



Protocol Number: C5691003/SGN35-031

Version: Amendment 7; 27-Aug-2025

Protocol Title: A Randomized, Double-blind, Placebo-Controlled, Active Comparator, Multicenter, Phase 3 Study of Brentuximab Vedotin or Placebo in Combination with Lenalidomide and Rituximab in subjects with Relapsed or Refractory Diffuse Large B-cell Lymphoma (DLBCL)

Study Name: ECHELON-3

Investigational Product: Brentuximab vedotin

Brief Title: Brentuximab Vedotin plus Lenalidomide and Rituximab for the Treatment of Relapsed/Refractory DLBCL

Phase: 3

US IND Number: 071634

EU Clinical Trial Number 2023-503384-41-00

ClinicalTrials.gov ID: NCT04404283

Sponsor: Seagen Inc. a wholly owned subsidiary of Pfizer
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Good Clinical Practice: The study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, EU-CTR guidance, and all applicable regulatory requirements.

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Document history

Version	Date
Original	29-Jan-2020
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Amendment 2	11-Sep-2020
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Amendment 4 CAN-1	24-Jan-2022
Amendment 4 GRB-1	19-May-2022
Amendment 5	04-Aug-2023
Amendment 6	23-Aug-2023
Amendment 6 KOR-01	13-Dec-2023
Amendment 7	27-Aug-2025

PROTOCOL AMENDMENT SUMMARY OF CHANGES (SOC) TABLE

Amendment 07 (27-Aug-2025) Overall Rationale for the Amendment: The primary purpose of this amendment is to align with Pfizer required safety reporting requirements, and to incorporate other Pfizer specific text, requirements, and formatting across the document. The amendment also defines the addition of a long-term extension phase (LTEP) to allow continued access to study treatment for any participant who is still on treatment and receiving clinical benefit after the final OS analysis based on the investigator's assessment through December 2026.

Note: the changes below are not due to any safety concerns.

Description of Change	Brief Rationale	Section # and Name
Substantial Modifications		
Added an LTEP for subjects who are still receiving treatment.	All study objectives have been met. LTEP being added to allow subjects still receiving clinical benefit to remain on study treatment after the final analysis.	Throughout
Added that subjects still receiving clinical benefit and remaining on study treatment after the final analysis may continue to receive study drug during LTEP through December 2026.	To allow subjects who are still receiving clinical benefit to remain on treatment.	Synopsis, Study Design, Duration of Treatment, Section 3.1 Summary of Study Design, Section 6.1, Schedule of Events, Section 6.8, Long-Term Extension Phase (LTEP), Appendix A: Schedule of Events

Description of Change	Brief Rationale	Section # and Name
Definition of women of childbearing potential and non-childbearing potential was updated to align with Pfizer preferred language	To align with Pfizer's protocol template	Section 4.4 Childbearing Potential
Added sections clarifying the preparation and dispensation for Lenalidomide and Rituximab	To align with Pfizer's protocol template	Section 5.5.5 Preparation and Dispensing (Lenalidomide) Section 5.6.5 Preparation and Dispensing (Rituximab)
Added section clarifying more specific instructions for management of allergic/hypersensitivity reactions	To align with Pfizer's protocol template	Section 5.9.2 Management of Allergic/Hypersensitivity Reactions
Language revised to have overdose reported to Safety only when associated with an SAE	To align with Pfizer's safety reporting process	Section 5.9.4 Management of Overdose
Added: "During the LTEP, efficacy assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care and recorded in the participant's medical record."	To clarify collection of efficacy assessments during the LTEP.	Synopsis, Efficacy Assessments and Section 7.2 Response/Efficacy Assessments, Appendix A: Schedule of Events
Clarified that only pregnancies and SAEs will be collected by the Sponsor during the LTEP using PSSA. All other assessments, including additional safety assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue as outlined in the schedule of events for subjects of child-bearing potential.	Clarification of safety data collection and reporting requirements during LTEP.	Synopsis, Safety Assessments, Section 6.4.1 Cycle 1 Day 1, Section 7.8 Safety Assessments, Section 7.8.1.2 Procedures for Eliciting and Recording Adverse Events, Appendix A: Schedule of Events
Added: "The study will end when the last LTEP subject has had their last visit/contact."	Defined end of study for subjects entering LTEP	Section 6.9 End of Study/End of Follow-Up
Added section indicating lack of efficacy as reportable event to Pfizer Safety only if associated with an SAE	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 7.8.1.2 Procedures for Eliciting and Recording Adverse Events
Added section including definition and reporting of medication errors	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 7.8.1. Adverse Events, Medication Errors
Confirmed DILI meeting Hy's law criteria updated to Pfizer criteria Addition of DILI criteria for patients with abnormal baseline laboratory values Added language for reporting potential DILI (Hy's law) cases which are to be reported as SAEs Added language that all participants presenting with moderate or severe abnormal laboratory tests and/or suspicions of DILI must be discussed with the medical monitor.	To support study transition to Pfizer Pharmacovigilance processes and systems	Section 7.8.1.2 Procedures for Eliciting and Recording Adverse Events
Non-Substantial Modification(s)		
Removal of all personal identifiable information from the protocol	The investigator's agreement and signature and study director/medical monitor's contact information are personal identifiable information	Title Page, Appendix E

Description of Change	Brief Rationale	Section # and Name
Removed EudraCT number, replaced with EU Clinical Trial number	Study has transitioned to CTIS	Title Page
Added GCP statement to title page	A single global version of the protocol is required per Pfizer SOPs. Statement is required in EU.	Title Page
Pfizer protocol and product number added to the Seagen number. Throughout the rest of the protocol, Seagen protocol and product number replaced by Pfizer protocol number	Alignment with Pfizer document format and requirements	Title Page Synopsis Footer
ClinicalTrials.gov indicated as per Pfizer requirement	Alignment with Pfizer document format and requirements	Title Page
Study Rationale, Ethical Considerations added to synopsis to align with Pfizer template	Alignment with Pfizer document format and requirements.	Synopsis
Clarified that breaking the blind may not occur prior to "final OS analysis" instead of "study closure".	To allow for unblinding of subject treatment assignment after the final analysis.	Section 3.2.3.4 Breaking the Blind
Added that for subjects continuing to LTEP, data will only be documented in the subject's medical record.	Clarification of data collection during LTEP.	Section 4.5 Removal of Subjects From Therapy or Assessment, Section 5.10 Treatment Compliance, Section 5.9.4 Management of Overdose
Clarified that dose modifications per protocol should be followed during LTEP.	To clarify guidance for dose modifications of brentuximab vedotin, lenalidomide, and rituximab during LTEP.	Section 5.4.3, 5.5.4, and 5.6.4 Dose Modifications
Clarified that administration of aspirin or other anticoagulation therapy is recommended per institutional guidelines for subjects receiving lenalidomide during LTEP and prophylactic G-CSF is recommended per institutional guidelines for subjects receiving brentuximab vedotin during LTEP.	To reduce concomitant medications required during LTEP for subjects not receiving lenalidomide or brentuximab vedotin, and to allow administration per institutional guidelines and investigator-assessment.	Section 5.8.1 Required Concomitant Therapy, Section 5.8.1.1 Granulocyte-colony Stimulating Factors
Added that no intervention will be provided per protocol to study participants beyond the end of the study (end of LTEP).	Clarified the access to study intervention after the end of the study (end of LTEP).	Section 5.11 Continued Access to Study Intervention After the End of the Study
Details on blinding and unblinding of subjects, investigators, and sponsor staff added	To align with Pfizer's Protocol Template	Section 3.2.3 Blinding and Unblinding
Contraception counseling added to align with Pfizer requirements	To align with Pfizer's Protocol Template.	Section 4.3 Contraception
Added clarification that testing of tumor tissue for CCI was done locally for enrollment	To clarify which tissue sample tests were performed locally for enrollment.	Section 3.1 Summary of Study Design
An SRSD was added for each IMP and NIMP/AxMP	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 5.2 Single Reference Safety Documents for Study Interventions
Details on storage temperature recording, temperature excursion management, product complaint reporting, IMP preparation and destruction added.	To align with Pfizer's Protocol Template.	Section 5.3 Preparation, Handling, Storage and Accountability
Language about remaining samples destruction added.	To align with Pfizer's Protocol Template	Section 4.5 Removal of Participants from Therapy or Assessment Section 4.5.2 Subject Withdrawal from Study

