the last patient in the main study. Efficacy results are presented by study phase, and for all evaluable patients treated at the recommended dose.

Patients will continue to be followed for survival and disease status every 12 weeks (±1 week) for 12 months, and then every 24 weeks (±2 weeks) until death or study closure or for up to 2 years from the date of the last patient enrolled. An updated analysis of the time-to-event efficacy endpoints and other selected study endpoints will be performed after all enrolled patients have had the opportunity to be followed for up to 2 years after enrollment of the last patient, denoting the end of the main study. This updated analysis may include data from the long-term follow-up period. Results of the updated analysis will be presented in an addendum to the CSR.

Data from the optional long-term follow-up will be analyzed after all participating patients have had the opportunity to complete 10 years of follow up from their date of enrollment in the main study and those results will be presented in a separate CSR addendum.

Study Overview Diagram



AVD+A: brentuximab vedotin, Adriamycin, vinblastine, and dacarbazine; C2D25: Cycle 2 Day 25; CT: computed tomography; EOT: End of Treatment; MRI: magnetic resonance imaging; PET: positron emission tomography; XRT: radiotherapy.

AVD+A indicates the actual order of drug administration.

* 30 days (±7 days) after completion of last dose of protocol therapy.

PET, CT, and MRI at C2D25 and 3-7 weeks after last dose of protocol therapy.

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Clinical Study Supplier List. The identified vendors in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

Takeda will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study medication, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

A+ABVD	brentuximab vedotin with standard doses of Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine
A+AVD	brentuximab vedotin with Adriamycin (doxorubicin), vinblastine, and dacarbazine
ABVD	Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine
AE	adverse event
ALCL	anaplastic large-cell lymphoma
ASCT	autologous stem cell transplant
ATA	antitherapeutic antibody
AUC	area under the concentration-time curve
AUC_{0-15}	area under the concentration-time curve from Day 0 to Day 15
AVD	Adriamycin (doxorubicin) vinblastine, and dacarbazine
BSA	body surface area
cAC10	CD30-directed monoclonal antibody
CDC	Centers for Disease Control and Prevention
C_{max}	maximum observed concentration
cHL	classical Hodgkin lymphoma
COVID-19	coronavirus disease 2019
CR	complete remission
CRO	contract research organization
CT	computed tomography
CYP	cytochrome P450
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
eCRF	electronic case report form
EFS	event-free survival
EMA	European Medicines Agency
EOT	End of Treatment (visit)
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HiB	hemophilus influenza type B
HL	Hodgkin lymphoma
CCI	[redacted]
HRS	Hodgkin Reed-Sternberg
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee

Ig	immunoglobulin
IRB	institutional review board
IRF	independent review facility
ISRT	involved site radiotherapy
IV	intravenous(ly)
IWG	International Working Group
JCV	John Cunningham virus
MedDRA	Medical Dictionary for Regulatory Activities
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
MUGA	multiple-gated acquisition scan
nATA	neutralizing antitherapeutic antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
OR	overall response
ORR	overall response rate
OS	overall survival
OSFU	overall survival follow-up
PD	progressive disease
CCI	[redacted]
PET	positron emission tomography
PET-	positron emission tomography negative
PET+	positron emission tomography positive
PFS	progression-free survival
PFSFU	progression-free survival follow-up
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PR	partial remission
PTE	pretreatment event
Q2W	every 2 weeks
RP2D	recommended phase 2 dose
SAE	serious adverse event
sALCL	systemic anaplastic large-cell lymphoma
SAP	statistical analysis plan
SOC	standard of care
SOE	Schedule of Events
SUSAR	suspected unexpected serious adverse reaction
TAb	total (free and conjugated) therapeutic antibody
TDC Americas Inc.	Takeda Development Center, Americas, Inc.
TEAE	treatment-emergent adverse event
T_{max}	time of first time of occurrence of C_{max}

ULN	upper limit of the normal range
US	United States
WHO	World Health Organization

3.4 Corporate Identification

TDC Americas	Takeda Development Center Americas, Inc.
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd
TDC Japan	Takeda Development Center Japan
Takeda	Millennium Pharmaceuticals, Inc, TDC Americas, TDC Asia, TDC Europe, TDC Japan

4.0 INTRODUCTION

4.1 Background

4.1.1 Disease Under Treatment

Hodgkin lymphoma (HL), a neoplasm of lymphoid tissue, is histopathologically defined by the presence of malignant Hodgkin Reed-Sternberg (HRS) cells in a background of inflammatory cells. The characteristic surface antigen expressed on HRS cells is CD30. In 2013 alone, it was estimated that approximately 9290 new cases of HL were diagnosed in the United States (US) [2]. In 2012, approximately 12,431 new cases of HL were diagnosed in the 28 major European Union (EU) countries [3], and approximately 898 new cases of HL were diagnosed in Canada [3].

Pediatric HL has an annual incidence of approximately 0.7 to 1.0 cases per 100,000 children in the US and in the EU [4] and is the childhood cancer with the highest cure rates, with historical overall survival (OS) rates of more than 90% in early-stage disease and up to 70% for advanced stage disease [5-8]. Five-year event-free survival (EFS) in pediatric HL is approximately 80% to 85% [9]. Pediatric patients aged less than 10 years had a significantly improved freedom from relapse and survival compared with adolescents, and a highly significant improved outcome compared with adults. Although pediatric patients present high cure rates, many multiagent regimens confer significant morbidity, including secondary malignancies, cardiovascular disease, thyroid function impairment, male infertility, pulmonary diseases, and infections [10-13]. Some of the serious sequelae of radiation and alkylating chemotherapy are most pronounced in younger patients, in whom growth and development are particularly active when therapy is administered. In addition, cardiac toxicity appears to be age related, with younger patients at the highest risk. Secondary malignancies, including breast cancer in female patients and secondary myeloid neoplasms, represent the leading cause of mortality in survivors of HL [14,15].

The proposed pediatric study has been designed to evaluate brentuximab vedotin as a component of a multiagent frontline chemotherapy regimen in patients with advanced stage, newly diagnosed HL, here defined as Stage III and Stage IV and a ≥50 Lansky Play-Performance or Karnofsky Performance Status. The primary objective of the study is to evaluate the safety and determine the recommended dose, and the secondary objectives include evaluation of efficacy, pharmacokinetics (PK), immunogenicity, the percentage of patients who have a negative positron emission tomography (PET) result (PET-; Deauville score ≤3) after 2 cycles of treatment, and the percentage of patients who have a positive PET result (PET+; Deauville score >3) after 6 cycles of treatment (see Appendix D).

4.1.2 Study Drug

Brentuximab vedotin (ADCETRIS, the first "A" in the treatment regimen acronym) is an antibody-drug conjugate. It consists of a CD30-directed monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the antimitotic small molecule monomethyl auristatin E (MMAE). cAC10 binds to the CD30 antigen, which has very low expression on normal cells but is

found at higher levels of expression on the HRS cells of HL, on anaplastic large-cell lymphoma (ALCL) cells, and on tumor cells of other varied lymphoproliferative disorders.

The European Medicines Agency (EMA) granted brentuximab vedotin conditional marketing authorization as ADCETRIS on 25 October 2012 for the treatment of adult patients with relapsed or refractory CD30+ HL after autologous stem cell transplant (ASCT) or after at least 2 previous treatments when ASCT or multiagent chemotherapy is not a treatment option, and for the treatment of adult patients with relapsed or refractory systemic anaplastic large-cell lymphoma (sALCL). In 2016, the EMA further approved ADCETRIS for the treatment of (1) adult patients with HL or sALCL who previously responded to ADCETRIS and who later relapse, and (2) adult patients with CD30+ HL at increased risk of relapse or progression following ASCT.

On 19 August 2011, the US Food and Drug Administration (FDA) granted accelerated approval to brentuximab vedotin as ADCETRIS for the treatment of patients with sALCL after failure of at least 1 prior multiagent chemotherapy regimen and for the treatment of patients with HL after failure of ASCT or after failure of at least 2 prior multiagent chemotherapy regimens in patients who are not ASCT candidates. In 2015, the US FDA further approved ADCETRIS for the treatment of patients with classical Hodgkin lymphoma (cHL) at high risk of relapse or progression as post–autologous hematopoietic stem cell transplantation consolidation.

4.2 Nonclinical Experience

Brentuximab vedotin has the potential to target and selectively deliver a potent cytotoxic agent to CD30+ tumor cells. It induces cell death of both HL and ALCL cell lines in vitro with subnanomolar concentrations producing 50% inhibition and has demonstrated antitumor activity in xenograft models of the same tumors.

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

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

4.3 Clinical Experience

More than 700 patients have received brentuximab vedotin monotherapy in 10 completed clinical studies. Six studies formed the basis for initial marketing authorizations of brentuximab vedotin for relapsed HL and systemic ALCL in the US, Europe, Canada, and additional countries.

Study SGN35-009 is a completed, phase 1, 2-arm, open-label, multicenter study in adults to evaluate the safety of brentuximab vedotin when administered in combination with standard

therapy, doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD), or a modified standard therapy, Adriamycin (doxorubicin), vinblastine, and dacarbazine (AVD). Adult patients received doses of 0.6, 0.9, or 1.2 mg/kg brentuximab vedotin with standard doses of ABVD (A+ABVD) or 1.2 mg/kg brentuximab vedotin with AVD (A+AVD), depending upon cohort assignment.

A total of 47 of 51 patients (92%) completed first-line therapy. At the completion of first-line therapy, 45 of the 47 patients (96%) achieved complete remission (CR), 21 of 22 patients (95%) in the A+ABVD regimen and 24 of 25 patients (96%) in the A+AVD regimen. A 3-year failure-free survival analysis showed 92% of patients treated in the A+AVD arm versus 79% of patients treated in the A+ABVD arm [16]. Of the 51 patients, 50 (98%) experienced at least 1 treatment-emergent adverse event (TEAE); 24 patients (96%) in the A+ABVD regimen and 26 patients (100%) in the A+AVD regimen. Overall, a total of 43 patients (84%) experienced at least 1 Grade ≥3 event; 22 of 25 patients (88%) in the A+ABVD regimen and 21 of 26 patients (81%) in the A+AVD regimen.

Fifty-one patients received at least 1 dose of A+ABVD (n=25) or A+AVD (n=26). Whereas no pulmonary toxicity was reported for patients who received A+AVD, noninfectious pulmonary toxicity was reported for patients who received A+ABVD, and the rate was higher than historical incidence reported with ABVD alone. Brentuximab vedotin combined with bleomycin was subsequently listed as contraindicated in the US Prescribing Information and in the EU Summary of Product Characteristics. The A+AVD regimen was well tolerated, and the CR rate among patients who received the combination was favorable.

Clinical Study C25002 is an ongoing phase 1/2 study of brentuximab vedotin in pediatric patients with relapsed or refractory sALCL or HL. The primary objectives of the study are to assess the safety and PK, and determine the pediatric maximum tolerated dose and/or recommended phase 2 dose (RP2D) of brentuximab vedotin in pediatric patients. Approximately 42 patients will be enrolled in the study. The phase 1 dose escalation arm of the study was planned to enroll 12 patients with any relapsed or refractory CD30+ hematologic malignancy. The 2 phase 2 arms of the study will enroll at least 15 evaluable patients diagnosed with relapsed or refractory sALCL and HL, respectively.

4.4 Potential Risks in Children

As detailed in Section 4.3, brentuximab vedotin monotherapy and multiagent therapy have demonstrated therapeutic activity in CD30+ hematological malignancies.

Brentuximab vedotin recognizes the CD30 antigen on tumor cells and normal activated T cells. In nonclinical toxicology studies, hypocellularity of the bone marrow and lymphoid depletion of the thymus were observed in rats and monkeys. It is possible that binding of brentuximab vedotin to normal CD30+ T cells could render these cells ineffective, thus leading to alterations in immune function. To date, the effect of brentuximab vedotin on the immune system of pediatric patients and the extent or duration of immune dysfunction following the completion of brentuximab vedotin therapy is unknown. Pediatric patients have rapidly developing immune systems characterized by continual exposure to neoantigens and a large thymus where T-cell selection is

actively engaged. CD30 is expressed on medullary cells of the thymus; however, the role of CD30 in T-cell selection is controversial [17,18]. Nonclinical data suggest a potential impact of brentuximab vedotin on thymic cell populations. Additionally, younger patients are more likely to have immune suppression after completion of chemotherapy, including the loss of protective serum antibody concentrations against vaccines. There is a reduction in vaccine-antigen-specific antibody concentrations after completion of chemotherapy [19].

The extent and duration of immune dysfunction following the completion of standard-dose chemotherapy will depend on the antineoplastic agent used and its dose intensity, and can therefore vary widely. This may influence immunity to vaccine antigens and responses to vaccination. Total B and T lymphocytes usually recover fully, quantitatively and functionally, 6 months after completion of chemotherapy; although in some cases, recovery may take up to 1 year. There is a reduction of immunoglobulin (Ig) levels after completion of chemotherapy, particularly of IgG2 levels. Normalization of Ig levels can take up to 1 year after completion of treatment. A recent study looking at immunity to vaccines at a median time of 7 months after completion of treatment for acute leukemia in British children demonstrated protective antibody concentrations for all patients to tetanus, 87% to hemophilus influenza type B (HiB), 71% to measles, 12% to *Neisseria meningitidis* group C (meningococcus C), and 11% to all 3 poliovirus serotypes. Therefore, to assess the effect of brentuximab vedotin on pediatric immune function, the duration of any changes to the levels of immunoglobulins (including IgG, IgA, and IgM), and the number and subsets of lymphocytes, such as T cell, B cell, and natural killer (NK) cell subsets, peripheral blood CD34+ cell counts, and vaccine-specific antibody levels (tetanus, HiB, and poliovirus) will be examined at baseline and at 6, 12, and 18 months (±1 month) after treatment is completed.