Description of Change	Brief Rationale	Section # and Name
Pfizer Safety added as new destination of safety reporting. PSSA added as electronic tool for reporting.	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Throughout protocol
Clarified that EOT samples are not required to be collected for subjects entering LTEP.	Clarification of sampling timepoints for subjects entering LTEP.	Section 7.4, Table 6
AE definition, AE/SAE recording/reporting requirements and procedures clarified	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 7.8.1 Adverse Events
Safety reporting period clarified in case a participant begins a new anticancer therapy.	To support Study transition to Pfizer Pharmacovigilance processes and systems	Section 7.8.1.3 Reporting Periods for Adverse Events and Serious Adverse Events
Revised language regarding exposure during pregnancy and added information on environmental and occupational exposure as well as exposure during breastfeeding	To support Study transition to Pfizer Pharmacovigilance processes and systems.	Section 7.8.1.2 Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure
Clarified that during LTEP, pregnancy testing will continue for subjects of child-bearing potential receiving lenalidomide according to Section 6.4.1, and that pregnancies should continue to be reported to the Sponsor using the PSSA.	Clarified pregnancy testing requirements for subjects receiving lenalidomide during the LTEP.	Section 7.8.2 Clinical Laboratory Tests
Clarified that local laboratory testing will be performed per institutional guidelines and investigator-determined usual and customary care during the LTEP.	Consistency with updates made in the document.	Section 7.8.2 Clinical Laboratory Tests
Subsections regarding data management procedures, investigator record retention, and data handling deleted as content was moved under Section 10 (Regulatory, ethical, and study oversight considerations)	To align with Pfizer's Protocol Template	Section 8 Data Quality Control and Quality Assurance
Added text to indicate data collection in CRF not needed during LTEP.	Guidance for data collection during the LTEP. Clarified that eCRFs will not be collected during the LTEP.	Section 8.1 Site Training and Monitoring Procedures, Section 8.2 Accuracy and Reliability of Data
Clarification added that Physical Examination is to be completed on day 1 of each cycle	To align with South Korean-specific protocol.	Section 6.4.2, Day 1 of Each Cycle
Added language requiring a protocol amendment incorporating any major modifications of the primary endpoint definitions or their analyses in the SAP.	To align with Pfizer's Protocol Template	Section 9.3 Statistical and Analytical Plans
Investigator's responsibility regarding IRB/IEC reporting requirements and study oversight according to ICH GCP added	To align with Pfizer's Protocol Template.	Section 10.1 Regulatory and Ethical Considerations
Sections added regarding data protection, public disclosure of study results, publication policy, use of medical records, and the sponsor's medically qualified individual.	To align with Pfizer's Protocol Template.	Section 10 Regulatory, ethical, and study oversight considerations
Added that the investigator may not delegate obtaining consent to local healthcare professional.	To align with Pfizer's Protocol Template.	Section 10.3 Informed Consent Process

Description of Change	Brief Rationale	Section # and Name
Corrections made to Schedule of Assessments per South Korean and EU-specific protocol added. Physical examination required on day 1 of each cycle as described in Section 8.4.2 Footnote (n) added to clarify that ECG may be collected throughout the study, as clinically indicated	To align with South Korean- and EU-specific protocol.	Section 6.1 Schedule of Events Section 6.4.2 Day 1 of Each Cycle Appendix A: Schedule of Events
Appendix E added for Country Specific Requirements	A single global version of the protocol is required per Pfizer SOPs. Differences across countries or regions are specified by country or region in Appendix E	Appendix E: Country-Specific Requirements
Added language regarding safety reporting of deaths to Swissmedic for participants in Switzerland	To conform with Swissmedic safety reporting requirements	Appendix E: Contry-Specific Requirements
Seagen updated to Seagen, Inc. a wholly owned subsidiary of Pfizer	Alignment with Pfizer document format and requirements.	Throughout protocol
Minor editorial modifications in the text, which are not provided in this summary of changes, were made for additional clarity	Minor updates and clarifications.	Throughout protocol

PROTOCOL SUMMARY

Synopsis

Protocol Number C5691003/SGN35-031	Product Name Brentuximab vedotin
Version Amendment 7	Sponsor Seagen Inc., a wholly owned subsidiary of Pfizer
Phase 3	21823 30th Drive SE Bothell, WA 98021, USA

Protocol Title

A randomized, double-blind, placebo-controlled, active-comparator, multicenter, phase 3 study of brentuximab vedotin or placebo in combination with lenalidomide and rituximab in subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) (ECHELON-3)

Regulatory Agency Identification Number(s):

US IND Number:	071634
EU Clinical Trial (CT) Number:	2023-503384-41-00
ClinicalTrials.gov ID:	NCT04404283
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C5691003/SGN35-031
Phase:	3

Study Rationale:

There is an unmet need for effective and well tolerated treatment options for patients with relapsed/refractory (R/R) DLBCL after 2 or more prior lines of systemic therapy. Earlier studies in patients with R/R DLBCL have shown promising activity with brentuximab vedotin monotherapy, brentuximab vedotin in combination with lenalidomide, and brentuximab vedotin in combination with rituximab. These data suggest that the combination of brentuximab vedotin, lenalidomide, and rituximab (BV+Len+R) may improve upon the modest activity of the combination of lenalidomide and rituximab in R/R DLBCL and support the further exploration in the Phase 3 ECHELON-3 study.

Study Objectives and Endpoints

Primary Objective	Corresponding Primary Endpoint
• Evaluate and compare overall survival (OS) between the 2 treatment arms in the intent-to-treat (ITT) population	• OS

Key Secondary Objectives	Corresponding Key Secondary Endpoints
Evaluate and compare progression-free survival (PFS) per Lugano 2014 by investigator between the 2 treatment arms in the ITT population	PFS per Lugano 2014 by investigator
Evaluate and compare the objective response rate (ORR) per Lugano 2014 by investigator between the 2 treatment arms in the ITT population	ORR per Lugano 2014 by investigator
Other Secondary Objectives	Corresponding Other Secondary Endpoints
Evaluate and compare the complete response (CR) rate per Lugano 2014 by investigator between the 2 treatment arms	CR rate per Lugano 2014 by investigator
Evaluate and compare duration of response (DOR) per Lugano 2014 by investigator between the 2 treatment arms	DOR per Lugano 2014 by investigator
Evaluate the safety and tolerability of the 2 treatment arms	Incidence, severity, and seriousness of adverse events (AEs) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0
Evaluate and compare OS between the 2 treatment arms in the CD30-positive population	OS in CD30-positive participants
Exploratory Objectives	Corresponding Exploratory Endpoints

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Study Population

Key eligibility criteria include participants aged 18 and older with relapsed/refractory (R/R) DLBCL with an eligible subtype; participants must have ≥ 2 prior lines of therapy and must be ineligible for stem cell transplant (SCT) or chimeric antigen receptor T-cell (CAR-T) therapy; participants must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2; participants must have a fluorodeoxyglucose (FDG)-avid disease by positron emission tomography (PET) and bidimensional measurable disease of at least 1.5 cm by computed tomography (CT), as assessed by the site radiologist.

Number of Planned Participants

Approximately 225 participants (approximately 113 participants per arm) will be randomized in this study.

Study Design

This is a randomized, double-blind, placebo-controlled, active-comparator, multicenter phase 3 study designed to evaluate the efficacy of brentuximab vedotin in combination with lenalidomide and rituximab versus placebo in combination with lenalidomide and rituximab for the treatment of participants with R/R DLBCL. All participants will receive primary granulocyte-colony stimulating factor (G-CSF) prophylaxis.

There was a safety run-in period prior to the randomized portion of the study. A safety monitoring committee (SMC) including 3 external members reviewed data from the first 6 participants who received open label brentuximab vedotin, lenalidomide, and rituximab. The safety data for the participants from this run-in period were evaluated after these participants completed the first cycle of treatment. The SMC did not identify any new safety signals or concerns, and the SMC approved proceeding with the randomized portion of the study.

After completion of the safety run-in period, subsequent participants will be randomized in a 1:1 manner to receive either brentuximab vedotin or placebo in combination with lenalidomide and rituximab CCI

The most recent tumor biopsy tissue will be submitted to a central pathology lab for determination of CD30 expression. All participants will be eligible for enrollment regardless of CD30 expression level. CD30 expression will be centrally determined by visual assessment of CD30 on tumor cells by immunohistochemistry (IHC), and CCI

After the final OS analysis, the study will transition to a long-term extension phase (LTEP). For participants in long-term follow-up, a last visit or contact will occur prior to the participant's discontinuation from participation in the study. Any participant on study treatment may transition to the long-term extension phase (LTEP) of the study. The Sponsor will provide continued access to study treatment for any participant who is still on treatment and receiving clinical benefit based on the investigator's assessment through December 2026.

Study Treatments, Dose, and Mode of Administration

Brentuximab vedotin, 1.2 mg/kg via intravenous (IV) infusion every 3 weeks

Placebo replacement for brentuximab vedotin will be administered via IV infusion every 3 weeks in the same manner as brentuximab vedotin

Lenalidomide, 20 mg orally daily

Rituximab, 375 mg/m², via IV infusion on Cycle 1 Day 1 and then every 3 weeks

Rituximab, 1400 mg, via subcutaneous injection (SQ) permitted every 3 weeks from Cycle 2 Day 1 through end of treatment (EOT). Either IV or SQ route of administration is permitted starting from Cycle 2 Day 1.

Duration of Treatment

Treatment may continue as long as there is clinical benefit (stable disease [SD] or better) without progression or unacceptable toxicity.

Participants still receiving clinical benefit and remaining on study treatment after the final OS analysis may continue receiving study intervention during the LTEP through December 2026.

Efficacy Assessments

Participants will be assigned a response status based on imaging and lymphoma assessments. Disease response will be assessed by the investigator according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas ([Cheson et al, 2014](#)). Radiographic disease evaluations, including CT scans of neck, chest, abdomen, and pelvis, will be assessed at baseline, then every 6 weeks from randomization until Week 48 (±7 days), then every 12 weeks (±7 days) thereafter. A PET scan is required at baseline and every 6 weeks from randomization until Week 48 (±7 days), then every 12 weeks (±7 days) thereafter. Once the PET is negative per the investigator, no further PET scans are required. Scans should be continued until radiographic documentation of disease progression, including for participants who have discontinued study treatment or initiated subsequent anticancer therapy and are in follow-up.

During the LTEP, efficacy assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care and recorded in the participant's medical record.

Pharmacokinetic and Immunogenicity Assessments

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Biomarker Assessments

CCI

Safety Assessments

Safety assessments will include the surveillance and recording of adverse events (AEs), physical examination findings, and laboratory tests.

Only pregnancies and SAEs will be collected by the Sponsor during the LTEP. All other assessments, including additional safety assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue as outlined in the schedule of events for participants of child-bearing potential.

Other Assessments

CCI

Statistical Methods

Stratification:

CCI

Sample Size Considerations:

Approximately 225 participants will be randomized in order to provide an adequate sample size to evaluate the primary endpoint of OS in the ITT population.

The null hypothesis of no difference in OS between the experimental and control arms will be tested in the ITT population at a 2-sided alpha of 0.05. The final analysis of OS will be performed after approximately 170 OS events have occurred. An interim analysis of OS for both efficacy and futility will be performed when approximately 75% of the events have occurred. The non-binding interim futility criteria is based on a hazard ratio (HR) boundary of >1.1 (experimental vs control arm). Efficacy criteria at the interim and final analysis for OS will be determined using an O'Brien-Fleming type boundary with an alpha spending approach and a 2-sided alpha of 0.05. Assuming an HR of 0.62, 170 OS events provides approximately 87% power in the ITT population. The median OS in the control arm is assumed to be 9 months based on Czuczman et al and Wang et al (Wang et al, 2013; Czuczman et al, 2017).

The key secondary endpoints of PFS and ORR per Lugano 2014 by investigator will be tested sequentially in the ITT population when the primary endpoint is positive.

Analysis Methods:

For the primary efficacy analysis of OS in the ITT population the stratified log-rank test will be used to compare OS between the 2 treatment arms. The HR will be estimated using a stratified Cox regression model. OS will also be summarized using the Kaplan-Meier method. Similar methods will be used for the key secondary efficacy endpoint of PFS and other time-to-event efficacy endpoints. ORR will be summarized by treatment arm and overall, and the difference in ORR will be presented; p-values will be calculated based on the

Cochran-Mantel-Haenszel test. Similar summaries will be presented for other binary endpoints.

Strata levels may be combined for stratified analyses if too few participants are included in certain strata levels; details for combining strata will be provided in the SAP.

Analysis Timing:

The estimated duration of the study is approximately 4 years from the randomization of the first subject (including approximately 2.5 years of enrollment and an approximate additional 18 months of follow-up to reach the final analysis of OS). An interim analysis of OS is also planned approximately 3 months after randomization of the last subject.

Ethical Considerations:

Despite the advances that have been made, there remains no single treatment regimen considered the global standard of care for R/R DLBCL after 2 or more prior lines of systemic therapy. The results of previous studies of brentuximab vedotin, lenalidomide, and rituximab, both alone and in various combinations, support the investigation of brentuximab vedotin, lenalidomide, and rituximab, in combination for R/R DLBCL, and there is favorable benefit-risk profile to support the rationale for this study. All patients enrolled in this study will receive either brentuximab vedotin or placebo in combination with lenalidomide and rituximab, a recommended regimen for treatment of patients with R/R DLBCL. Taking into account the measures to minimize risk to participants, the potential risks associated with brentuximab vedotin, lenalidomide, and rituximab in combination are justified by the anticipated benefits that may be afforded to participants with R/R DLBCL after at least 2 prior lines of systemic therapy.

- Participants may experience improvements during the study and may benefit from more intense monitoring and more frequent assessments compared to usual standard of care. Participants who continue to experience clinical benefit may be eligible to continue receiving study treatments after the trial is over. Participants may benefit from contributing to the understanding of R/R DLBCL.
- There may be side effects that come from the combination of brentuximab vedotin, lenalidomide, and rituximab that aren't found in people who only take 1 or 2 of these drugs. Since this is the first clinical study to study the combination of brentuximab vedotin, lenalidomide, and rituximab, the risk of side effects from combining these study drugs is not known yet.
- Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. In addition, participants of childbearing potential must agree to use appropriate contraception methods.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	antidrug antibody
ADC	antibody-drug conjugate
ADCP	antibody-dependent cellular phagocytosis
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATMP	advanced therapy medicinal product
β -HCG	beta human chorionic gonadotropin
BICR	blinded independent central review
BV	brentuximab vedotin
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor T-cell
CI	confidence intervals
C _{max}	maximum plasma concentration
C _{trough}	trough concentration
CBC	complete blood count
C _{eo}	end of infusion
C-G	Cockcroft-Gault
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CR	complete response
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DILI	drug-induced liver injury
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
eGFR	estimated glomerular filtration rate
EOT	end of treatment
GCB	germinal-center B-cell-like
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
G-CSF	granulocyte-colony stimulating factor
GFR	glomerular filtration rate
G-PPP	Global Pregnancy Prevention Program
GVHD	graft-versus-host disease
HBcAb	hepatitis B core antibody

HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HSCT	hematopoietic stem cell therapy
HR	hazard ratio
IB	Investigator's brochure
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	independent ethics committee
IHC	immunohistochemistry
IPI	International Prognostic Index
IND	investigational new drug
INN	International Nonproprietary Name
IRB	institutional review board
ITT	intent-to-treat
IUD	intrauterine device
IV	intravenous
LDH	lactate dehydrogenase
LTEP	Long-term extension phase
MCL	mantle cell lymphoma
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MMAE	monomethyl auristatin E
MREC	Medical Research Ethics Committee
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCCN FACT-Lym	National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy-Lymphoma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphomas
NOS	Not otherwise specified
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
P-gp	P-glycoprotein
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	Pharmacokinetic(s)
PmD	progressive metabolic disease

PML	progressive multifocal leukoencephalopathy
PN	peripheral neuropathy
PR	partial response
PRO	patient-reported outcomes
PSSA	Pfizer SAE Submission Assistant
R/R	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
Scr	serum creatinine
SCT	stem cell transplant
SD	stable disease
SMC	safety monitoring committee
TSH	thyroid stimulating hormone
ULN	upper limit of normal

1. INTRODUCTION

1.1. Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common of the aggressive non Hodgkin lymphomas (NHL) in the US and accounts for approximately 30% of NHLs diagnosed annually (Al-Hamadani et al, 2015). It is estimated that 74,200 new NHL patients will be diagnosed in the US in 2019, with 19,970 dying from the disease (Society, 2019). According to the current Surveillance Epidemiology and End Results data, the median age at diagnosis is 66 years (<https://seer.cancer.gov/statfacts/html/dlbcl.html>). DLBCL is usually aggressive, marked by rapidly growing tumors in lymph nodes, spleen, liver, bone marrow, or other organs (Martelli et al, 2013; Li et al, 2018). DLBCL is a potentially curable disease, with a significant proportion of patients cured with modern chemoimmunotherapy. The current standard treatment for DLBCL is taxing on patients' quality of life, with most patients reporting much worse quality-of-life scores than the general population (Oerlemans et al, 2014; Oerlemans et al, 2015). Nonetheless, for those patients not cured by standard initial therapy, the prognosis remains generally poor and DLBCL still accounts for the highest number of deaths per year of all the NHL histologies (Simpson et al, 2007; Martin et al, 2008; Seshadri et al, 2008; Elstrom et al, 2010; Gisselbrecht et al, 2010; Howlader et al, 2016).

1.1.1. Standard Treatment of Relapsed/Refractory DLBCL

The current standard regimen for the management of advanced stage DLBCL is rituximab, CHOP, which achieves a cure in many patients. Despite recent progress in improving prognosis, 20% to 50% of patients develop relapsed/refractory (R/R) disease (Crump et al, 2017). Of the patients who relapse, only 30% to 40% will respond to salvage chemotherapy. Those patients who respond to salvage chemotherapy may receive autologous stem cell transplant (SCT) therapy; however, about 50% of those patients will eventually relapse after autologous SCT. For patients with R/R DLBCL, the treatment decision is determined based on various factors such as the stage, age, presence of bulky disease, and International Prognostic Index (IPI). The long-term survival of these patients with R/R DLBCL is poor, as reported in the SCHOLAR-1 study, with a median overall survival (OS) of <10 months across all standard treatments (Crump et al, 2017). For patients who progress after these standard treatments, antiCD19 chimeric antigen receptor T-cell (CART) therapy is the remaining option.