To address safety concerns regarding growth and development in children treated with brentuximab vedotin, Centers for Disease Control and Prevention (CDC)-recommended growth charts for persons aged 2 to 19 years will be used. Clinical charts are available for boys and for girls at cdc.gov/growthcharts/clinical_charts.htm. A sexual maturity scale such as the one developed by Tanner is used to assess the physical developmental stage of a patient. This scale assigns a Tanner stage of 1 (prepubertal) to 5 (adult) to girls based on breasts and pubic hair and to boys based on genitalia and pubic hair.

For specific risks associated with brentuximab vedotin, refer to Section 6 of the IB.

4.5 Rationale for the Proposed Study

Including brentuximab vedotin as a component of multiagent chemotherapy in pediatric patients with newly diagnosed HL may provide clinical benefit by decreasing the need for radiotherapy following chemotherapy, thereby reducing the risks of late effects associated with radiotherapy, including secondary malignancies, cardiac toxicity, and thyroid dysfunction. The safety, tolerability, recommended dosing, PK, immunogenicity, and antitumor activity of brentuximab vedotin alone or in a multiagent chemotherapy regimen have not been studied for first-line treatment of HL in a pediatric population. ABVD treatment of advanced stage HL is associated with a 5-year progression-free survival (PFS) rate of 76%. [20] This standard of care (SOC)

generally includes involved-field radiation therapy following chemotherapy in patients with a suboptimal response to chemotherapy alone. Because of the increased risk of late effects associated with radiotherapy, including secondary malignancies, cardiac and pulmonary toxicities, and endocrine dysfunction, a focus of research in pediatric HL has been on minimizing the need for radiotherapy.

The single-agent activity of brentuximab vedotin has been demonstrated in adult (SG035-0003) relapsed/refractory HL, and the pediatric RP2D for brentuximab vedotin is being investigated in clinical Study C25002 (safety and dose escalation) in pediatric patients diagnosed with relapsed or refractory HL and sALCL. Safety and feasibility of brentuximab vedotin administered at 1.2 mg/kg every 2 weeks have been demonstrated in a phase 1 study in adult first-line HL (SGN35-009) as part of a combination chemotherapy regimen with AVD. Because the PK of brentuximab vedotin is linear, the administration of 1.2 mg/kg intravenously (IV) every 2 weeks or 1.8 mg/kg IV every 3 weeks should result in similar time-averaged exposures. Furthermore, no dose-limiting toxicities (DLTs) were observed in the 1.2 mg/kg dose cohort of Study SGN35-009. Additionally, of the 4 agents in the ABVD regimen, bleomycin is most associated with unpredictable, life-threatening pulmonary toxicity [21]. For patients on ABVD therapy who develop pulmonary toxicity, standard practice is to continue first-line therapy with AVD while omitting bleomycin. The replacement of brentuximab vedotin for bleomycin in an AVD combination regimen may provide an improvement in PFS over the standard ABVD regimen and eliminate the risk of bleomycin-associated pulmonary toxicity.

Therefore, brentuximab vedotin at 1.2 mg/kg every 2 weeks in combination with multiagent chemotherapy AVD is being evaluated for safety and efficacy in a phase 3 study, ECHELON-1 (C25003), in adults with newly diagnosed, advanced stage, cHL. The ECHELON-1 A+AVD regimen arm in adult patients with newly diagnosed, advanced stage HL will serve as a basis for extrapolation for this pediatric study of safety and tolerability of brentuximab vedotin at doses to achieve exposures in pediatric patients with newly diagnosed, advanced stage cHL comparable to adults. The pediatric dose that will provide a similar exposure to that seen in the adult population was estimated in a preliminary analysis of brentuximab vedotin exposure in the pediatric Study C25002. In that study, the area under the concentration-time curve (AUC) of brentuximab vedotin in pediatric patients was found to be lower than that seen in adults after the same 1.8 mg/kg dose. (Preliminary estimates of Geomean AUC were 76 and 63, respectively, for adults in Study SG035-0001 and for pediatric patients in Study C25002). At the lower pediatric age of 4 years with a typical body weight of 16 kg, the AUC of brentuximab vedotin was estimated to be approximately 43 µg/mL*day. Simulations from a population PK analysis of the data showed that dosing pediatric patients based on body surface area normalizes the difference in exposure in adult and pediatric patients. Based on the adult exposure from the 1.8 mg/kg dose, 71.5 mg/m^2 was found to provide a similar exposure in pediatric patients across the age range of 4 to 17 years. Extrapolation of the above single-agent exposure experience to the dosing in the multiagent first-line setting in which adult brentuximab vedotin dosing was 1.2 mg/kg every 2 weeks (Q2W), the pediatric dosing is calculated to be approximately 48 mg/m^2 Q2W.

Although excessive toxicity of A+AVD is not expected, this study will include a plan to de-escalate the brentuximab vedotin dose if patients show excessive toxicity to the regimen.

Replacing bleomycin with brentuximab vedotin in ABVD therapy may provide clinical benefit to pediatric patients with newly diagnosed HL by decreasing the risks of pulmonary toxicity and of late undesirable effects associated with radiotherapy.

The recommended dose of brentuximab vedotin in adult patients with relapsed/refractory HL or ALCL is 1.8 mg/kg administered IV every 3 weeks until a maximum of 16 cycles, disease progression, or unacceptable toxicity. At this dose and schedule, the most common adverse events (AEs) were peripheral sensory neuropathy, fatigue, nausea, diarrhea, pyrexia, upper respiratory tract infection, neutropenia, and vomiting. These events have been primarily mild or moderate in severity. The planned dose of brentuximab vedotin in this study is 48 mg/m^2 Q2W, which should provide the same exposure as the adult dose of 1.2 mg/kg Q2W, based on population PK modeling and simulation, as described earlier.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Phase 1 Primary Objective

The primary objective is:

- To assess the safety and tolerability, and to identify the recommended dose of brentuximab vedotin when combined with multiagent chemotherapy regimen AVD for first-line treatment of advanced stage HL in pediatric patients.

5.1.2 Phase 1 Secondary Objectives

The secondary objectives are:

- 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 C_{max} (T_{max}) of brentuximab vedotin, 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 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 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.

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[redacted]

5.1.4 Phase 2 Primary Objectives

- To evaluate the CR rate 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 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 able to complete 6 cycles of protocol therapy at the recommended dose.

5.1.5 Phase 2 Secondary Objectives

- To evaluate the PFS, EFS, OS, and 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 ATA and ATA status on the safety, efficacy, and 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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[redacted]

5.2 Endpoints

5.2.1 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 adverse events (SAEs) from the first dose of protocol therapy through 30 days after administration of the last dose of protocol therapy.

5.2.2 Phase 1 Secondary Endpoints

- Mean C_{max} and mean AUC_{0-15} of brentuximab vedotin (serum), TAb (serum), and MMAE (plasma).
- Median T_{max} of brentuximab vedotin (serum), TAb (serum), and MMAE (plasma).
- Percentage of patients who achieve a CR per independent review facility (IRF) assessment at End of Treatment (EOT) per International Working Group (IWG) criteria [1].
- Percentage of patients who achieve a PR per IRF assessment at EOT per IWG criteria [1].
- Percentage of patients who achieve an overall response (OR) per IRF assessment at EOT per IWG criteria [1].
- 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 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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5.2.4 Phase 2 Primary Endpoints

- Percentage of patients who achieve a CR per IRF assessment at EOT per IWG criteria [1].
- 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 [1].
- Percentage of patients who achieve an OR per IRF assessment at EOT per IWG criteria [1].
- Percentage of patients who are able to complete 6 cycles of protocol therapy at the recommended dose.

5.2.5 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 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 (serum), TAb (serum), and MMAE (plasma).
- Median T_{max} of brentuximab vedotin (serum), TAb (serum), and MMAE (plasma).

- 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 STUDY DESIGN

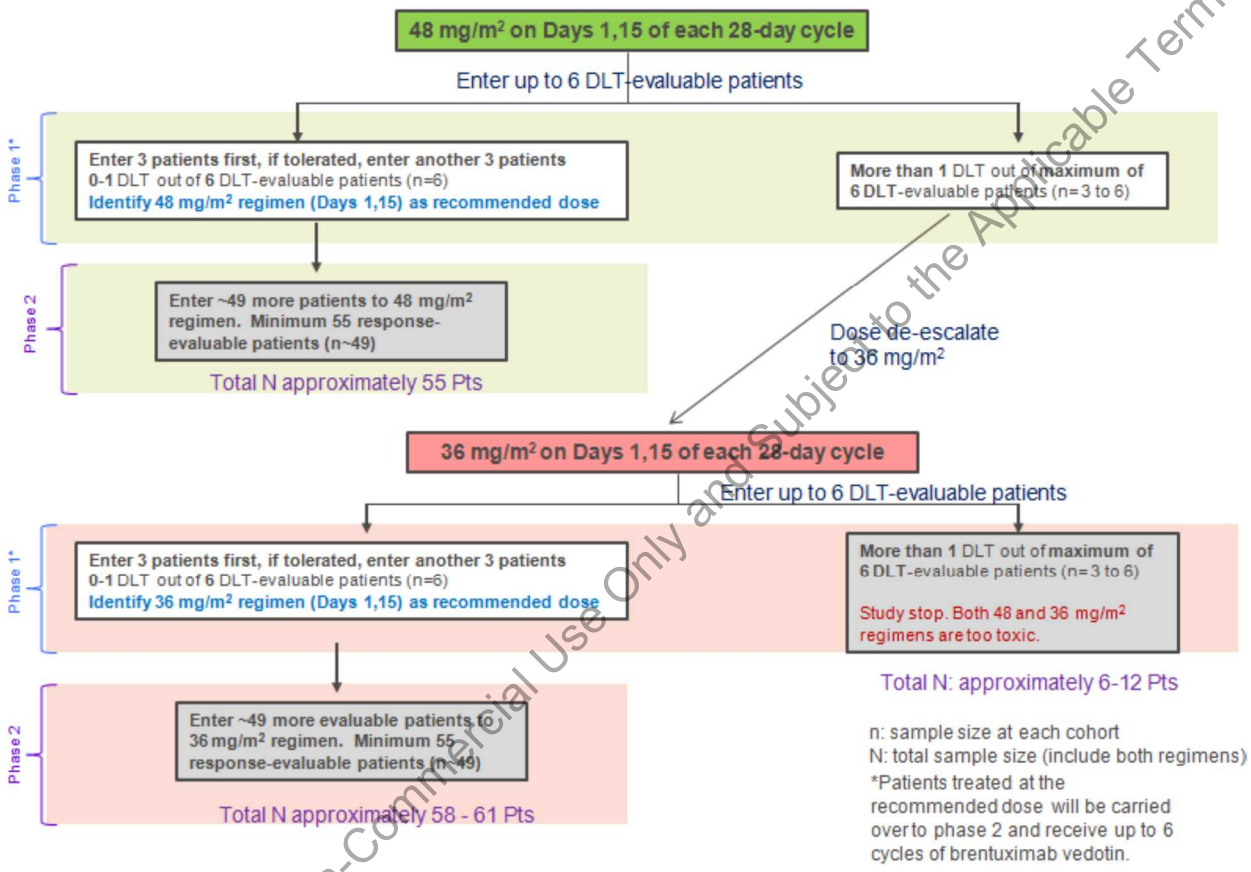
6.1 Overview of Study Design

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. A current widely used SOC regimen for this population is multiagent therapy ABVD. 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). This study will be the first company-sponsored study to administer brentuximab vedotin as a combination component for pediatric patients.

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 (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. An End-of-Cohort meeting scheduled by the sponsor will occur after the last patient in each cohort has completed the DLT observation period. Enrollment will be on hold pending the documented outcome of this meeting. Once the recommended dose is identified, additional patients will be enrolled in the phase 2 portion as described below, so that the total number of evaluable patients

will be at least 55, including the patients treated at the recommended dose in phase 1. The Dosing Schema is presented in Figure 6.a.

Figure 6.a Dosing Schema



DLT: dose-limiting toxicity; Pts: patients.

The phase 1 portion of the study will enroll up to 6 DLT-evaluable patients at a brentuximab vedotin dose of 48 mg/m^2 to determine the recommended dose. 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 DLTs occur 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. Available PK data will be reviewed together with the safety data to guide the final decision on the recommended dose. Refer to Section 8.1 for a description of the protocol therapy.

Given the known safety profile of this regimen in adult patients and the importance of dose intensity in the first-line treatment of HL, this study will begin with a dose that is expected to deliver equivalent brentuximab vedotin exposure to that in the adult regimen (see Section 4.5). If at any time more than 1 patient out of a maximum of 6 DLT-evaluable patients treated with the protocol therapy experiences a DLT, the brentuximab vedotin dose will be reduced to 36 mg/m^2. Refer to Section 8.3 for dose de-intensification rules. 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 experiences 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.