1.1.2. Chimeric Antigen Receptor T-Cell Therapy

Studies of anti-CD19 CAR-T therapy have demonstrated a high rate of response in R/R Bcell lymphomas after conventional therapy has failed. However, many patients are not eligible or unable to receive such therapy due to geographic, financial, or other barriers. Results showed that many responses have been ongoing beyond 4 years, suggesting that this therapy may be potentially curative (Crump, 2016). Two recent studies of the anti-CD19 CAR T-cell therapies axicabtagene ciloleucel (axi-cel) and tisagenlecleucel, demonstrated important response rates, with durable responses seen in patients who achieved complete response (CR) (Neelapu et al, 2017; Schuster et al, 2019). Of the 101 patients with R/R DLBCL, primary mediastinal B-cell lymphoma, or transformed follicular lymphoma who were dosed with axi-cel, 82% had an objective response and 54% had a CR. At 18 months, the OS rate was 52%

(Neelapu et al, 2017). Similarly, of the 93 patients with R/R DLBCL who received tisagenlecleucel, 40% had a CR with an overall 65% relapse-free rate at 12 months after initial response (79% for patients with CR) (Schuster et al, 2019). In both the axi-cel and tisagenlecleucel studies, the safety profile was similar; the most common adverse events (AEs) of any grade across both studies were cytokine release syndrome (93% and 58%, respectively), pyrexia (85% and 35%, respectively), and neutropenia (84% and 34%). AntiCD19 CAR-T therapy is therefore a new treatment option for some patients with R/R DLBCL, but many patients will not achieve durable CR.

1.2. Brentuximab Vedotin

Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC) consisting of 3 components: 1) the chimeric IgG1 antibody cAC10, specific for human CD30; 2) the microtubule-disrupting agent monomethyl auristatin E (MMAE); and 3) a protease-cleavable linker that covalently attaches MMAE to cAC10. Targeted delivery of MMAE to CD30-expressing tumor cells is the primary mechanism of action of brentuximab vedotin (Kung Sutherland et al, 2006). Binding of MMAE to tubulin disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic death of the cell. Other nonclinical studies suggest additional contributory mechanisms of action, including antibody-dependent cellular phagocytosis; bystander effects on nearby cells in the tumor microenvironment due to released MMAE; and immunogenic cell death due to endoplasmic reticulum stress which drives exposure of immune activating molecules that can promote a T-cell response (Oflazoglu et al, 2007a; Cheson et al, 2014; Muller et al, 2014; Gardai et al, 2015b; Kim et al, 2015b; Cao et al, 2016a).

A complete summary of the clinical and nonclinical data relevant to the investigational product and its study in human participants is provided in the Investigator's Brochure (IB).

1.3. Lenalidomide

Lenalidomide is currently approved in the US for the treatment of relapsed or refractory mantle cell lymphoma (MCL), multiple myeloma (MM), and myelodysplastic syndromes (MDS) at a recommended starting dose of 25 mg orally once daily for 21 days every 28 days (REVLIMID Prescribing Information, Celgene Corp., Oct 2019).

Lenalidomide is a more potent molecular analog of thalidomide. In vitro, lenalidomide has 3 main activities: direct anti-tumor effect, inhibition of angiogenesis, and immunomodulation. In vivo, lenalidomide induces tumor cell apoptosis directly and indirectly by inhibition of bone marrow stromal cell support, by anti-angiogenic and antiosteoclastogenic effects, and by immunomodulatory activity. Lenalidomide has a broad range of activities that can be exploited to treat many hematologic and solid cancers. Lenalidomide has a black box warning for embryo-fetal toxicity, hematologic toxicity, and venous thromboembolism.

Lenalidomide is rapidly absorbed after oral administration. After single and multiple doses of lenalidomide in patients with MM or MDS, the maximum plasma concentrations (C_{max}) occurred at 1 hour (approximately 0.5 to 6 hours) postdose. Multiple doses of lenalidomide at the recommended dosage does not result in drug accumulation. Administration of a single 25

mg dose of lenalidomide with a high-fat meal in healthy patients reduces the extent of absorption, with an approximate 20% decrease in area under the concentration-time curve and 50% decrease in C_{max} . In the studies where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. The prescribing information of lenalidomide suggested lenalidomide can be administered with or without food. The mean half-life of lenalidomide is 3 to 5 hours in patients with MM, MDS, or MCL. Lenalidomide is not anticipated to be subjected to pharmacokinetic (PK) drug-drug interactions when co-administered with cytochrome P450 (CYP) inhibitors, inducers, or substrates. Despite being a weak substrate of P-glycoprotein (P-gp) in vitro, lenalidomide does not have clinically significant PK interactions with P-gp substrates/inhibitors in controlled studies. Renal function is the only important factor affecting lenalidomide plasma exposure, starting dose need to be adjusted based on the creatinine clearance value (<60 mL/min). Age (39 to 85 years), body weight (33 to 135 kg), sex, race, and type of hematological malignancies (MM, MDS, or MCL) did not have a clinically relevant effect on lenalidomide clearance in adult patients.

A phase 2/3 randomized, NCCN-listed study of lenalidomide monotherapy versus chemotherapy was conducted in participants with R/R DLBCL. Lenalidomide-treated participants had an objective response rate (ORR) of 27.5% as compared with 11.8% in investigator's choice chemotherapy (ORR were similar regardless of immunohistochemistry [IHC]-defined DLBCL subtype). Median progression-free survival (PFS) was increased in participants receiving lenalidomide (13.6 weeks) versus investigator's choice (7.9 weeks; $P=0.041$), with greater improvements in nongerminal-center B-cell-like (GCB) participants (15.1 versus 7.1 weeks, respectively; $P=0.021$) compared with GCB (10.1 versus 9.0 weeks, respectively; $P=0.550$) (Czuczman et al, 2017).

The combination of brentuximab vedotin and lenalidomide was explored in a phase 1 study; see Section 3.2 for details.

1.4. Rituximab

Rituximab is a genetically engineered chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). Rituximab is marketed in the US and the European Union (EU) for use in combination chemotherapy for previously untreated NHL, including indolent B-cell lymphomas and DLBCL; it is also approved for chronic lymphocytic leukemia (CLL) and other diseases.

Brentuximab vedotin in combination with rituximab has been evaluated in non-Hodgkin lymphoma participants in a phase 2 trial (SGN35-012). The combination of lenalidomide and rituximab has been explored in clinical studies; see Section 1.5 for more details. For more details on rituximab, see the rituximab and the rituximab and hyaluronidase package inserts (RITUXAN Prescribing Information, Genentech Inc., Sep 2019; RITUXAN HYCELA Prescribing Information, Genentech Inc., Mar 2021).

1.5. Lenalidomide and Rituximab in Combination

Two phase 2 studies have evaluated the safety and efficacy of lenalidomide in combination with rituximab in R/R non-Hodgkin's lymphoma. The first study enrolled multiple histologies. For those participants with DLBCL (n=32), the ORR was 28% with a CR rate of 22% and a median PFS of 2.8 months and OS of 10.2 months. There were no significant differences in clinical responses by DLBCL subtype (Wang et al, 2013). The second study evaluated only participants with DLBCL (n=23); all participants were elderly and ineligible for autologous SCT. The ORR was 35% and the CR rate was 30%. Disease-free survival at 12 months was 33% with an OS of 55.1% at 18 months (Zinzani et al, 2011).

2. OBJECTIVES

This study will evaluate the efficacy of brentuximab vedotin in combination with lenalidomide and rituximab among participants with relapsed or refractory DLBCL. Specific objectives and corresponding endpoints for the study are summarized below (Table 1).

Table 1. Objectives and corresponding endpoints

Primary Objective	Corresponding Primary Endpoint
• Evaluate and compare overall survival (OS) between the 2 treatment arms in the intent-to-treat (ITT) population	• OS
Key Secondary Objectives	Corresponding Key Secondary Endpoints
• Evaluate and compare progression-free survival (PFS) per Lugano 2014 by investigator between the 2 treatment arms in the ITT population	• PFS per Lugano 2014 by investigator
• Evaluate and compare the objective response rate (ORR) per Lugano 2014 by investigator between the 2 treatment arms in the ITT population	• ORR per Lugano 2014 by investigator
Other Secondary Objectives	Corresponding Other Secondary Endpoints
• Evaluate and compare the complete response (CR) rate per Lugano 2014 by investigator between the 2 treatment arms	• CR rate per Lugano 2014 by investigator
• Evaluate and compare duration of response (DOR) per Lugano 2014 by investigator between the 2 treatment arms	• DOR per Lugano 2014 by investigator
• Evaluate the safety and tolerability of the 2 treatment arms	• Incidence, severity, and seriousness of adverse events (AEs) per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0
• Evaluate and compare OS between the 2 treatment arms in the CD30-positive population	• OS in CD30-positive participants

Table 1. Objectives and corresponding endpoints

Exploratory Objectives	Corresponding Exploratory Endpoints
CCI	

3. INVESTIGATIONAL PLAN

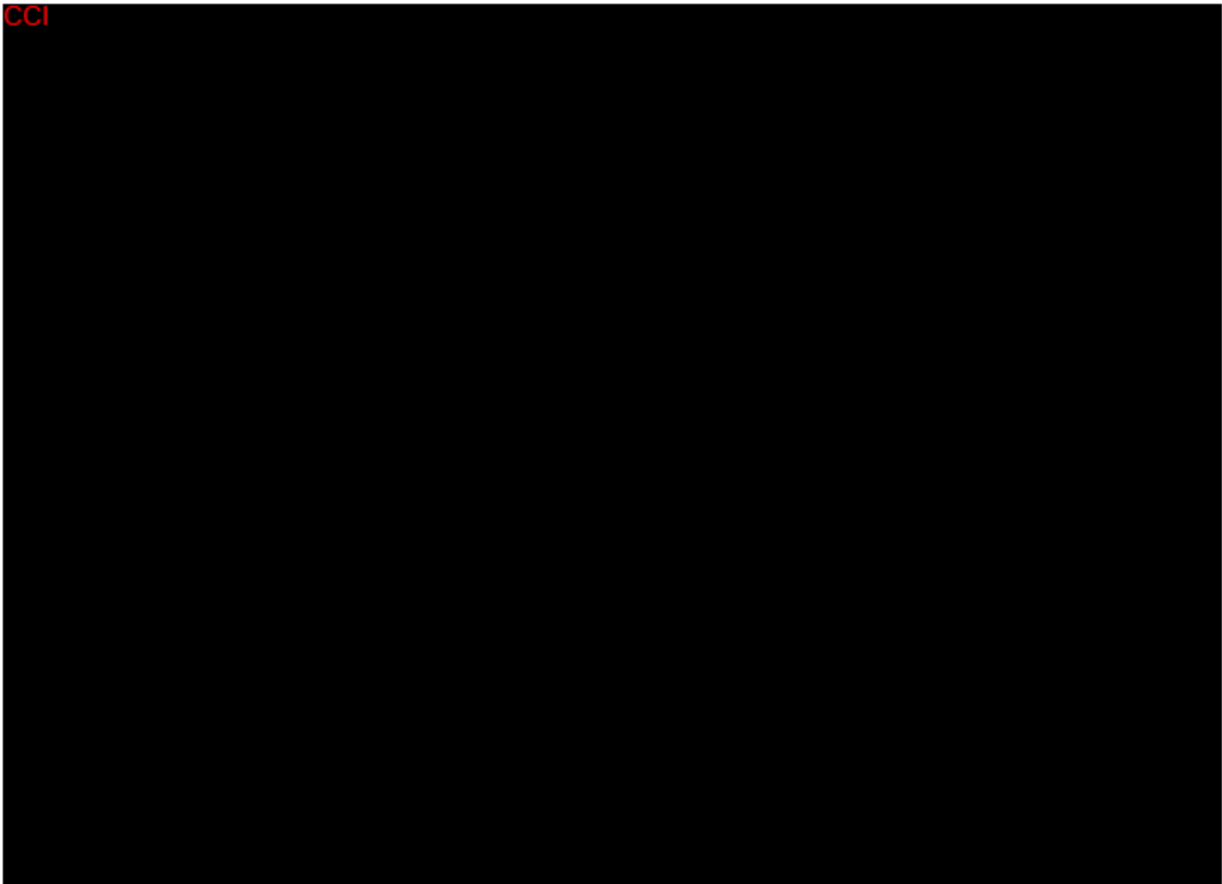
3.1. Summary of Study Design

This is a randomized, double-blind, placebo-controlled, active-comparator, multicenter phase 3 study designed to evaluate the efficacy of brentuximab vedotin in combination with lenalidomide and rituximab versus placebo in combination with lenalidomide and rituximab for the treatment of participants with relapsed or refractory DLBCL. Eligible participants include those that have received ≥ 2 prior lines of therapy and must be ineligible for SCT or CAR-T therapy.

There was a safety run-in period prior to the randomized portion of the study. A safety monitoring committee (SMC) including 3 external members reviewed data from the first 6 participants who received open label brentuximab vedotin, lenalidomide, and rituximab. The safety data for the participants from this run-in period were evaluated after these participants completed the first cycle of treatment. The SMC did not identify any new safety signals or concerns, and the SMC approved proceeding with the randomized portion of the study.

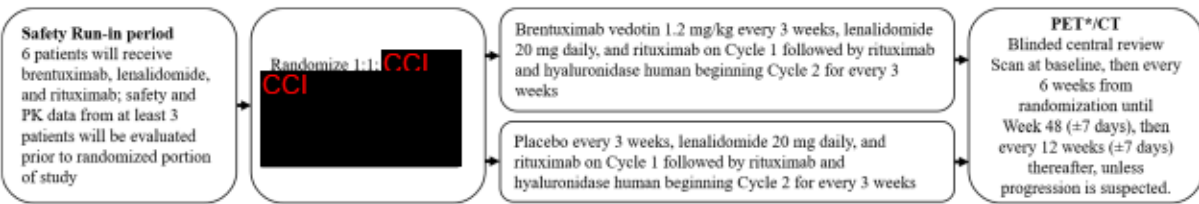
After completion of the safety run-in period, subsequent participants will be randomized in a 1:1 manner to receive either brentuximab vedotin or placebo in combination with lenalidomide and rituximab CCI

The most recent tumor biopsy tissue will be submitted to a central pathology lab for determination of CD30 expression. All participants will be eligible for enrollment regardless of CD30 expression level. CD30 expression will be centrally determined by visual assessment of CD30 on tumor cells by IHC, and CCI



The study design is presented in Figure 1.

Figure 1: Study design



* Once PET is negative, no further PET scans are required.

Treatment may continue as long as there is clinical benefit (stable disease [SD] or better) without progression or unacceptable toxicity. The study ends when the last subject completes

the last visit, last contact, discontinues from the study, or is lost to follow-up, whichever occurs first. In addition, the sponsor may terminate the study at any time (see Section 10.10).

After the final OS analysis, the study will transition to a long-term extension phase (LTEP). For participants in long-term follow-up, a last visit or contact will occur prior to the participant's discontinuation from participation in the study. Any participant on study treatment may transition to the LTEP of the study. The Sponsor will provide continued access to study treatment for any participant who is still on treatment and receiving clinical benefit based on the investigator's assessment through December 2026.

3.2. Discussion and Rationale for Study Design

Participants with R/R DLBCL who relapse after HSCT, or who are not candidates for HSCT, generally have poor outcomes and are in need of new treatments. There is sound rationale for combining brentuximab vedotin, lenalidomide and rituximab in the treatment of R/R DLBCL. In a recent phase 1 trial, 37 participants with R/R DLBCL were treated with brentuximab vedotin in combination with lenalidomide. The ORR (proportion of participants with CR or partial response [PR]) for all participants was 56.7% (21 of 37 participants). For the CD30-positive population, the ORR was 73.3% (11 of 15 participants), whereas the ORR for the CD30 <1% population was 45.6% (10/22). The median follow-up time was 14.3 months (range: 1 to 56.7 months). The median duration of remission for participants with CR or PR was 13.2 months (range: 3.2 to 55.2 months). For participants with CR, PR, or SD >6 months, the median duration of remission was 11.70 months (range: 3.2 to 55.2 months). The PFS and OS results appear similar in both the CD30-positive and CD30 <1% groups. The PFS in the combined population is 10.2 months and the median OS is 14.2 months (manuscript in preparation). Overall, the study showed long term efficacy outcomes were comparable among the CD30-positive population and CD30-negative population (Ward et al, 2022). Furthermore, from a pre-clinical perspective, while targeted delivery of MMAE to CD30-expressing tumor cells is the primary mechanism of action of brentuximab vedotin (Kung Sutherland et al, 2006), other nonclinical studies suggest additional contributory mechanisms of action (brentuximab vedotin IB v20), including antibody dependent cellular phagocytosis, bystander effects on nearby cells in the tumor microenvironment, and immunogenic cell death (Ofiazoglu et al, 2007b; Li et al, 2014; Muller et al, 2014; Gardai et al, 2015a; Kim et al, 2015a; Cao et al, 2016b). These effects may enhance the activity of brentuximab vedotin through immune-mediated mechanisms that are independent of CD30 tumor expression. Based on the clinical data and pre-clinical hypothesis, there is a similar time-to-event clinical benefit on time-to-event endpoints anticipated in both the CD30-positive and CD30-negative population allowing for a streamlined design and analysis in the ITT population.

In a phase 1 dose-escalation study of brentuximab vedotin in combination with lenalidomide (manuscript in preparation), the maximum tolerated dose (MTD) was defined as 1.2 mg/kg intravenous (IV) administered every 3 weeks with 20 mg lenalidomide daily administered orally. The majority of participants received primary granulocyte-colony stimulating factor (G-CSF) prophylaxis.

The dose of rituximab to be administered in combination with brentuximab vedotin and lenalidomide is the standard approved dose for participants with previously untreated

DLBCL when given in combination with CHOP or other anthracycline-based chemotherapy regimens. There is no standard dose or schedule for rituximab in the relapsed or refractory setting; however, the selected dose and schedule has been safely and effectively employed in combination with various single- and multi-agent chemotherapy regimens for this subject population (Gisselbrecht et al, 2010; NCCN, 2012).