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective date 14 June 2010 [22]. DLTs are defined in Section 8.2.

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 (see Section 9.8). Patients may discontinue protocol therapy at any time.

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

Serial blood samples will be obtained at prespecified time points as described in the Schedule of Events (SOE) (Appendix A) for determination of the serum concentration of brentuximab vedotin and TAb, plasma concentrations of MMAE, and to determine if patients are positive for ATA and nATA.

Response to treatment and disease status assessments will be evaluated according to the IWG Revised Criteria for Response Assessment for Malignant Lymphoma [1]. These disease assessments will be performed by investigators and an IRF at times specified in the 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.

For patients receiving radiation at EOT, the following guidance is provided: ISRT will consist of 2100cGy in 14 fractions of 150cGy per day. Treatment should be given 5 days per week. All fields should be treated once per day. Treatment should begin no later than 4 weeks after completion of the last cycle of chemotherapy provided that the blood count recovery has occurred. Patients requiring radiation above and below the diaphragm should be treated with sequential rather than concurrent fields. The site of bulkiest involvement should be treated first, and the second field should be treated with adequate hematologic recovery.

Patients will be followed for survival until the sooner of death, study closure, or up to 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. For each patient electing to participate, the optional long-term follow-up will start 2 years after the date of the specific patient's EOT visit. Regardless of participation in the optional 10-year long-term follow-up study, patients will continue with the main study for up to 2 years after enrollment of the last patient, as specified in Section 9.5.

6.2 Number of Patients

At least 55 evaluable patients will be enrolled in this study from 14 study centers globally. Enrollment is defined as the date of first dose of protocol therapy.

Patients who are withdrawn from the study before the completion of the DLT observation period for reasons other than DLTs will be replaced. Additional patients may be enrolled to ensure a total of at least 55 evaluable patients at the recommended dose.

6.3 Duration of Study

6.3.1 Duration of an Individual Patient's Study Participation

Patients will receive a maximum of 6 cycles of treatment with protocol therapy.

Following the last dose of protocol therapy, patients will be followed for a minimum of 30 days to permit the detection of any delayed TEAEs. Patients will be followed for survival until the sooner of death or study closure or up to 2 years after enrollment of the last patient.

All patients will be offered the opportunity to participate in an optional long-term follow-up, which focuses on the collection of long-term safety and survival data (refer to Section 9.13).

6.3.2 End of Study/Study Completion Definition and Planned Reporting

Primary Completion Study Completion

As prespecified in the approved SAP, the analyses for reporting the results of the study's primary endpoints in the CSR were performed after all patients had the opportunity to be followed for 15 months after enrollment of the last patient in the main study.

Patients will continue to be followed for survival and disease status every 12 weeks (±1 week) for 12 months, and then every 24 weeks (±2 weeks) until death or study closure or for up to 2 years

from the date of the last patient enrolled. An updated analysis of the time-to-event efficacy endpoints and other selected study endpoints will be performed after all enrolled patients have had the opportunity to be followed for up to 2 years after enrollment of the last patient, denoting the end of the main study. This updated analysis may include data from the long-term follow-up period. Results of this updated analysis will be presented in an addendum to the CSR.

Data from the optional long-term follow-up will be analyzed after all participating patients have had the opportunity to complete 10 years of follow-up from their date of enrollment in the main study and those results will be presented in a separate CSR addendum.

6.3.3 Timeframes for Primary and Secondary Endpoints to Support Disclosures

Refer to Table 6.a for disclosures information for all primary and secondary endpoints.

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame [a]
Phase 1 Primary		
• Determination of the recommended dose of brentuximab vedotin in combination with AVD in a pediatric population.	The recommended dose of brentuximab vedotin in combination with AVD for a pediatric population on the basis of the safety, tolerability, and preliminary PK and efficacy data (if available).	Up to 6 months
• 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.	The percentage of patients in the Safety Population who experience TEAEs for up to 6 months of treatment plus 30 days following the end of study treatment.	Up to 7 months
• 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.	The percentage of patients in the Safety Population who experience treatment-emergent SAEs for up to 6 months of treatment plus 30 days following the end of study treatment.	Up to 7 months

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame [a]
Phase 1 Secondary		
• Mean C_{max} and mean AUC_{0-15} of brentuximab vedotin (serum), TAb (serum), and MMAE (plasma).	Mean maximum concentration and AUC from Day 0 to Day 15 for brentuximab vedotin and TAb in serum and MMAE in plasma based on data from the PK Population.	Up to 15 days
• Median T_{max} of brentuximab vedotin (serum), TAb (serum), and MMAE (plasma).	First time of occurrence of maximum (peak) concentration for a single dose of brentuximab vedotin for patients in the PK Population.	Up to 15 days
• Percentage of patients who achieve a CR per IRF assessment at EOT per IWG criteria.	Percentage of patients in the Response-Evaluable Population who achieve a complete response based on the IRF assessment at the EOT visit based on the IWG criteria.	Up to 7 months
• Percentage of patients who achieve a PR per IRF assessment at EOT per IWG criteria.	Percentage of patients in the Response-Evaluable Population who achieve a partial response based on the IRF assessment at the EOT visit based on the IWG criteria.	Up to 7 months
• Percentage of patients who achieve an OR per IRF assessment at EOT per IWG criteria.	Percentage of patients in the Response-Evaluable Population who achieve an overall response based on the IRF assessment at the EOT visit based on the IWG criteria.	Up to 7 months
• Percentage of patients whose disease is PET- after 2 cycles of protocol therapy per IRF assessment.	Percentage of patients in the Response-Evaluable Population whose disease is negative per PET after 2 cycles of protocol therapy per IRF assessment.	Up to 2 months
• Percentage of patients whose disease is PET+ after 6 cycles of protocol therapy per IRF assessment.	Percentage of patients in the Response-Evaluable Population whose disease is positive per PET after 6 cycles of protocol therapy per IRF assessment.	Up to 6 months
• Percentage of patients who are ATA 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.	Percentage of patients in the safety population who are ATA 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.	Up to 7 months
• Impact of ATA and nATA on the safety, efficacy, and PK endpoints.	Impact of ATA and nATA on the safety, efficacy, and PK endpoints.	Up to 24 months

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame [a]
Phase 2 Primary		
• Percentage of patients who achieve a CR per IRF assessment at EOT per IWG criteria.	Percentage of patients in the Response-Evaluable Population who achieve a complete response based on the IRF assessment at the EOT visit based on the IWG criteria.	Up to 7 months
• Percentage of patients whose disease is PET- after 2 cycles of protocol therapy per IRF assessment.	Percentage of patients in the Response-Evaluable Population whose disease is negative per PET after 2 cycles of protocol therapy per IRF assessment.	Up to 2 months
• Percentage of patients who achieve a PR per IRF assessment at EOT per IWG criteria.	Percentage of patients in the Response-Evaluable Population who achieve a partial response based on the IRF assessment at the EOT visit based on the IWG criteria.	Up to 7 months
• Percentage of patients who achieve an OR per IRF assessment at EOT per IWG criteria.	Percentage of patients in the Response-Evaluable Population who achieve an overall response based on the IRF assessment at the EOT visit based on the IWG criteria.	Up to 7 months
• Percentage of patients who are able to complete 6 cycles of protocol therapy at the recommended dose.	Percentage of patients in the Response-Evaluable Population who are able to complete six 28-day cycles of treatment at the recommended dose.	Up to 6 months
Phase 2 Secondary		
• PFS, EFS, OS, DOR.	Progression- and event-free survival, overall survival, and duration of response.	Up to 24 months
• Percentage of patients receiving irradiation for HL following study treatment.	Percentage of patients receiving irradiation for HL after up to 6 months of study treatment.	Up to 24 months.
• 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.	The percentage of patients in the Safety Population who experience TEAEs for up to 6 months of treatment plus 30 days following the end of study treatment.	Up to 7 months
• 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.	The percentage of patients in the Safety Population who experience treatment-emergent SAEs for up to 6 months of treatment plus 30 days following the end of study treatment.	Up to 7 months

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame [a]
• Percentage of patients who are ATA 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.	Percentage of patients in the safety population who are ATA 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.	Up to 7 months
• Impact of ATA and nATA on the safety, efficacy, and PK endpoints.	Impact of ATA and nATA on the safety, efficacy, and PK endpoints.	Up to 24 months
• Mean C_{max} and mean AUC_{0-15} of brentuximab vedotin (serum), TAb (serum), and MMAE (plasma).	Mean maximum concentration and AUC from Day 0 to Day 15 for brentuximab vedotin and TAb in serum and MMAE in plasma based on data from the PK Population.	Up to 15 days
• Median T_{max} of brentuximab vedotin (serum), TAb (serum), and MMAE (plasma).	First time of occurrence of maximum (peak) concentration for a single dose of brentuximab vedotin for patients in the PK Population.	Up to 15 days
• Percentage of patients who experience peripheral neuropathy, regardless of seriousness, from the first dose of protocol therapy through study closure.	Percentage of patients who experience peripheral neuropathy, regardless of seriousness, from the first dose of protocol therapy through study closure.	Up to 24 months
• Time to onset and time to resolution for all peripheral neuropathy events.	Time from first dose of protocol therapy to onset, and time from onset to resolution for all peripheral neuropathy events.	Up to 24 months
• Immune reconstitution (peripheral blood CD34+ count; enumeration of the total lymphocyte count and lymphocyte subsets; total Ig and IgG, IgM, IgA levels; and levels of 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).	Immune reconstitution (peripheral blood CD34+ count; enumeration of the total lymphocyte count and lymphocyte subsets; total immunoglobulin and IgG, IgM, IgA levels; levels of 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).	Up to 24 months

AE: adverse event; ATA: antitherapeutic antibody; AVD: Adriamycin (doxorubicin), vinblastine, and dacarbazine; AUC: area under the concentration-time curve; AUC_{0-15}: area under the concentration-time curve from Day 0 to Day 1; C_{max}: maximum observed concentration; CR: complete remission; DOR: duration of response; EFS: event-free

Table 6.a Primary and Secondary Endpoints for Disclosures

Endpoint	Definition	Maximum Time Frame [a]

survival; EOT: End of Treatment (visit); HiB: hemophilus influenza type B; HL: Hodgkin lymphoma; Ig: immunoglobulin; IRF: independent review facility; IWG: International Working Group; MMAE: monomethyl auristatin E; nATA: neutralizing antitherapeutic antibody; OR: overall response; PET: positron emission tomography; PFS: progression-free survival; PK: pharmacokinetic(s); PR: partial remission; SAE: serious adverse event; TAb: total (free and conjugated) therapeutic antibody; TEAE: treatment-emergent adverse event; T_{max}: time of occurrence of maximum (peak) concentration.

[a] Time to last assessment for that endpoint for an individual patient.

6.3.4 Total Study Duration

It is anticipated that this study, including the follow-up period, will last approximately 55 months. All patients will be offered the opportunity to participate in an optional long-term follow-up that is for at least 10 years from the individual patient's enrollment.

7.0 STUDY POPULATION

Male or female patients aged 5 to <18 years with newly diagnosed, classical CD30+, advanced stage (Stage III or Stage IV) HL who are treatment naïve with Karnofsky Performance Status or Lansky Play-Performance ≥50.

7.1 Inclusion Criteria

Each patient must meet all the following inclusion criteria to be enrolled in the study:

1. Male or female patients aged 5 to <18 years.
2. Histologically confirmed CD30+ cHL.
3. Advanced stage, newly diagnosed HL (Stage III and Stage IV disease) (refer to Appendix E).
4. Treatment-naïve HL.
5. Have performance scores of ≥50 for Lansky Play-Performance or Karnofsky Performance Status (refer to Appendix F and Appendix G, respectively).
6. Patients must have bidimensional measurable disease as documented by radiographic technique per IWG criteria [1].
7. Female patients who:
   - Are surgically sterile, *OR*
   - If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing the informed consent through 6 months after the last dose of protocol therapy, or

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- Agree to practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of protocol therapy, *OR*
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

8. Voluntary written consent (and institution-specific assent as appropriate based upon patient comprehension) must be given before the performance of any study-related procedure not part of standard medical care, with the understanding that consent/assent may be withdrawn by the patient or patient guardian at any time without prejudice to future medical care.
9. Suitable venous access for the study-required procedures.
10. Clinical laboratory values within 4 days before the first dose of protocol therapy as follows:
    - Absolute neutrophil count ≥1,500/µL unless there is known HL marrow involvement.
    - Platelet count ≥75,000/µL unless there is known HL marrow involvement.
    - Total bilirubin ≤1.5×the upper limit of the normal range (ULN) for age or ≤3×ULN for patients with indirect hyperbilirubinemia due to Gilbert's syndrome.
    - Alanine aminotransferase or aspartate aminotransferase ≤2.5 × ULN for age.
    - Creatinine clearance or radioisotope glomerular filtration rate ≥70 mL/min/1.73m^2 or a serum creatinine based on age/gender as follows:

Age	Maximum serum creatinine (mg/dL)*	
	Male	Female
2 to <6 years	0.8	0.8
6 to <10 years	1	1
10 to <13 years	1.2	1.2
13 to <16 years	1.5	1.4
≥16 years	1.7	1.4

*Derived from the Schwartz formula for estimating, utilizing child length and stature data published by the CDC.