Both brentuximab vedotin (see IB) and lenalidomide (see Section 1.3) have single-agent activity in R/R DLBCL and unique mechanisms of action. Potential mechanisms for lenalidomide's activity include augmentation of innate and adaptive immune function, alterations of the cytokine profile of the tumor microenvironment, and effects on angiogenesis. Combinations of lenalidomide with agents that have minimal effect on these components of the immune system, such as brentuximab vedotin, are less likely to have antagonistic effects. Rituximab, lenalidomide, and brentuximab vedotin all have manageable safety profiles, making this an attractive combination in multiply relapsed and heavily pretreated participants, regardless of CD30 expression.

3.2.1. Method of Assigning Participants to Treatment Arms

There was a safety run-in period prior to the randomized portion of the study. A SMC including 3 external members reviewed data from the first 6 participants who received open label brentuximab vedotin, lenalidomide, and rituximab.

After completion of the safety run-in period, subsequent participants will be randomized 1:1 to either brentuximab vedotin in combination with lenalidomide and rituximab, or placebo in combination with lenalidomide and rituximab. CCI

3.2.2. Rationale for Selection of Doses

In a phase 1 dose-escalation study of brentuximab vedotin in combination with lenalidomide (manuscript in preparation), the maximum tolerated dose (MTD) was defined as 1.2 mg/kg IV administered every 3 weeks with 20 mg lenalidomide daily administered orally. The majority of participants received primary G-CSF prophylaxis. The initially investigated dose of lenalidomide in R/R NHL was 25 mg daily on Days 1 to 21 of a 28-day cycle (Wiernik et al, 2008; Witzig et al, 2011). The first clinical experience with lenalidomide in R/R classical Hodgkin lymphoma given in an uninterrupted fashion, at 25 mg daily, demonstrated only a small increase in toxicity compared to lenalidomide given in an interrupted fashion (Fehniger et al, 2011). In an ongoing phase 1 trial of lenalidomide and brentuximab vedotin in participants with R/R DLBCL (NCT02086604), the MTD was determined to be 1.2 mg/kg of brentuximab vedotin once every 3 weeks and 20 mg daily of lenalidomide (Ward et al, 2015). Since the dose limiting toxicities of brentuximab vedotin and lenalidomide are peripheral neuropathy (PN) and myelosuppression, respectively, overlapping toxicity between the 2 agents should be limited. The eligible subject population is appropriate for characterizing the relationship of CD30 expression with antitumor activity and for assessment of disease-related symptoms.

Rituximab is a chimeric murine/human IgG1 kappa anti-CD20 monoclonal antibody, and is approved by the US Food and Drug Administration (FDA) for the treatment of Non-Hodgkin's Lymphoma (NHL). The CD20 marker is a transmembrane protein that is present on >90% of B cell lymphomas including DLBCL. The Fab domain binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions. Possible mechanisms of cell lysis include both complement-dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC) (RITUXAN Prescribing Information, Genentech Inc., Sep 2019). Rituximab is a standard component of the frontline therapy for DLBCL, including the RCHOP regimen. Furthermore, rituximab is routinely included in the treatment of R/R DLBCL, with the NCCN guidelines (v6.2019) including rituximab for many of the regimens recommended as second line or subsequent therapy for R/R DLBCL. The combination of brentuximab vedotin and rituximab was evaluated in a phase 2 clinical trial in participants with non-Hodgkin lymphoma (SGN35-012).

The combination of rituximab with lenalidomide in participants with R/R DLBCL has been utilized in recent years. There is evidence of synergistic activity of this combination in preclinical NHL models (Wu et al, 2008; Reddy et al, 2017). Wang et al (2013) treated 32 participants with R/R DLBCL with the combination and noted an ORR of 28%, including 22% CR's, and a median OS = 10.2m. There was evidence of activity in both GCB and non-GCB subtypes. NCCN guidelines (v6.2019) include the combination of lenalidomide ± rituximab (non-GCB) as one of the recommendations for second line and subsequent therapy for participants who are not candidates for transplant.

3.2.3. Blinding and Unblinding

This is a randomized, double-blind, placebo-controlled, active-comparator study.

3.2.3.1. Blinding of Participants

Participants enrolled in the randomized portion of the study will be blinded to their assigned study intervention.

3.2.3.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to the participant's assigned study intervention.

Participants will be assigned to receive study intervention according to the assigned treatment group from the randomization scheme. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the randomized portion of the study.

In order to maintain this blind, an otherwise uninvolved third party will be responsible for administration of the study intervention. This includes ensuring that there are no differences in time or effort taken to administer the study intervention and no blinded site staff are able to view the administration.

In the event of a Quality Assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

Site staff responsible for receiving, storing, dispensing, preparing, and administering the study intervention will be unblinded.

3.2.3.3. Blinding of the Sponsor

Sponsor staff will be blinded to participant's assigned study intervention, except for sponsor staff involved in the assignment or distribution of study intervention. Representatives from several specific functional areas will also be unblinded to all subject treatment assignments prior to interim analysis database lock. These individuals will not be Study Team members and will have limited interactions with the Study Team.

Sponsor staff may be unblinded after the interim analysis as described in Section 9.3.5.1 is performed if the threshold for efficacy is crossed.

3.2.3.4. Breaking the Blind

Unblinding a subject's treatment assignment prior to the final OS analysis or disease progression must be limited to safety emergency circumstances where knowledge of the treatment assignment would affect decisions regarding the immediate management of the subject. In the event of such an emergency circumstance, a formal unblinding procedure, carried out by a third-party organization, will be followed to allow the investigator to immediately access a subject's treatment assignment. Information on study treatment assignment should not be distributed to any other personnel involved in the clinical trial. In the event of any emergency unblinding, Pfizer is to be notified within 24 hours of the occurrence.

4. STUDY POPULATION

Participants must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of a good clinical practice audit and/or health regulatory authority inspection. Subject re-screening is allowed for this study.

4.1. Inclusion Criteria

1. Participants with relapsed or refractory diffuse and transformed large B-cell lymphoma (R/R DLBCL). DLBCL and CCI will be histologically determined by the most recent local pathology assessment for the purposes of study eligibility and stratification. The following subtypes of DLBCL are eligible for enrollment:
 - a. Not otherwise specified (NOS)
 - b. Intravascular large B-cell lymphoma
 - c. DLBCL associated with chronic inflammation
 - d. EBV-positive NOS
 - e. ALK-positive
 - f. T-cell/histiocyte-rich large B-cell lymphoma
 - g. Primary mediastinal large B-cell lymphoma

- h. High-grade B-cell lymphoma with translocations of MYC and BCL2 and/or BCL6 (double-/triple-hit lymphoma)
 - i. High-grade NOS B-cell lymphomas
 - j. Primary cutaneous DLBCL (leg type)
 - k. DLBCL arising from transformed indolent lymphomas/leukemias
 - l. Follicular lymphoma Grade 3b
2. Participants must have R/R disease following ≥ 2 lines of prior systemic therapy. For participants with transformed DLBCL (subtype k), at least the last systemic therapy used must have been for DLBCL.
 3. Participants must be HSCT or CAR-T ineligible according to the investigator and must meet at least one of the following criteria:
 - a. One or more co-morbidities, including cardiac, pulmonary, renal or hepatic dysfunction that in the opinion of the investigator make the subject medically unfit to receive HSCT or CAR-T therapy.
 - b. Active disease following induction and salvage chemotherapy
 - c. Inadequate stem cell mobilization (for HSCT)
 - d. Relapse following prior HSCT or CAR-T
 - e. Unable to receive CAR-T therapy due to financial, geographic, insurance, or manufacturing issues.
 4. Participants must have tumor tissue submitted to the central pathology lab for the determination of CD30 expression, which will be centrally determined by visual assessment for any detectable level of CD30 on tumor cells by IHC. The most recent biopsy available that contains viable DLBCL tissue should be submitted. CCI [REDACTED]
 5. Age 18 and older.
 6. An Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2.
 7. Participants must have fluorodeoxyglucose (FDG)-avid disease by positron emission tomography (PET) and bidimensional measurable disease of > 1.5 cm by computed tomography (CT), as assessed by the site radiologist within 28 days of Day 1.
 - a. PET and CT imaging performed prior to consent but within 28 days of Day 1 can be used.

8. The following baseline laboratory data within 28 days of Day 1:
 - a. Absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$. If recent G-CSF has been used, the ANC result must be ≥ 14 days after last dose of pegylated G-CSF or ≥ 7 days after last dose of G-CSF.
 - b. Platelet count $\geq 50,000/\mu\text{L}$ at least 7 days after last treatment for DLBCL with no platelet transfusion during this 7-day period.
 - c. For participants whose last therapy was CAR-T therapy, the ANC and platelet count requirements must be met at least twice during screening, with the measurements at least 7 days apart.
 - d. Hemoglobin ≥ 8.0 g/dL and have not received a transfusion in the 7 days prior to testing.
 - e. Serum bilirubin ≤ 1.5 x upper limit of normal (ULN) or ≤ 3 x ULN for participants with Gilbert's disease or documented hepatic involvement with lymphoma.
 - f. Estimated glomerular filtration rate (eGFR) ≥ 45 mL/min using the Cockcroft-Gault (C-G) formula, with serum creatinine (Scr) reported in mg/dL.
 - o $\text{eGFR (mL/min)} = ([140 - \text{age}] \times \text{weight [kg]} \times 0.85 [\text{if female}]) / (\text{Scr} \times 72)$
 - g. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 x ULN or 5.0 x ULN for participants with documented hepatic involvement with lymphoma.
 - h. Labs performed prior to consent but within 28 days of Day 1 can be used.
9. Participants of childbearing potential, as defined in Section 4.3, under the following conditions.
 - a. Must avoid pregnancy for at least 4 weeks before beginning lenalidomide therapy, during therapy, during dose interruptions, and for at least 12 months after completing therapy. Participants must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of birth control simultaneously: one highly effective form of contraception – tubal ligation, intrauterine device (IUD), hormonal (birth control pills, injections, hormonal patches, vaginal rings, or implants), or partner's vasectomy, and 1 additional effective contraceptive method – male latex or synthetic condom, diaphragm, or cervical cap (see [Appendix C](#)), beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions, and continuing for 12 months following discontinuation of study drug (brentuximab vedotin, rituximab, or lenalidomide). Two negative beta human chorionic gonadotropin (β -HCG) pregnancy tests must be obtained prior to initiating therapy. The first test must be a serum β -HCG pregnancy test and the second test can either be a serum or urine β -HCG pregnancy test. The first test should be performed within 10 to 14 days and the second test performed within 24 hours prior to receiving lenalidomide therapy. Afterwards, a serum β -HCG pregnancy test must be administered weekly during the first month, then at least monthly thereafter in

females with regular menstrual cycles or every 2 weeks in participants with irregular menstrual cycles.

- b. Must agree not to try to become pregnant during the study and for at least 12 months after the final dose of study drug.
- c. Must agree not to breastfeed or donate ova, starting at time of informed consent and continuing through 12 months after the final dose of study drug.
- d. If sexually active in a way that could lead to pregnancy, must consistently use 2 methods of birth control as described in Inclusion criterion 9a, starting at time of informed consent and continuing throughout the study and for at least 12 months after the final dose of study drug.

10. Participants who can father children, under the following conditions:

- a. Must agree not to donate sperm starting at time of informed consent and continuing throughout the study period and for at least 12 months after the final dose of study drug.
- b. If sexually active with a person of childbearing potential in a way that could lead to pregnancy, must consistently use 2 methods of birth control (see [Appendix C](#)) starting at time of informed consent and continuing throughout the study and for at least 12 months after the final dose of study drug.
- c. If sexually active with a person who is pregnant or breastfeeding, must consistently use one of the contraception options (see [Appendix C](#)) starting at time of informed consent and continuing throughout the study and for at least 12 months after the final dose of study drug.

11. The following requirements for participants who are known to be human immunodeficiency virus (HIV) positive:

- CD4+ T-cell counts ≥ 350 cells/mm³ within 28 days of Day 1
- No acquired immune deficiency syndrome-defining opportunistic infection within the past 12 months
- On established highly active antiretroviral therapy for at least 4 weeks with an HIV viral load less than 400 copies/mL within 28 days of Day 1 (see Section 5.8.2 for participants receiving strong CYP3A inhibitors).

12. The subject must provide written informed consent.

4.2. Exclusion Criteria

- 1. History of another malignancy within 2 years before the first dose of study drug or any evidence of residual disease from a previously diagnosed malignancy. Exceptions are malignancies with a negligible risk of metastasis or death (eg, 5-year OS $\geq 90\%$), such as carcinoma in situ of the cervix, non-melanoma skin carcinoma, localized prostate cancer, ductal carcinoma in situ, or Stage I uterine cancer.

2. History of progressive multifocal leukoencephalopathy (PML).
3. Active cerebral/meningeal disease related to the underlying malignancy. Participants with a history of cerebral/meningeal disease related to the underlying malignancy are allowed if prior CNS disease has been effectively treated and without progression for at least 3 months.
4. Any uncontrolled Grade 3 or higher (per NCI CTCAE version 5.0) viral, bacterial, or fungal infection within 2 weeks prior to the first dose of study drug. Routine antimicrobial prophylaxis is permitted.
5. Chemotherapy, radiotherapy, biologics, and/or other antitumor treatment with immunotherapy that is not completed 3 weeks prior to first dose of study drug, unless underlying disease has progressed on treatment.
6. Participants who are breastfeeding.
7. Known hypersensitivity to any study drug or excipient contained in the drug formulation of the study drugs.
8. Any contraindication to associated study treatments.
9. Known to be positive for hepatitis B by surface antigen expression. Participants who are hepatitis B surface antigen (HBsAg) negative but hepatitis B core antibody (HBcAb) positive are eligible, but should start hepatitis B prophylaxis therapy prior to receiving the first dose of rituximab. Known to be positive for hepatitis C (HCV) infection (either confirmed positive by polymerase chain reaction [PCR] or on antiviral therapy for hepatitis C within the last 6 months). Participants who have been treated for hepatitis C infection are permitted if they have documented sustained virologic response of 12 weeks.
10. Participants with previous allogeneic HSCT if they meet either of the following criteria:
 - <100 days from HSCT
 - Active acute or chronic graft-versus-host disease (GVHD) or receiving immunosuppressive therapy as treatment for or prophylaxis against GVHD.
11. Previous treatment with brentuximab vedotin or lenalidomide
 - a. Previous treatment with other vedotin-based ADCs is permitted if the last dose is at least 6 months prior to Day 1.
12. Current therapy with immunosuppressive medications (including steroids), other systemic anti-neoplastic, or investigational agents.
 - i. Prednisone (or equivalent) ≤ 10 mg/day may be used for non-lymphomatous purposes.
13. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, pulmonary embolism, or cardiac symptoms

consistent with New York Heart Association (NYHA) Class III-IV within 6 months prior to the first dose of study drugs.

14. Congestive heart failure, Class III or IV, by the NYHA criteria (see [Appendix D](#)).
15. Grade 2 or higher peripheral sensory or motor neuropathy at baseline.
16. Other serious underlying medical condition that, in the opinion of the investigator, would impair the subject's ability to receive or tolerate the planned treatment, and complete study assessments.

4.3. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is using an appropriate method of contraception for the individual participant and their partner(s) from the permitted list of contraception methods (see [Appendix C](#)) and will confirm that the participant has been instructed in its consistent and correct use.

At time points indicated in the SoE ([Appendix A](#)), the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of 2 selected methods of contraception ([Appendix C](#)), considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

4.4. Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Postmenopausal with 1 of the following conditions:
 - Documented hysterectomy
 - Documented bilateral salpingectomy

- Documented bilateral oophorectomy

For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator judgement will determine childbearing status and study eligibility.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

- Postmenopausal female:
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

4.5. Removal of Participants From Therapy or Assessment

Pfizer or their designee must be notified if a subject is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the subject's medical records and case report form (CRF). For participants continuing to LTEP, the reason for treatment discontinuation will only be documented in the participant's medical record.

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specific follow-up procedures. Every attempt should be made to follow the subject until progression, death, or administrative study closure.

Final assessments will be performed before any other therapeutic intervention if possible. Additionally, any subsequent treatments should be documented on the subject's medical records and CRF. For participants continuing to LTEP, subsequent treatments will only be documented in the participant's medical record.

4.5.1. Discontinuation of Study Treatment

A subject's study treatment may be discontinued for any of the following reasons:

- Progressive disease (PD)
- AE
- Pregnancy
- Investigator decision
- Subject decision, non-AE
 - Note: Ensure that participants who decide to stop treatment because of an AE are not included in this rationale.
- Study termination by sponsor
- Other

Participants who discontinue from study treatment will remain on study for follow-up unless they specifically withdraw consent for any further contact with them or persons previously authorized by the participant to provide this information. The withdrawal of consent should

be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures, post-treatment study follow-up, and/or review of medical records. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local laws.

4.5.2. Subject Withdrawal From Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study may include:

- Subject withdrawal of consent
- Study termination by sponsor
- Lost to follow-up
- Death
- Other

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

5. TREATMENTS

5.1. Treatments Administered

Study interventions are all prespecified IMPs and NIMPs/AxMPs, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to the treatment regimens which consist of either brentuximab vedotin or placebo in combination with lenalidomide and rituximab. Brentuximab vedotin is an ADC consisting of the antibody cAC10, specific for human CD30; the microtubule disrupting agent MMAE; and a protease cleavable linker that covalently attaches MMAE to cAC10. Lenalidomide induces tumor cell apoptosis directly and indirectly by inhibition of bone marrow stromal cell support, by anti-angiogenic and anti-osteoclastogenic effects, and by immunomodulatory activity. Rituximab is a chimeric monoclonal antibody that recognizes CD20, a cell surface antigen typically found on B-lymphocytes and most B-cell lymphomas.

If one or more components of the combination are discontinued due to toxicity, the remaining agents may be continued.

For the control arm (placebo in combination with lenalidomide and rituximab), the site pharmacist will prepare a placebo replacement for brentuximab vedotin (eg, normal saline) to be administered in the same manner as brentuximab vedotin.

Detailed information describing the preparation, administration, and storage of all investigational products can be found in the Pharmacy Instructions/IP Manual.