- Hemoglobin ≥8 g/dL (patients may be transfused to meet eligibility criteria).

7.2 Exclusion Criteria

1. Nodular lymphocyte predominant HL.
2. Known active cerebral/meningeal disease, including signs or symptoms of progressive multifocal leukoencephalopathy (PML) or any history of PML.
3. Any sensory or motor peripheral neuropathy.
4. Female patients who are breastfeeding or have a positive serum or urine pregnancy test during the Screening period or a positive serum or urine pregnancy test on Day 1 before the first dose of protocol therapy.
5. Any serious medical or psychiatric illness that could, in the investigator's or medical monitor's opinion, potentially interfere with the completion of treatment according to this protocol.
6. Symptomatic neurologic disease compromising normal activities of daily living or requiring medications.
7. Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics within 2 weeks before the first study protocol therapy.
8. Known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin or any component of AVD.
9. Known human immunodeficiency virus positive.
10. Known hepatitis B surface antigen positive or known or suspected active hepatitis C infection, as determined by hepatitis B DNA or hepatitis C RNA, respectively, in blood.
11. Diagnosed or treated for another malignancy within 3 years before the first dose or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
12. Use of any strong or listed moderate cytochrome P450 (CYP) 3A4 inhibitors <2 weeks before the first dose of protocol therapy (please refer to the Study Manual for an example list of prohibited CYP3A4 inhibitors).
13. Any of the following cardiovascular conditions or values within 6 months before the first dose of protocol therapy:
    - Shortening fraction of <27% by echocardiogram or, if echocardiogram not feasible, ejection fraction of <50% by radionuclide angiogram (RNA or MUGA [multiple-gated acquisition scan]).
    - New York Heart Association Class III or IV heart failure (see Appendix H).
    - Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure, angina, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.

8.0 PROTOCOL THERAPY

8.1 Protocol Therapy Administration

All protocol-specific criteria for administration of protocol therapy must be met and documented before drug administration. Protocol therapy will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The components of A+AVD used in this study are considered investigational medicinal products and will be supplied by the study sponsor, as outlined in Section 8.10.

A+AVD consists of brentuximab vedotin (ADCETRIS) 48 or 36 mg/m^2, plus doxorubicin 25 mg/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2.

- **A**: Doxorubicin: 25 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle.
- **V**: Vinblastine: 6 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle.
- **D**: Dacarbazine: 375 mg/m^2 will be administered by IV infusion on Days 1 and 15 of each 28-day cycle.

AVD is to be administered first, in the stated order, per institutional guidelines. If an investigator needs to choose a different order of administration of the protocol therapy components, this must first be discussed with the contract research organization (CRO) and/or the Takeda medical monitor.

Brentuximab vedotin is to be administered after AVD:

- **A:** brentuximab vedotin (ADCETRIS): 48 or 36 mg/m^2 will be administered by IV infusion over approximately 30 minutes on Days 1 and 15 of each 28-day cycle; the infusion is to start approximately 1 hour after the conclusion of the dacarbazine administration.

  In the absence of infusion toxicities, the infusion rate for all patients must be calculated to achieve a 30-minute (approximate) brentuximab vedotin infusion period.

  Brentuximab vedotin must not be administered as an IV push or bolus. It must be administered through a dedicated IV line and cannot be mixed with other medications.

  Dosing is based on patients' body surface area (BSA) according to the institutional standard; however, doses must be adjusted for patients who experience a ≥10% change in BSA from the most recent dose calculation. For patients with a BSA of >2.5 m^2, the dose will be calculated based on a BSA of 2.5 m^2 for these individuals, as the maximum dose of brentuximab vedotin that a patient can receive is 120 mg. The dose will be rounded to the nearest whole number of milligrams.

  Further brentuximab vedotin administration information can be found in the Pharmacy Manual.

8.2 Definitions of DLT

Toxicity will be evaluated according to the NCI CTCAE, Version 4.03, effective 14 June 2010 [23]. These criteria are provided in the Study Manual.

The DLT observation period comprises Cycle 1+28 days (from first dose through Study Day 56). Patients who receive study treatment in Cycles 1 and 2 without dose delay will be observed for DLTs through Cycle 2 (Day 56). Patients who discontinue treatment, do not receive the full course of protocol therapy, or have a delay in therapy will also be observed for DLTs through Day 56. Patients will be monitored through all cycles of protocol therapy for treatment-related toxicities.

DLT will be defined as any of the following events with onset during the DLT observation period that are considered by the investigator to be at least possibly related to therapy with brentuximab vedotin:

- Any nonhematologic Grade ≥3 toxicity except for the following: Any nonhematologic toxicity Grade ≥3 that occurs in the absence of optimal supportive therapy (eg, antiemetic, antidiarrheal, etc) and lasting more than 5 consecutive days (such as vomiting, diarrhea, constipation, pyrexia, infection, or mucosal inflammation). Grade 3 or greater nonhematologic toxicity that is controllable to Grade 2 or less with appropriate treatment will not be considered dose-limiting DLT (excludes Grade 3 alopecia).
- Treatment delay of more than 14 days.

Asymptomatic laboratory abnormalities should not be considered DLTs with the exclusion of Grade 2 pancreatitis (enzyme elevation only without clinical and/or radiographic findings).

8.3 Regimen De-Intensification Rules

If more than 1 patient experience a DLT during the DLT observation period, a dose de-intensification schedule will be implemented in which brentuximab vedotin will be decreased by 25% to 36 mg/m^2 (See Figure 6.a).

8.4 Dose Modification Guidelines

8.4.1 Recommended Brentuximab Vedotin Dose Modifications for Treatment-Associated Toxicity

Table 8.a details the recommended brentuximab vedotin dose modifications to be enacted in the event of treatment-associated toxicity.

In the case of brentuximab vedotin-specific toxicity (ie, severe neuropathy during or after brentuximab vedotin) or other unexpected severe AEs, the sponsor should be consulted to discuss therapeutic alternatives.

Table 8.a Recommended Brentuximab Vedotin Dose Modifications for Treatment-Associated Toxicity

Toxicity	Grade ≤2		Grade ≥3	
Nonhematologic (excluding neuropathy)	Continue at same dose level.		Hold A+AVD dosing until toxicity has resolved to Grade ≤2 or has returned to baseline [a, b, c].	
Hematologic	Continue at same dose level.		For neutropenia, manage with growth factors (G-CSF or GM-CSF) per institutional guidelines. G-CSF use is not permitted in the DLT observational period (Cycle 1+28 days in phase 1). For thrombocytopenia, consider platelet transfusion and/or proceed according to institutional guidelines. For anemia, manage per institutional guidelines.	
Peripheral neuropathy	**Grade 1** Continue at same dose level.	**Grade 2** Reduce brentuximab vedotin dose by 25% and resume treatment; if already reduced by 25%, continue dosing at that level.	**Grade 3** Withhold brentuximab vedotin until toxicity is Grade ≤2, then reduce dose by 25% and resume treatment. If already reduced by 25%, consult with sponsor. (AVD may be continued or held concurrently at physician's discretion.)	**Grade 4** Discontinue brentuximab vedotin.

A+AVD: brentuximab vedotin, Adriamycin, vinblastine, and dacarbazine; AVD: Adriamycin (doxorubicin), vinblastine, and dacarbazine; DLT: dose-limiting toxicity; G-CSF: granulocyte colony stimulating factor; GM-CSF: granulocyte macrophage colony stimulating factor.

[a] Patients who develop clinically insignificant Grade 3 or 4 electrolyte laboratory abnormalities may continue study treatment without interruption.

[b] Dose modifications for nonhematologic toxicity may be considered after discussion with the medical monitor.

[c] In the case of dose delays >2 weeks, a discussion with the medical monitor should occur.

8.4.2 Reference Therapy Dose Modifications

AVD treatment should be modified or discontinued per applicable package insert instructions.

8.4.3 Criteria for Dose Administration

Treatment with protocol therapy will occur on Days 1 and 15 of 28-day cycles. For a new cycle of treatment to begin or for study treatment to be administered on Day 15, the patient must meet the following criteria:

- Recovery from treatment-related toxicity per Table 8.a.
- General condition satisfactory.

8.5 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Any investigational agent other than A+AVD, including agents that are commercially available for indications other than HL that are under investigation for the treatment of HL.
- Any anticancer treatment with activity against HL other than A+AVD.
- Radiotherapy for disease under study before the EOT disease assessment.
- The concomitant use of brentuximab vedotin and bleomycin has resulted in increased pulmonary toxicity versus bleomycin alone. Coadministration of brentuximab vedotin and bleomycin is contraindicated.
- Any strong and listed moderate CYP3A4 inhibitors are prohibited, except moderate inhibitors when necessary for the medical management of a patient. Please refer to the Study Manual for an example list of prohibited CYP3A4 inhibitors. Patients will be closely monitored for the possibility of excess toxicity.

8.6 Permitted Concomitant Medications and Procedures

The following medications and procedures are allowed during the study:

- The use of local steroid treatments such as topical, inhalational, and ophthalmic steroids is permitted. Corticosteroids are permitted as part of a chemotherapy premedication regimen or for the treatment of HL symptoms per institutional standards.
- Radiotherapy for the emergency treatment of local HL-related symptoms (eg, spinal cord compression) is permitted, as long as such treatment does not interfere with staging/response assessment.
- Radiotherapy is recommended following the EOT disease assessment for patients who have PET+ sites at Cycle 2 disease assessment.
- Antiemetics are permitted per institutional standards. Due to its activity as a moderate CYP3A4 inhibitor, the use of aprepitant should be reserved for nausea/vomiting that is refractory to other agents.
- Patients may receive concomitant hormonal therapy provided they have been on a stable dosage for at least 1 month before enrollment. No restrictions are placed upon the use of birth control.
- The use of platelet and/or red blood cell supportive growth factors or transfusions when applicable is allowed.
- The use of colony stimulating factors for the treatment or prevention of neutropenia per institutional practice is permitted during therapy. G-CSF use is not permitted in the DLT observational period (Cycle 1 + 28 days in phase 1).

8.7 Precautions and Restrictions

8.7.1 Infusion-Related Reactions

All infusions should be administered at a site properly equipped and staffed for anaphylaxis should it occur. Medications for treatment of hypersensitivity reactions, such as epinephrine, antihistamines, and steroids, should be available for immediate use in the event of a reaction during administration and also during the observation period following brentuximab vedotin infusion.

8.7.2 Pregnancy

It is not known what effects brentuximab vedotin has on human pregnancy or development of the embryo or fetus. It is also not known how brentuximab vedotin affects mother's milk or an unborn child. Therefore, patients who are breastfeeding and pregnant women are not allowed to take part in the study. Female patients participating in this study should avoid becoming pregnant, nursing a baby, or donating an egg or eggs (ova); and male patients should avoid impregnating a female partner or donating sperm during the study and for up to 6 months following the last dose of protocol therapy. Nonsterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified in the following:

Female patients must meet 1 of the following:

- Surgically sterile, or
- If they are of childbearing potential, agree to practice 1 highly effective method of contraception and 1 additional effective (barrier) method at the same time, from the time of signing of the informed consent form through 6 months after the last dose of protocol therapy, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

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

- Practice effective barrier contraception during the entire study treatment period and through 6 months after the last dose of protocol therapy, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

8.8 Management of Clinical Events

If dose alterations are necessary as a result of the events detailed in the following, please refer to Section 8.4.

8.8.1 Nausea and/or Vomiting

Although this study will not require prophylactic antiemetics, there is no prohibition against their use. Five-hydroxytryptamine 3 serotonin receptor antagonists and corticosteroids should be tried first. Due to its activity as a moderate CYP3A4 inhibitor, the use of aprepitant should be reserved for nausea/vomiting that is refractory to other agents.

8.8.2 Diarrhea

Prophylactic antidiarrheals will not be used in this protocol; however, patients will be instructed to take antidiarrheal medication(s) for the treatment of treatment-emergent diarrhea at the physician's discretion until they are diarrhea-free for at least 12 hours. Fluid intake should be maintained to avoid dehydration.

8.8.3 Infusion-Related Reactions

Infusion-related reactions may occur during the infusion of brentuximab vedotin. The infusion should be administered at a site properly equipped and staffed to manage an infusion-related reaction, including anaphylaxis should it occur. The patient should be observed for approximately 60 minutes following infusion of brentuximab vedotin. During this observation period, the IV line should remain open for at least 1 hour to allow administration of IV drugs if necessary. All supportive measures consistent with optimal patient care will be given throughout the study according to institution standards. Medications for infusion-related reactions, such as epinephrine and antihistamines, should be available for immediate use.

If anaphylaxis occurs, the administration of brentuximab vedotin should be immediately and permanently discontinued and appropriate medical therapy administered. If an infusion-related reaction occurs, the infusion should be interrupted and appropriate medical management instituted. Patients who have experienced a prior infusion-related reaction should be premedicated according to institutional guidelines for subsequent infusions. Premedication may include acetaminophen, an antihistamine, and a corticosteroid.

8.8.4 Peripheral Neuropathy

AEs of peripheral neuropathy will be monitored closely throughout the study. These events may include, but are not limited to: peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, hypoesthesia, polyneuropathy, muscular weakness, and demyelinating polyneuropathy. Such events, regardless of seriousness, will be followed for all changes in severity until 30 days after the last dose of protocol therapy, and recorded in the electronic case report form (eCRF). Thereafter, all ongoing events will be followed for improvement until the sooner of resolution to baseline or study closure, and recorded in the eCRF. Any ongoing events which worsen without initiation of subsequent anticancer therapy should also be recorded in the

eCRF. Events that are higher than Grade 1 will result in brentuximab vedotin dose modification described in Section 8.4.

Study treatment–related peripheral neuropathy that is ongoing at the time of the first annual visit for the optional long-term follow-up will be assessed for improvement until the sooner of resolution to baseline or completion of the optional long-term follow-up (ie, at least 10 years after the patient's enrollment) and recorded in the eCRF. Any ongoing events which worsen without initiation of subsequent anticancer therapy should also be recorded in the eCRF.

8.8.5 Suspected PML

Signs and symptoms of PML may include altered mental status; motor deficits, such as hemiparesis or ataxia; visual disturbances; or higher cortical dysfunction, such as dysphasia or agnosia. Seizures have also been reported in patients with PML (approximately 20%). The onset of neurological deficits may occur over weeks to months. See the IB for further details.

If PML is suspected, hold further brentuximab vedotin dosing and undertake a diagnostic workup that may include (but is not limited to)**:**

- Neurologic examinations, as warranted.
- Brain magnetic resonance imaging (MRI): Features suggestive of PML include presence of unifocal or multifocal lesions, mainly of the white matter, which are typically non-enhancing and do not have mass effect.
- Polymerase chain reaction analysis: John Cunningham virus (JCV) DNA detectable in cerebrospinal fluid or there is evidence of JCV in a brain biopsy.
- Neurology consultation.

If PML is confirmed, permanently discontinue treatment with brentuximab vedotin.

8.9 Blinding and Unblinding

This is an open-label study.

8.10 Description of Investigational Agents

8.10.1 Brentuximab Vedotin

Brentuximab vedotin will be supplied by the sponsor. Brentuximab vedotin for Injection is a sterile, preservative-free, white to off-white lyophilized cake for reconstitution for IV administration. Brentuximab vedotin for Injection is supplied in single-use, Type 1 borosilicate glass vials with FluroTec-coated butyl rubber stoppers and aluminum seals. Each vial of the product contains brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80. The lyophilized product, after reconstitution with 10.5 mL sterile Water for Injection, United States Pharmacopeia or an equivalent standard, yields 11 mL of brentuximab vedotin solution (5 mg/mL).

8.10.2 Doxorubicin

Doxorubicin will be supplied by the sponsor, depending on regional availability. Additional details are provided in the applicable package insert.

8.10.3 Vinblastine

Vinblastine will be supplied by the sponsor, depending on regional availability. Additional details are provided in the applicable package insert.

8.10.4 Dacarbazine

Dacarbazine will be supplied by the sponsor, depending on regional availability. Additional details are provided in the applicable package insert.

8.11 Preparation, Reconstitution, and Dispensation

Parenteral drug products should be inspected visually for particulate matter and discoloration before administration, whenever solution and container permit.

8.11.1 Brentuximab Vedotin

Brentuximab vedotin is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling brentuximab vedotin.

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

Study treatment vials are single-use containers. Any partially used vials or diluted dosing solutions are to be discarded using appropriate institutional drug disposal procedures.

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

The appropriate amount of reconstituted study treatment will be withdrawn from the vial(s) and diluted in an infusion bag according to the instructions provided in the Pharmacy Manual. Refer to the Pharmacy Manual for more specific instructions on drug preparation.

8.11.2 Doxorubicin

Doxorubicin will be supplied by the sponsor, depending on regional availability. Additional details are provided in the applicable package insert.

8.11.3 Vinblastine

Vinblastine will be supplied by the sponsor, depending on regional availability. Additional details are provided in the applicable package insert.

8.11.4 Dacarbazine

Dacarbazine will be supplied by the sponsor, depending on regional availability. Additional details are provided in the applicable package insert.

8.12 Packaging and Labeling

Vials of study treatment will be packaged in cardboard kits. Each kit will contain 1 vial of investigational product. Vials and kits will be labeled to meet country-specific regulatory requirements.

8.13 Storage, Handling, and Accountability

Drug accountability instructions are provided in the Pharmacy Manual.

8.13.1 Brentuximab Vedotin

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

Study treatment does not contain preservatives; therefore, opened and reconstituted vials of study treatment must be used within 24 hours when stored under refrigeration at 2°C to 8°C. Reconstituted study treatment should not be stored at room temperature. It is recommended that study treatment vials and solutions be protected from direct sunlight until the time of use. **Reconstituted vials must not be shaken**.

8.13.2 Doxorubicin

Doxorubicin will be supplied by the sponsor, depending on regional availability. Additional details are provided in the applicable package insert.

8.13.3 Vinblastine

Vinblastine will be supplied by the sponsor, depending on regional availability. Additional details are provided in the applicable package insert.

8.13.4 Dacarbazine

Dacarbazine will be supplied by the sponsor, depending on regional availability. Additional details are provided in the applicable package insert.

9.0 STUDY CONDUCT

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

9.1 Study Personnel and Organizations

The contact information for the medical monitor for this study, the central laboratory and any additional clinical laboratories, the coordinating investigator for each member state/country, and

the CRO team may be found in the Study Manual. A full list of investigators is available in the sponsor's investigator database.

9.2 Arrangements for Recruitment of Patients

Recruitment and enrollment strategies for this study may include recruitment from the investigator's local practice or referrals from other physicians. If advertisements become part of the recruitment strategy, they will be reviewed by the institutional review board (IRB)/ independent ethics committee (IEC).

9.3 Treatment Group Assignments

This is a single-arm study with no reference therapy. Treatment group assignments are not applicable.

9.4 Study Procedures

Refer to the SOE (Appendix A) for timing of assessments. Additional details are provided as necessary in the sections that follow.

9.4.1 Informed Consent

Each patient's parents (or patient's legal guardian) must provide written informed consent, and each patient must provide written assent as appropriate for age, before any study-required procedures are conducted, unless those procedures are performed as part of the patient's standard care.

Patients reaching an age that is not covered by their pediatric assent should provide re-assent for their appropriate age group to remain in the study. Patients who reach the age of consent must provide consent with a signed ICF to remain in the study.

All eligible patients, even those who discontinue early, are to be offered the option to participate in the optional long-term follow-up and acceptance or rejection is to be documented.

For participation in the optional long-term follow-up, each patient's parent(s) (or patient's legal guardian) must provide written informed consent, and each patient must provide written assent or consent, as appropriate for age.

9.4.2 Patient Demographics

The date of birth, race, ethnicity, and sex of the patient are to be recorded during Screening, as allowed.

9.4.3 Medical History

During the Screening period, a complete medical history will be compiled for each patient. The history will emphasize the background and progress of the patient's malignancy. Stage at initial diagnosis will be assessed per the Ann Arbor Staging System for Hodgkin Lymphoma (see

Appendix E). Evidence of bone marrow involvement and extranodal involvement at initial diagnosis will also be collected.

In addition, concomitant medications will be recorded as specified in Section 9.4.16.

9.4.4 Enrollment

A patient is considered to be enrolled in the study at the time of first dose of protocol therapy.

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

9.4.5 Patient Height, Weight and Body Surface Area

Height and weight will be measured at the times specific in the SOE (Appendix A) to support the development assessment (See Section 9.4.10) and dosing.

BSA used for dosing calculations will be collected on each dosing day.

9.4.6 Physical Examination

A physical examination, including focused lymphoma assessment and peripheral neuropathy assessment, will be completed per SOC at the times specified in the SOE (Appendix A).

9.4.7 Pregnancy Test

A serum or urine pregnancy test will be performed for female patients of childbearing potential as outlined in the SOE (Appendix A).

9.4.8 Vital Signs

Vital sign measurements include seated (after 3-5 minutes in this position) measurements of diastolic and systolic blood pressure, heart rate, and temperature at the times specified in the SOE (Appendix A).

9.4.9 Lansky Play-Performance or Karnofsky Performance Status

Lansky Play-Performance or Karnofsky Performance Status are to be assessed as specified in the SOE (Appendix A). See Appendix F for Lansky Play-Performance. See Appendix G for Karnofsky Performance Status.

9.4.10 Development Assessment

Development assessment will be done as specified in the SOE (Appendix A) and will include weight-for-age and stature-for-age percentiles, and the Tanner Scale.

Height and weight will be collected to determine the weight-for-age and stature-for-age percentiles.

The Tanner Scale will be performed to assess physical developmental stage (See Appendix I).

9.4.11 Clinical Chemistry and Hematology

Clinical chemistry and hematology evaluations will be performed locally.

Blood samples for analysis of the clinical chemistry and hematology parameters shown in Table 9.a will be obtained at the time points specified in the SOE (Appendix A).

Table 9.a Clinical Chemistry and Hematology Tests

Hematology	Serum Chemistry		Other
Hematocrit	Albumin	Chloride	Hemoglobin A1C
Hemoglobin	Alkaline phosphatase (ALP)	γ-glutamyl transferase (GGT)	Troponin T [a]
Leukocytes with differential	ALT	Glucose	
Neutrophils (absolute neutrophil count; ANC)	AST	Lactate dehydrogenase (LDH)	
Platelet (count)	Total bilirubin	Magnesium	
	Blood urea nitrogen (BUN)	Phosphate	
	Calcium	Potassium	
	Carbon dioxide (CO_2)	Sodium	
	Creatinine (for age and gender)	Urate	

ALT: alanine aminotransferase; AST: aspartate aminotransferase.
[a] Troponin T is the only test collected at the optional long-term follow-up visits.

9.4.12 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be administered at the time points specified in the SOE (Appendix A).

9.4.13 Echocardiogram

Echocardiograms will be administered at the time points specified in the SOE (Appendix A). If echocardiogram is not feasible, radionuclide angiogram (RNA or MUGA) will be performed at all time points specified in the SOE (Appendix A). The same modality should be used from screening and throughout the study.

CCI

[redacted]

CCI

[redacted]

9.4.16 Concomitant Medications and Procedures

Medications used by the patient and therapeutic procedures completed by the patient will be recorded in the eCRF at the time points specified in the SOE (Appendix A). See Section 8.5 and Section 8.6 for a list of medications and therapies that are prohibited or allowed during the study.

9.4.17 Adverse Events

Monitoring of AEs, serious and nonserious, will be conducted throughout the study as specified in the SOE (Appendix A). Refer to Section 10.0 for details regarding definitions, documentation, and reporting of pretreatment events (PTEs), AEs, and SAEs. Changes in the severity of events relating to peripheral neuropathy will be recorded as described in Section 10.3.

9.4.18 Disease Assessment

9.4.18.1 Imaging, Restaging, and Radiation Therapy Guidance

Disease assessments will be performed as specified in the SOE (Appendix A) until PD is documented by the investigator, death occurs, or the study ends. If for any reason other than death or documented PD a patient discontinues protocol therapy after Cycle 2 Day 25 but before completion of EOT disease assessments, every effort must be made to obtain computed tomography (CT), MRI, and PET scans before initiation of subsequent therapy for HL. Additional assessments may be necessary when clinically indicated.

Patients will undergo CT with contrast as appropriate, MRI, and PET to monitor and assess PD according to the IWG Revised Response Criteria for Malignant Lymphoma [1]. CT scans will be used to evaluate the chest only; MRI will be used to evaluate the neck, abdomen, and pelvis. When possible, the same qualified physician will interpret results to reduce variability. Radiographic images will be maintained at the site, and test results and physician findings will be filed in patient source documents. In addition, radiographic images will be provided to the IRF for assessment.

Restaging will be performed to assess the status of the patient's underlying disease after completion of Cycle 2 treatment. 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. Radiotherapy should not be administered on the lung or spleen if those sites are PET- after the completion of Cycle 2, even if there is a persistence of PET activity in other sites. The target volume of irradiation should be based on initial nodal and extranodal involvement, as demonstrated by the baseline PET at the time of diagnosis [24-26].

Restaging will also be performed at the EOT disease assessment to determine if there is the need for radiotherapy in addition to any radiotherapy requirements identified at the end of Cycle 2.

Only residual lymph nodes >1 cm that are still PET+ at EOT should be considered for radiotherapy. Extranodal lesions should require radiotherapy only if 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.

For patients receiving radiation at EOT, the following guidance is provided: ISRT will consist of 2100cGy in 14 fractions of 150cGy per day. Treatment should be given 5 days per week. All fields should be treated once per day. Treatment should begin no later than 4 weeks after completion of the last cycle of chemotherapy provided that the blood count recovery has occurred. Patients requiring radiation above and below the diaphragm should be treated with sequential rather than concurrent fields. The site of bulkiest involvement should be treated first and the second field should be treated with adequate hematologic recovery.

9.4.18.2 B Symptoms Assessments

B symptoms assessments, including fever, night sweats, and weight loss, will be evaluated at the time points indicated in the SOE (Appendix A).

9.4.18.3 Bone Marrow Assessments

Bone marrow biopsy will be collected as indicated in the SOE (Appendix A).

9.4.18.4 Biopsy Related to Disease Assessment

Biopsy specimens will not be collected for this study. However, the results of diagnostic biopsies must be recorded, documenting a diagnosis of CD30+ cHL. Additionally, the results of any biopsies related to disease assessment that are performed during the course of the study must be recorded.

9.4.19 PK Measurements

Blood samples for PK analysis will be collected as specified in the SOE (Appendix A). Samples will be analyzed for serum concentrations of brentuximab vedotin and TAb and plasma concentrations of MMAE (see Section 13.1.5). Population PK methodologies may be used to determine PK parameters.

Refer to the Laboratory Manual for information on collection, processing, storage, and shipment of samples to a central laboratory.

9.4.20 Immunogenicity

Blood samples will be collected as specified in the SOE (Appendix A) to evaluate serum ATA and nATA. On dosing days, the blood samples for ATA and nATA assessment must be collected before dosing. Neutralizing ATA assessment will be performed for ATA-positive samples only.

The incidence of ATA and nATA to brentuximab vedotin will be assessed (see Section 9.4.20) and the impact of ATA and nATA on PK, efficacy, and safety will also be assessed.

Refer to the Laboratory Manual for information on collection, processing, storage, and shipment of samples to a central laboratory.

9.4.21 Immune Reconstitution

The effects of protocol therapy on the pediatric peripheral immune system will be examined at the time points specified in the SOE (Appendix A) by measuring peripheral blood cell populations and the circulating Ig subclasses as follows:

- IgG.
- IgM.
- IgA.
- CD34+ cell count.
- Tetanus antibodies.
- HiB.
- Polio serotypes.
- Total Ig.
- Lymphocyte count.
- Lymphocyte subsets.

Peripheral cell populations will be examined using serum from the heparinized blood specimens collected. Cellular populations including T-cell subsets (T helper, cytotoxic, and memory cells), B cells, NK cells, granulocytes, and CD34+ cell count will be measured using flow cytometry. Immunoglobulin subclasses will be examined using standard clinical laboratory procedures.

Refer to the Laboratory Manual for information on collection, processing, storage, and shipment of samples to a central laboratory.

9.5 Completion of Treatment

Patients will be considered to have completed treatment if they complete 6 cycles of treatment with protocol therapy, experience PD, or die before completing protocol therapy.

9.6 Completion of Study

Patients will be considered to have completed the study if they meet both of the following criteria:

- Completed treatment (Section 9.5).
- Have been followed for up to 2 years after enrollment of the last patient or have died.

9.7 Completion of Optional Long-term Follow-up

Patients will be considered to have completed the optional long-term follow-up if they have been followed for at least 10 years from their enrollment date in the main study or have died.

9.8 Discontinuation of Treatment With Protocol Therapy and Patient Replacement

Protocol therapy must be permanently discontinued for patients meeting any of the following criteria:

- Completed 6 cycles of protocol therapy.

- Investigator, patient, or patient's legal guardian deems it is in the patient's best interest to discontinue. (The reason justifying study treatment withdrawal must be documented in the eCRF.)
- PD.

Treatment with protocol therapy may also be discontinued for any of the following reasons:

- AE.
- Protocol violation.
- Unsatisfactory therapeutic response.
- Study terminated by sponsor.
- Withdrawal by patient or patient's guardian.
- Lost to follow-up.
- Other.

Once protocol therapy has been discontinued, all study procedures outlined for the EOT visit will be completed as specified in the SOE (Appendix A). The primary reason for protocol therapy discontinuation will be recorded on the eCRF.

Patients who are withdrawn from study before the completion of the DLT observation period for reasons other than DLT will be replaced. Additional patients may be enrolled to ensure up to 55 evaluable patients at the recommended dose.

9.9 Withdrawal of Patients From Study

Prior to completion of the treatment period and up to 2 year follow-up, a patient may be withdrawn from the study for any of the following reasons:

- Death.
- Lost to follow-up.
- Study terminated by sponsor.
- Withdrawal by patient or patient's guardian.
- Other.

The consequence of study withdrawal is that no new information will be collected from the withdrawn patient and added to the existing data or any database.

9.10 Withdrawal of Patients from Optional Long-term Follow-up

Prior to completion of the optional long-term follow-up, a patient may be withdrawn for any of the following reasons:

- Death.

- Study terminated by sponsor.
- Withdrawal by patient or patient's guardian.
- Other.

9.11 Study Compliance

Protocol therapy will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). The appropriate study personnel will maintain records of study drug receipt, dispensing, and destruction/returns.

9.12 Posttreatment Follow-up Assessments (PFS and OS)

Patients will have an EOT assessment visit 30±7 days after receiving their final dose of protocol therapy.

Patients who stop treatment for any reason other than PD as assessed by the investigator or the start of subsequent anticancer therapy will have progression-free survival follow-up (PFSFU) visits at the site every 12 weeks (±1 week) for 12 months and then every 24 weeks (±2 weeks) for up to 2 years until the occurrence of PD, the start of subsequent anticancer therapy, the patient withdraws consent for further follow-up, or the study ends. During follow-up, all patients who start radiotherapy must be recorded. Patients who discontinue treatment for PD or the start of subsequent anticancer therapy will be followed for OS only.

After the occurrence of PD or the start of subsequent anticancer therapy, patients will continue to have overall survival follow-up (OSFU) visits every 24 weeks (±2 weeks) until the sooner of death or study closure or for up to 2 years from the date of the last patient enrolled. Survival and disease status information may be collected by methods that include, but are not limited to, telephone, email, or mail, or retrieved from online or other databases (eg, social security indexes). In addition, details of subsequent anticancer therapy will be collected.

An End-of-Study eCRF is to be completed at the time the patient discontinues from the follow-up period of the main study. A separate End-of-Study eCRF is to be completed for all participating patients upon their completion of the optional long-term follow-up period (see Section 9.13).

NOTE: Related SAEs must be reported to the Global Pharmacovigilance department or designee. This includes deaths that the investigator considers related to protocol therapy that occur during the posttreatment follow-up. Refer to Section 10.0 for details regarding definitions, documentation, and reporting of SAEs.

9.13 Optional Long-term Follow-up

All study patients will be offered the opportunity to participate in an optional long-term follow-up to assess safety and survival annually. Patients participating in the optional long-term follow-up will commence their first optional long-term follow-up visit 2 years after the patient's EOT visit and continue with annual visits until at least 10 years from the date of patient enrollment.

Regardless of the patient's decision to participate in the optional long-term follow-up, patients are to continue with their posttreatment follow-up in the main study until the main study has completed, which is up to 2 years after the enrollment of the last patient to the study. For patients participating in the optional long-term follow-up, visits may initially overlap with the main study.

The assessments to be performed at each annual visit are listed here and outlined in the SOE for the optional long-term follow-up (Appendix A):

- Informed consent/assent.
  - To be obtained no later than at the first optional long-term follow-up annual visit.
- Height, weight, and vital signs.
- Lansky Play-Performance or Karnofsky Performance status, as appropriate for age (see Appendix F and Appendix G).
- Targeted physical examination for medically relevant body systems with focus on:
  - Development assessment (see Appendix I).
  - Cardiac function abnormalities.
  - Development of any secondary malignancy (NOTE: Reoccurrence of HL with the same histology as baseline should not be considered a secondary malignancy.)
  - Ongoing peripheral neuropathy assessment:
    i. Study treatment–related peripheral neuropathy that is ongoing at the time of the first annual visit for the optional long-term follow-up will be assessed for improvement until the sooner of resolution to baseline or completion of the optional long-term follow-up (ie, at least 10 years after the patient's enrollment) and recorded in the eCRF. Any ongoing events which worsen without initiation of subsequent anticancer therapy should also be recorded in the eCRF.
  - Immune function abnormalities:
    i. For patients demonstrating or reporting any signs or symptoms of impaired immune function, appropriate blood tests (such as peripheral lymphocyte differentiation and activation, Ig levels, vaccine and antigen responses) are recommended, and results recorded in the eCRF.
- Blood chemistry for troponin T (refer to Table 9.a).
  - Cardiac investigations, including such procedures as ECG, ECHO or MUGA, are recommended if troponin T levels are abnormal or there are other abnormal cardiac findings.
- Treatment-related SAEs defined as investigator-assessed as related to brentuximab vedotin.
- Pregnancy/partner pregnancy (refer to Section 10.4).

- Recording of any anticancer therapy, including radiotherapy, and response since the last visit.
  - CT, MRI and PET scans are not required as part of the annual visits for the optional long-term follow-up. However, the investigator's assessment of response determined from a scan performed either as SOC prior to initiation of any subsequent anticancer therapies for cHL is to be recorded in the eCRF.
  - Treatment dates and regimens of any other anticancer therapy for the patient's cHL and any investigator-assessed response before initiation of subsequent anticancer therapy for cHL, and investigator-assessed best response to subsequent therapies, will be recorded in the eCRF.
- If a patient refuses to return to the clinic for annual study visits, information can be collected via telephone contact reports at the time of the regularly scheduled study visits; however, this is not preferred. If any concerns relating to study treatment are identified by the investigator during this telephone consultation with the patient, the investigator should request that the patient attend an in-person clinic visit to complete the assessments outlined above and in the SOE (Appendix A) for the optional long-term follow up visits, or alternatively, have the patient visit their personal physician / other consultant for appropriate follow-up. Any results generated outside of the investigative site must be obtained by the investigator and recorded in the eCRF.
- Efforts will be made to avoid any patient being lost to follow-up during the conduct of the study. Before patients are considered lost to follow-up, a minimum of 2 documented telephone contact attempts must be made, and 1 certified letter must be sent within 6 weeks of the most recent planned study visit in an effort to contact patients.
- If a patient has been documented as lost to follow-up or if the site staff becomes aware of a patient's death between planned annual visits, then the following information must also be obtained and recorded in the eCRF:
  - Survival status or date of death.
- Survival information may be collected by methods that include, but are not limited to, telephone, email, mail, or retrieved from online or other databases (eg, social security indexes) as permitted by local regulations.
- A separate End-of-Study eCRF will be completed for all participating patients upon their completion of the optional long-term follow-up period.

9.14 COVID-19 Considerations

At the time of the COVID-19 outbreak, patient EOT visits were in progress. Delays to these visits were permitted as necessary based on site/regional restrictions.

No restrictions are placed on patients receiving the COVID-19 vaccine. As of the time of the COVID-19 vaccine availability, all patients have completed the treatment period of the study and are participating in posttreatment follow-up and/or long-term follow-up. Administration of the

COVID-19 vaccine to patients therefore does not need to be reported on the concomitant medication log.

For patients who are unable to attend a protocol-required study visit either because the site has COVID-19 restrictions at the time of the visit or the patient is unable to attend due to COVID-19, telephone contact may be made to collect any data that are possible outside of the study visit. Thereafter, every effort should be made to have the visit rescheduled as soon as it is safe to have the patient come to the study site to complete the procedures. Procedures may be performed late and recorded as Unscheduled if they do not fall within the visit period. Subsequent protocol-required visits should be scheduled according to the original EOT date and not delayed visit dates. Delayed or missed protocol-required study visits will be documented as protocol deviations but specified as due to COVID-19.

Monitoring of study data may be delayed due to COVID-19 restrictions at a site or, where available, remote source data verification and monitoring may be implemented. However, if a study analysis is pending, every effort should be made by site staff to accommodate the study monitor in verifying data, including by remote means where applicable, or other acceptable methods.

Should a study patient become infected with COVID-19 and have an outcome of death, the death should be reported as survival data.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 PTE Definition

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

10.1.2 AE Definition

AE means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of protocol therapy.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

10.1.3 SAE Definition

SAE means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph in Section 10.2 on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

In this study, intensity for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [23]. Clarification should be made between an SAE and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

10.2 Procedures for Recording and Reporting AEs and SAEs

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate page of the eCRF (see Section 10.3 for the period of observation). Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an

AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event.

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

SAE Reporting Contact Information

CCI [redacted]

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (eg, surgery was performed earlier or later than planned).

For both serious and nonserious AEs, the investigator must determine both the severity (toxicity grade) of the event and the relationship of the event to protocol therapy administration. For serious PTEs, the investigator must determine both the severity (toxicity grade) of the event and the causality of the event in relation to study procedures.

Severity (toxicity grade) for each AE, including any lab abnormality, will be determined using the NCI CTCAE, Version 4.03, effective date 14 June 2010 [23]. The criteria are provided in the Study Manual.

Relationship of the event to protocol therapy administration (ie, its causality) will be determined by the investigator responding yes (related) or no (unrelated) to this question: "Is there a reasonable possibility that the AE is associated with the protocol therapy?"

10.3 Monitoring of AEs and Period of Observation

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

- AEs will be reported from the signing of the informed consent form (ICF)/assent form through 30 days after administration of the last dose of protocol therapy and recorded in the eCRFs. All events relating to peripheral neuropathy, regardless of seriousness, will be followed for all changes in severity until 30 days after the last dose of protocol therapy, and recorded in the

eCRF. Thereafter, all ongoing events will be followed for improvement until the sooner of resolution to baseline or study closure, and recorded in the eCRF. Any ongoing events which worsen without initiation of subsequent anticancer therapy should also be recorded in the eCRF.

- Study treatment–related peripheral neuropathy that is ongoing at the time of the first annual visit for the optional long-term follow-up will be assessed for improvement until the sooner of resolution to baseline or completion of the optional long-term follow-up (ie, at least 10 years after the patient's enrollment) and recorded in the eCRF. Any ongoing events which worsen without initiation of subsequent anticancer therapy should also be recorded in the eCRF.
- SAEs
  - Serious PTEs will be reported to the Takeda Global Pharmacovigilance department or designee from the time of the signing of the ICF up to first dose of protocol therapy, and recorded in the eCRF.
  - Related and unrelated treatment-emergent SAEs will be reported to the Takeda Global Pharmacovigilance department or designee from the first dose of protocol therapy through 30 days after administration of the last dose of protocol therapy and recorded in the eCRF. After this period, including during the optional long-term follow-up, only related SAEs must be reported to the Takeda Global Pharmacovigilance department or designee. SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

AEs or SAEs recorded due to COVID-19 should be prefaced by the term, "COVID-19" or "suspicion of COVID-19" to facilitate coding, as explained in the eCRF guidelines.

10.4 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue protocol therapy. The sponsor must also be contacted immediately by faxing a completed Pregnancy Form to the Takeda Global Pharmacovigilance department or designee (see Section 10.2). The pregnancy must be followed for the final pregnancy outcome.

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

10.5 Procedures for Reporting Product Complaints or Medication Errors (Including Overdose)

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately report this via the phone numbers or email addresses below:

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. Whereas overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error (including overdose) situation should immediately report this via the phone numbers or email addresses provided below.

Call center	Phone number	E-mail	Fax
CCI			

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to CCI (refer to Section 10.2)

10.6 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the EMA, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as an expedited report within 7 calendar days for fatal and life-threatening events and 15 calendar days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal product's administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to his or her IRB or IEC in accordance with national regulations.

11.0 STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, clinical endpoint committee, or adjudication committee will be used in this study.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. If selected for coding, AEs, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each patient who receives protocol therapy.

The sponsor or its designee will supply investigative sites with access to eCRFs and will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit

the information collected in the performance of this study to the sponsor, CRO partners, and regulatory authorities. Investigative sites must complete eCRFs in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Any change of, modification of, or addition to the data on the eCRFs should be made by the investigator or appropriate site personnel. Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change.

The principal investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the principal investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

During the COVID-19 pandemic, remote source data verification or review may be performed if permitted by regional regulations (see Section 9.14).

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long-term legibility. Furthermore, ICH E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the investigator and sponsor.

Refer to the Clinical Study Site Agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized before database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

The populations used for analysis will include the following:

Safety Population

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

PK Population

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

Immune Reconstitution Population

Patients with sufficient dosing and sufficient immune reconstitution blood sampling to allow for immune reconstitution evaluation will be included in the Immune Reconstitution Population.

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.

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

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized, including gender, age, race, weight, height, BSA, disease stage, performance score, and other parameters as appropriate. No inferential statistics will be carried out.

13.1.3 Efficacy Analysis

Analysis of efficacy measures will be descriptive. ORR, CR rate, and PR rate at EOT will be assessed by IRF and by investigators per IWG criteria [1]. The percentage of patients whose disease is PET- after 2 cycles of A+AVD chemotherapy and the percentage of patients whose disease is PET+ after 6 cycles will also be evaluated. Other efficacy endpoints, including PFS, EFS, OS, and DOR, will also be explored. The percentage of patients receiving irradiation for HL following study treatment will be summarized.

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13.1.5 PK Analysis

Descriptive statistics (eg, number of patients, arithmetic mean, geometric mean, standard deviation, median, percentage of coefficient of variation, minimum, and maximum) will be used to summarize brentuximab vedotin and TAb concentrations in serum, and concentrations of MMAE in plasma by dose group. Mean plasma concentration data will be plotted over time by dose group. PK parameters (C_{max}, AUC_{0-15}, T_{max}) will be calculated from individual plasma (MMAE) or serum (brentuximab vedotin, TAb) concentration-time data using noncompartmental methods and summarized descriptively by analyte and dose group.

13.1.6 Immunogenicity Analysis

Immunogenicity parameters (ATA positive, ATA titer and nATA positive in serum) will be analyzed using the Safety Population - immunogenicity evaluable patients and descriptive statistics. The relationship of immunogenicity responses to PK, efficacy, and safety will be explored.

13.1.7 Immune Reconstitution Analysis

Descriptive statistics for the actual values (and/or the changes from baseline) of immune reconstitution (enumeration of the total lymphocyte count and lymphocyte subsets; total Ig and IgG, IgM, and IgA levels; levels of the antibodies to tetanus, HiB, and polio serotypes; and peripheral blood CD34+ cell count) will be presented for all scheduled measurements over time.

13.1.8 PK Modeling

PK modeling using population analysis may be additionally performed to describe pediatric PK and estimate individual PK parameters for brentuximab vedotin and MMAE in this study. This

analysis may additionally use data collected in other clinical studies of brentuximab vedotin. The analysis plan for such modeling and the results of these analyses will be reported separately.

13.1.9 Safety Analysis

Safety will be evaluated by the incidence of AEs, severity and type of AEs, and by changes from baseline in the patient's vital signs, neuropathy assessment, and clinical laboratory results using the Safety Population. 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. TEAEs that occur after administration of the first dose of protocol therapy and through 30 days after the last dose of protocol therapy will be tabulated. AEs will be tabulated according to the MedDRA and will include the following categories:

- TEAEs.
- Drug-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher drug-related TEAEs.
- SAEs.

A listing of TEAEs resulting in protocol therapy discontinuation will be provided. The individual patient's information on the DLTs will also be presented in a listing.

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 also be plotted for key laboratory parameters. Shift tables for laboratory parameters will be generated based on changes in NCI CTCAE grade from baseline to the worst postbaseline value. Graphical displays of key safety parameters, such as scatter plots of baseline versus worst postbaseline values, may be used to understand the brentuximab vedotin safety profile.

Descriptive statistics for the actual values (and/or the changes from baseline) of vital signs, weight, and development assessment results over time will be tabulated by scheduled time point. The results of lymphoma assessment and Lansky/Karnofsky scores over time will also be tabulated.

All concomitant medications collected from Screening through the study period will be classified to generic terms according to the WHO Drug Dictionary.

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

13.2 Interim Analysis and Criteria for Early Termination

An interim futility analysis will be conducted after 25 patients have completed 6 cycles of study therapy and had their EOT response assessment. The study may be terminated early in the case of inferior efficacy.

13.3 Time Points for Additional Analyses

As prespecified in the approved SAP, the primary analyses for reporting the results of the primary endpoints in the CSR were performed after all enrolled patients had the opportunity to be followed for 15 months after enrollment of the last patient in the main study. Efficacy results are presented by study phase, and for all evaluable patients treated at the recommended dose.

Patients will continue to be followed for survival and disease status every 12 weeks (±1 week) for 12 months, and then every 24 weeks (±2 weeks) until death or study closure or for up to 2 years after enrollment of the last patient. An updated analysis of the time-to-event efficacy endpoints and other selected study endpoints will be performed after all enrolled patients have had the opportunity to be followed for up to 2 years after enrollment of the last patient, denoting the end of the main study. This updated analysis may include data from the long-term follow-up period. Results of the updated analysis at the end of the main study will be presented in an addendum to the CSR.

Data from the optional long-term follow-up will be analyzed after all participating patients have had the opportunity to complete 10 years of follow up from their date of enrollment in the main study and those results will be presented in a separate CSR addendum.

13.4 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 that the true ORR for the A+AVD regimen is 90%, with 55 evaluable patients and a 2-sided type I error of α=0.2, the study would have approximately 78% power to state that the ORR is greater than 80%.

Analyses will be primarily descriptive in nature. No formal statistical tests will be performed.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's Binder, study medication, subject medical records, informed consent and assent documentation, documentation of subject authorization to use

personal health information (if separate from the informed consent and assent forms), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

During the COVID-19 pandemic, remote source data verification or review may be performed if permitted by regional regulations (see Section 9.14).

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation).

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the sponsor or designee for any significant deviation from the protocol.

See Section 9.14 for deviations specific to COVID-19 or pandemic restrictions.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments. If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those American sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the informed consent and assent forms, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent and assent must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives notification, no protocol activities, including screening may occur.

Sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent and Assent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent and assent forms, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent and assent forms and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent and assent are given. The informed consent and assent forms will detail the requirements of the participant and the fact that

he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent and assent forms, and if applicable, the subject authorization form. The informed consent and assent forms, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent and assent forms, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject or subject's parent/legal guardian. It is the responsibility of the investigator to explain the detailed elements of the informed consent and assent forms, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject or subject's parent/legal guardian. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent and assent forms and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and assent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent and assent forms and subject authorization (if applicable) at the time of consent and assent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent and assent forms, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent and assent in the subject's medical record. Copies of the signed informed consent and assent forms, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent and assent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent and assent. The date the revised consent and assent were obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent and assent forms.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to

the sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating trial sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to Takeda providing this information to callers must provide Takeda with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study subjects. Refer to the Clinical Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.
4. Ensure that study related procedures, including study specific (non-routine/non-standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
5. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
6. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
7. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
8. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
9. Obtain valid informed consent from each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
10. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

11. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
12. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
13. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, US, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study medication.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix D Deauville Criteria for PET

Score	
1	no uptake
2*	uptake ≤mediastinum
3*	uptake >mediastinum but ≤ liver
4	Uptake moderately increased compared to the liver at any site.
5	Uptake markedly increased compared to the liver at any site or/and new sites of disease.

Source: Meignan et al (2018). [27]

* If mediastinal blood pool activity is equal or greater than liver then the uptake within the lesion should be compared with liver (lesion uptake less than liver=score 2; lesion uptake equal to liver=score 3).

Appendix E Ann Arbor Staging System for Hodgkin Lymphoma

Stage	Definition
I	Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring)
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (the mediastinum is a single site; hilar lymph nodes should be considered "lateralized" and, when involved on both sides, constitute Stage II disease)
III	Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm
III_1	Subdiaphragmatic involvement limited to spleen, splenic hilar nodes, celiac nodes, or portal nodes
III_2	Subdiaphragmatic involvement includes paraaortic, iliac, or mesenteric nodes plus structures in III_1
IV	Involvement of extranodal site(s) beyond that designated as "E" More than 1 extranodal deposit at any location Any involvement of liver or bone marrow
A	No symptoms
B	Unexplained weight loss of >10% of the body weight during the 6 months before staging investigation Unexplained, persistent, or recurrent fever with temperatures >38ºC during the previous month Recurrent drenching night sweats during the previous month
E	Localized, solitary involvement of extralymphatic tissue, excluding liver and bone marrow

Source: Harrison's Manual of Medicine, 17th Edition.

Appendix F Lansky Play-Performance Scale for Children

The Play-Performance Scale for Children is designed to provide a standardized measure of the performance status of the child with cancer. Have the parent select the description that best describes the child's play during the past week, averaging out good days and bad days.

Score	Performance
100	Fully active, normal
90	Minor restrictions in physically strenuous activity.
80	Active, but tires more quickly.
70	Both greater restriction of and less time spent in play activity.
60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Gets dressed but lies around much of the day; no active play; able to participate in all quiet play and activities.
40	Mostly in bed; participates in quiet activities.
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities.
10	No play; does not get out of bed.
0	Unresponsive.

Source: Lansky et al (1987). [28]

Appendix G Karnofsky Performance Status

Percent	Description
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity, minor signs or symptoms of disease.
80	Normal activity with effort, some signs or symptoms of disease.
70	Cares for self. Unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization is indicated although death not imminent.
20	Hospitalization necessary, very sick, active supportive treatment necessary.
10	Moribund, fatal processes progressing rapidly.
0	Dead

Sources: Karnofsky et al (1949); [29] Péus et al (2013). [30]

Appendix H New York Heart Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Ninth Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix I Tanner Scale

Criteria for Distinguishing Tanner Stages 1 to 5 During Female Pubertal Maturation

Stage	Breast	Pubic Hair
1 (prepubertal)	No palpable glandular tissue or pigmentation of areola; elevation of areola only	No pubic hair; short, fine vellus hair only
2	Glandular tissue palpable with elevation of breast and areola together as a small mound; areolar diameter increased	Sparse, long, pigmented terminal hair chiefly along the labia majora
3	Further enlargement without separation of breast and areola; although more darkly pigmented, areola still pale and immature; nipple generally at or above midplane of breast tissue when individual is seated upright	Dark, coarse, curly hair, extending sparsely over mons
4	Secondary mound of areola and papilla above breast	Adult-type hair, abundant but limited to mons and labia
5 (adult)	Recession of areola to contour of breast; development of Montgomery's glands and ducts on areola; further pigmentation of areola; nipple generally below midplane of breast tissue when individual is seated upright; maturation independent of breast size	Adult-type hair in quantity and distribution; spread to inner aspects of the thighs in most racial groups

Data from Ross GT: Disorders of the ovary and female reproductive tract. In Wilson JD, Foster DW (eds): Textbook of Endocrinology, 7th ed. Philadelphia, WB Saunders, 1985, p 206.

Pubertal Stages in Boys

Stage	Pubic Hair	Genital
1	Absence of pubic hair	Childlike penis, testes, and scrotum (testes 2 mL)
2	Sparse, lightly pigmented hair mainly at the base of the penis	Scrotum enlarged with early rugation and pigmentation; testes begin to enlarge (3–5 mL)
3	Hair becomes coarse, darker, and more curled and more extensive	Penis has grown in length and diameter; testes now 8–10 mL; scrotum more rugated
4	Hair adult in quality, but distribution does not include medial aspect of thighs	Penis further enlarged with development of the glans; scrotum and testes (10–13 mL) further enlarged
5	Hair is adult and extends to thighs	Penis and scrotum fully adult; testes 15 mL and greater

Modified from Marshall WA, Tanner JM: Variation in pattern of pubertal changes in boys. Arch Dis Child 1970;45:13–23.

Appendix J Detailed Description of Amendments to Text Changes

- Detailed Description of Amendments to Text.
- Strikethrough font indicates text that has been deleted from Protocol Amendment 3. Red, bold font denotes text that has been added. Typographical, punctuation, grammar, and formatting errors may also have been corrected but these are not listed individually.

The primary section(s) of the protocol affected by the changes in Amendment 04 are indicated. The corresponding text has been revised throughout the protocol.

Change 1.: Update the sponsor's name to Takeda Development Center (TDC) Americas, Inc.

The primary change occurs on the Title Page.

Revised Text: **Takeda Development Center (TDC) Americas, Inc.**
95 Hayden Avenue, Lexington, Massachusetts 02421 USA
Please note: TDC Americas, Inc. may be referred to in this protocol as "sponsor" or "Takeda".
~~Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited~~
~~Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium", "Sponsor", or "Takeda".~~

Rationale for Change: Update the name of the legal entity responsible for the study.

The following sections also contain this change:

Section 2.0 STUDY SUMMARY; Name of Sponsor(s):
Revised text: **Takeda Development Center (TDC) Americas, Inc.** ~~Millennium Pharmaceuticals, Inc~~.

Section 3.4 Corporate Identification
Revised text:
TDC Americas **Takeda Development Center Americas, Inc.**
TDC Asia **Takeda Development Center Asia, Pte Ltd**
TDC Europe **Takeda Development Centre Europe Ltd**
TDC Japan **Takeda Development Center Japan**
Takeda **Millennium Pharmaceuticals, Inc, TDC Americas, TDC Asia, TDC Europe, TDC Japan**
~~Millennium~~ ~~Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited~~.

Change 2.: Clarify definitions of the end of the main study and optional long-term follow-up.

The primary change occurs in Section 2.0 STUDY SUMMARY.

Study Design:
Revised text: Survival will be assessed until the sooner of death, study closure, or up to 2 years after enrollment of the last patient. **The main study will be considered to be complete when all patients have had the opportunity to be followed for up to 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~~ **their date of** enrollment **in the main study**.

Rationale for Change: With the addition of an optional long-term follow-up period (Protocol Amendment 3), the revised text delineates the end of the main study from the end of long-term follow-up.

The following sections also contain this change:
Period of Evaluation:
All patients will be offered the opportunity to participate in an optional long-term follow-up, for at least 10 years from ~~patient~~ **their date of** enrollment **in the main study**.

Section 9.7 Completion of Optional Long-term Follow-up
Revised text: Patients will be considered to have completed the optional long-term follow-up if they have been followed for at least 10 years ~~after~~ **from their** enrollment **date in the main study** or have died.

Change 3.: Clarify the time points for analysis and reporting of the study results.

The primary change occurs in Section 2.0 STUDY SUMMARY.

Added text:
Planned Reporting: As prespecified in the approved SAP, the analyses for reporting the results of the study's primary endpoints in the clinical study report (CSR) were performed after all enrolled patients had the opportunity to be followed for 15 months after enrollment of the last patient in the main study. Efficacy results are presented by study phase, and for all evaluable patients treated at the recommended dose.

Patients will continue to be followed for survival and disease status every 12 weeks (±1 week) for 12 months, and then every 24 weeks (±2 weeks) until death or study closure or for up to 2 years from the date of the last patient enrolled. An updated analysis of the time-to-event efficacy endpoints and other selected study endpoints will be performed after all enrolled patients have had the opportunity to be followed for up to 2 years after enrollment of the last patient, denoting the end of the main study. Results of the updated analysis will be presented in an addendum to the CSR.

Data from the optional long-term follow-up will be analyzed after all participating patients have had the opportunity to complete 10 years of follow up from their date of enrollment in the main study and those results will be presented in a separate CSR addendum.

Rationale for Change: The decision to analyze the study data and report the results in the CSR at the time point of 15 months after enrollment of the last patient was made in consultation with and by agreement of the EMA PDCO. Based on the results from a similar study conducted in an adult patient population with advanced-stage cHL (ECHELON-1; NCT01712490), the sponsor concluded that the event kinetics observed between 15 months and 24 months in ECHELON-1 are likely to be mirrored in this study (C25004), and that very few additional events would occur between 15 months and 2 years to make a clinically meaningful difference in the results of the time-to-event efficacy endpoints. Results of an updated analysis of time-to-event efficacy endpoints that is planned after all patients have had the opportunity to be followed for at least 2 years after last patient enrollment will be presented in an addendum to the CSR. A separate CSR addendum is planned to report the results from the optional long-term follow-up.

The following sections also contain this change:
Section 6.3.2 End of Study/Study Completion Definition and Planned Reporting

Revised text: Primary Completion/Study Completion
As prespecified in the approved SAP, the analyses for **reporting the results of the study's primary endpoints in the CSR** ~~will be conducted a minimum of 8 weeks~~ **were performed after patients had the opportunity to be followed for 15 months after enrollment of the last patient** ~~receives the last dose of protocol therapy.~~**in the main study.**

Patients will continue to be followed for survival and disease status every 12 weeks ~~after the last patient receives the last dose of protocol therapy.~~**(±1 week) for 12 months, and then every 24 weeks (±2 weeks) until death or study closure or for up to 2 years from the date of the last patient enrolled.** An updated analysis ~~on~~ **of** the **time-to-event** efficacy endpoints **and other selected study endpoints** will be ~~conducted~~ **performed** after all **enrolled** patients ~~enrolled in the study~~ have had the opportunity to be followed for up to 2 years after enrollment of the last patient, ~~and will be included~~ **denoting the end of the main study. This updated analysis may include data from the long-term follow-up period. Results of this updated analysis will be presented** in an addendum to the ~~clinical study report~~. **CSR**.

Data from the optional long-term follow-up will be ~~considered complete when~~ **analyzed after all participating patients** ~~enrolled in the study~~ **have had the opportunity to** ~~be followed for up to 2~~ **complete 10 years** ~~after~~ **of follow-up from their date of enrollment** ~~of~~ **in the** ~~last patient. Data from the optional long-term follow-up~~ **main study and those results will be** ~~analyzed separately~~ **presented in a separate CSR addendum**.

Section 13.3 Time Points for Additional Analyses
Added text: 13.3 Time Points for Additional Analyses
As prespecified in the approved SAP, the primary analyses for reporting the results of the primary endpoints in the CSR were performed after all enrolled patients had the opportunity to be followed for 15 months after enrollment of the last patient in the main study. Efficacy results are presented by study phase, and for all evaluable patients treated at the recommended dose.

Patients will continue to be followed for survival and disease status every 12 weeks (±1 week)

for 12 months, and then every 24 weeks (±2 weeks) until death or study closure or for up to 2 years after enrollment of the last patient. An updated analysis of the time-to-event efficacy endpoints and other selected study endpoints will be performed after all enrolled patients have had the opportunity to be followed for up to 2 years after enrollment of the last patient, denoting the end of the main study. This updated analysis may include data from the long-term follow-up period. Results of the updated analysis at the end of the main study will be presented in an addendum to the CSR.

Data from the optional long-term follow-up will be analyzed after all participating patients have had the opportunity to complete 10 years of follow-up from their date of enrollment in the main study and those results will be presented in a separate CSR addendum.

Change 4.: Provide additional drug accountability instructions.

The primary change occurs in Section 9.11 Study Compliance.

Revised text: The appropriate study personnel will maintain records of study drug receipt, ~~and~~ dispensing, **and destruction/returns.**

Rationale for Change: Include study drug destruction and return as an important component of the study drug accountability process.

Change 5.: Clarify instructions for completion of the End-of-Study eCRFs for the main study and the optional long-term follow-up.

The primary change occurs in Section 9.12, Posttreatment Follow-up Assessments (PFS and OS).

Revised text: ~~The~~ **An** End-of-Study eCRF is to be completed at the time the patient discontinues from the follow-up period **of the main study**. **A separate End-of-Study eCRF will be completed for all participating patients upon completion of the optional long-term follow-up period (see Section 9.13).**

Rationale for Change: Clarify the requirement for completion of an End-of-Study eCRF for patients at the end of their participation in the main study and the optional long-term follow-up, if applicable.

Change 6.: Provide additional guidance for study conduct during the optional long-term follow-up.

The primary change occurs in Section 9.13 Optional Long-term Follow-up.

Added text:

- **If a patient refuses to return to the clinic for annual study visits, information can be collected via telephone contact reports at the time of the regularly scheduled study visits; however, this is not preferred. If any concerns relating to study treatment are identified by the investigator during this telephone consultation with the patient, the investigator should request that the patient attend an in-person clinic visit to complete the assessments outlined above and in the SOE for the optional long-term follow-up visits, or alternatively, have the patient visit their personal physician / other consultant for appropriate follow-up. Any results generated outside of the investigative site must be obtained by the investigator and recorded in the eCRF.**
- **Efforts will be made to avoid any patient being lost to follow-up during the conduct of the study. Before patients are considered lost to follow-up, a minimum of 2 documented telephone contact attempts must be made, and 1 certified letter must be sent within 6 weeks of the most recent planned study visit in an effort to contact patients.**
- **If a patient has been documented as lost to follow-up or if the site staff becomes aware of a patient's death between planned annual visits, then the following information must also be obtained and recorded in the eCRF:**
- **A separate End-of-Study eCRF will be completed for all participating patients upon completion of their optional long-term follow-up period.**

Rationale for Change: Provide more specific instructions for study conduct during optional long-term follow-up.

Change 7.: Describe modifications in study conduct instituted because of the COVID-19 pandemic.

The primary change occurs in Section 9.14 COVID-19 Considerations.

Added Text: **Section 9.14 COVID-19 Considerations**
At the time of the COVID-19 outbreak, patient EOT visits were in progress. Delays to these visits were permitted as necessary based on site/regional restrictions.

No restrictions are placed on patients receiving the COVID-19 vaccine. As of the time of the COVID-19 vaccine availability, all study patients have completed the treatment period of the study and patients are participating in posttreatment follow-up and/or long-term follow-up. Administration of the COVID-19 vaccine to study patients therefore does not need to be reported on the concomitant medication log.

For patients who are unable to attend a protocol-required study visit either because the site has COVID-19 restrictions at the time of the visit or the patient is unable to attend due to COVID-19, telephone contact may be made to collect any data that are possible outside of the study visit. Thereafter, every effort should be made to have the visit rescheduled as soon as it is safe to have the patient come to the study site to complete the procedures. Procedures may be performed late and recorded as Unscheduled if they do not fall within the visit period.

Subsequent protocol-required visits should be scheduled according to the original EOT date and not delayed visit dates. Delayed or missed protocol-required study visits will be documented as protocol deviations but specified as due to COVID-19.

Monitoring of study data may be delayed due to COVID-19 restrictions at a site or, where available, remote monitoring may be implemented. However, if a study analysis is pending, all effort should be made by site staff to accommodate the study monitor in verifying data, including by remote means where applicable, or other acceptable methods.

Should a study patient become infected with COVID-19 and have an outcome of death, this event would be reported for survival data.

Rationale for Change: Describe the required modifications in study conduct because of the COVID-19 pandemic.

The following sections also contain this change:

Section 10.3 Monitoring of AEs and Period of Observation
Added text: AEs or SAEs recorded due to COVID-19 should be prefaced by the term, "COVID-19" or "suspicion of COVID-19" to facilitate coding, as explained in the eCRF guidelines.
Section 12.1 eCRFs
Added text: During the COVID-19 pandemic, remote source data verification or review may be performed if permitted by regional regulations (see Section 9.14).
Section 14.1 Study-Site Monitoring Visits
Added text: During the COVID-19 pandemic, remote source data verification or review may be performed if permitted by regional regulations (see Section 9.14).
Section 14.2 Protocol Deviations
Added text: See also Section 9.14 for deviations specific to COVID-19 restrictions.

Change 8.: Clarify the circumstances for collection of survival data.

The primary change occurs in the Schedule of Events for Optional Long-term Follow-up.

Added text: Survival status or date of death: X (**only for patients who are lost to follow-up or die between planned annual visits**).

Rationale for Change: Provide more specific instructions pertaining to circumstances for collection of survival data during long-term follow-up.

Change 9.: Update the names and titles of the protocol signatories.

The primary change occurs in Section 1.2 Approval.

Revised text: PPD

Rationale for Change: Provide the name and title of the current responsible Takeda medical officer and other protocol signatories.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Clinical Pharmacology Approval	14-Jun-2021 14:53 UTC
	Clinical Approval	14-Jun-2021 14:54 UTC
	Biostatistics Approval	14-Jun-2021 14:55 UTC
	Clinical Science Approval	14-Jun-2021 15:10 UTC