5.2. Single Reference Safety Documents for Study Interventions

Single reference safety documents (SRSD) for each of the study interventions are summarized in Table 2.

Table 2. Single Reference Safety Documents for Study Interventions

Study Intervention	SRSD
Brentuximab vedotin	Investigator's brochure
Lenalidomide	Investigator's brochure
Rituxan Hycela	EU SmPC
Rituximab	EU SmPC

5.3. Preparation, Handling, Storage and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.
3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.
4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to labeled storage conditions as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the in the pharmacy instructions/IP Manual.
5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. See the pharmacy instructions/IP manual for storage conditions of the study intervention once reconstituted and/or diluted.

6. Study interventions should be stored in their original containers.
7. The investigator, institution, head of the medical institution, (where applicable) or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records such as IPAL or sponsor-approved equivalent). All study interventions will be accounted for using a study intervention accountability form/record.
8. Further guidance and information for the final disposition of unused study interventions are provided in the pharmacy instructions/IP manual . All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.

5.4. Brentuximab Vedotin

Detailed information describing the preparation, administration, and storage of brentuximab vedotin is located in the Pharmacy Instructions/IP Manual.

5.4.1. Description

Brentuximab vedotin is a sterile, preservative free, white to off-white lyophilized cake or powder supplied by Pfizer in single-use vials for reconstitution for IV administration. Each vial of the product contains brentuximab vedotin, trehalose, sodium citrate, and polysorbate 80. See the Pharmacy Instructions/IP Manual for further information.

5.4.2. Dose and Administration

Brentuximab vedotin 1.2 mg/kg will be administered on Day 1 of each 21-day cycle by IV infusion given over approximately 30 minutes to participants randomized to treatment with brentuximab in combination with lenalidomide and rituximab. In the absence of infusion-related reactions, the infusion rate for all participants should be calculated in order to achieve a 30-minute infusion period. Brentuximab vedotin must not be administered as an IV push or bolus. Brentuximab vedotin should not be mixed with other medications.

Weight-based dosing is based on subject actual body weight. Doses must be adjusted for participants who experience a $\geq 10\%$ change in weight from baseline. Subject weight must be measured during all relevant assessment windows as described in the schedule of events. Other dose adjustments for changes in body weight are permitted per institutional standard. Rounding is permissible within 5% of the nominal dose. **An exception to weight-based dosing is made for participants weighing greater than 100 kg; doses will be capped at 100 kg for these individuals. The maximum dose calculated per cycle in this study is 120 mg for participants receiving the 1.2 mg/kg dose level.**

5.4.3. Dose Modifications

Table 3 describes the recommended dose modifications for study treatment associated toxicity.

Doses reduced for treatment-related toxicity should not be re-escalated without discussion with the sponsor. In the event of dose modification or discontinuation of brentuximab vedotin, the other study agents may continue to be administered. Brentuximab vedotin dosing may continue to be administered if either or both of the other study agents are discontinued. If the delay in brentuximab vedotin/ placebo is greater than one week the next dose will be given at the next cycle. For Grade 3 or 4 electrolyte abnormalities that last longer than 72 hours, are clinically complicated, don't resolve spontaneously, or don't respond to conventional medical interventions, discuss with Medical Monitor before the next dose.

If brentuximab vedotin, rituximab, or both are held at a cycle and lenalidomide is being continued, the cycle is considered to have begun. If the patient can be treated with either or both drugs within 7 days of the delay, the dose should be given for that cycle. If not, the drugs should be eliminated for that cycle and would be administered at the next cycle once the reason for the hold has resolved. The minimum time between doses of either brentuximab vedotin or rituximab is 14 days.

If all drugs at a cycle are being held the entire cycle should be delayed until treatment resumes. Visits occurring between cycles would be considered unscheduled visits. The following cycle visit date would be calculated from the start of the delayed cycle, not C1D1.

Dose modifications as described in this section should continue to be followed during LTEP.

Table 3. Recommended dose modifications for brentuximab vedotin-associated toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Sensory Neuropathy	Continue BV/placebo at same dose level	Continue BV/placebo at same dose level	Withhold BV/placebo until PN is $\leq$ Grade 2, then reduce dose to 0.9 mg/kg and resume treatment; if already at 0.9 mg/kg, continue dosing at that dose.	Discontinue treatment with BV/placebo
Motor Neuropathy	Continue BV/placebo at same dose level	Reduce BV/placebo dose to 0.9 mg/kg and resume treatment	Discontinue treatment with BV/placebo	Discontinue treatment with BV/placebo
Non-hematologic (except peripheral neuropathy)	Continue BV/placebo at same dose level	Continue BV/placebo at same dose level	Withhold BV/placebo until toxicity is $\leq$ Grade 2 or has returned to baseline, then resume treatment at the same dose level ^b .	Withhold BV/placebo until toxicity is $\leq$ Grade 2 or has returned to baseline, then reduce dose to 0.9 mg/kg and resume

Table 3. Recommended dose modifications for brentuximab vedotin-associated toxicity

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
				treatment, or discontinue at the discretion of the investigator ^{a,b,c} .
Hematologic ^d	Continue BV/placebo at same dose level	Continue BV/placebo at same dose level	Hold BV/placebo dose until event resolves to Grade ≤ 2 or baseline. Follow lenalidomide dose modifications as noted in Section 5.5.4. Rituximab dose may be held if, in the opinion of the investigator, it is felt to be a potentially contributing factor. ^e	

a. Dose reductions below 0.9 mg/kg are not allowed, and toxicities should be managed with dose delays.

b. For Grade 3 or 4 electrolyte abnormalities that last longer than 72 hours, are clinically complicated, don't resolve spontaneously, or don't respond to conventional medical interventions, discuss with Medical Monitor before the next dose.

c. Treatment should be discontinued for participants who experience Grade 4 infusion-related reactions.

d. Support with blood product transfusions allowed per institutional standard of care.

e For recurrent Grade 4 neutropenia, after lenalidomide discontinuation, consider dose reduction or discontinuation of BV/placebo. Discuss with Medical Monitor.

5.4.4. Preparation and Dispensing

Detailed drug preparation instructions are provided in the pharmacy binder.

Brentuximab vedotin vials are provided via single-use containers. Any partially used vials or diluted dosing solutions should be discarded using appropriate institutional drug disposal procedures.

Brentuximab vedotin should be reconstituted with the appropriate amount of Sterile Water for Injection, US Pharmacopeia or equivalent (see Pharmacy Instructions/IP Manual for details). The vial should be gently swirled until the contents are completely dissolved. The vial must not be shaken. The reconstituted drug product should be inspected visually for any particulate matter and discoloration.

The required volume of reconstituted drug product should be diluted into an infusion bag. The bag should be gently inverted to mix the solution. The bag must not be shaken. Prior to administration, the reconstituted and diluted drug product should be inspected visually for any particulate matter and discoloration.

Detailed drug preparation instructions are provided in the Pharmacy Instructions/IP Manual.

5.5. Lenalidomide

Detailed information describing the preparation, administration, and storage of lenalidomide is located in the lenalidomide package insert.

5.5.1. Description

All participants in this study will receive lenalidomide. Lenalidomide is an immunomodulatory drug. See the lenalidomide package insert (REVLIMID Prescribing Information, Celgene Corp., Oct 2019) for further details.

5.5.2. Method of Procurement

Commercially available lenalidomide will be provided by the Sponsor.

5.5.3. Dose and Administration

Lenalidomide 20 mg will be administered orally once daily. For participants whose baseline eGFR is 45-59 mL/min, see Section 5.5.4.3.

Lenalidomide should be administered with water. The capsule(s) should be swallowed intact and participants should not attempt to chew capsules, open capsules or dissolve them in water. Each dose of lenalidomide should be taken with or without food, at approximately the same time each day.

Females of childbearing potential are suggested not to handle or administer lenalidomide unless they are wearing gloves.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If a dose is missed for the entire day, it should not be made up.

Participants in the US must be registered into the mandatory lenalidomide REMS® program. Participants outside the US must follow their country specific Risk Minimization Program (Global Pregnancy Prevention Program [G-PPP]). Per standard lenalidomide REMS/risk minimization programs (G-PPP) requirements, all physicians who prescribe lenalidomide for research participants enrolled into this trial must comply with all requirements of the lenalidomide REMS/risk minimization programs.

5.5.4. Dose Modifications

Dose modification guidelines as summarized in this section are recommended to manage Grade 3 or 4 thrombocytopenia (Section 5.5.4.1) or neutropenia (Section 5.5.4.2) or other Grade 3 or 4 toxicities (Section 5.5.4.4) considered to be related to lenalidomide. In the event of dose modification or discontinuation of lenalidomide, the other study agents may continue to be administered. Lenalidomide may continue to be administered if brentuximab vedotin or rituximab dosing is permanently discontinued due to toxicity. A 5 mg increase in lenalidomide dose after a prior dose reduction will be permitted only after discussion with the Medical Monitor.

Dose modifications as described in this section should continue to be followed during LTEP.

5.5.4.1. Platelet Counts

Table 4. Thrombocytopenia during treatment

When Platelets	Recommended Course
Fall to <50,000 mcL	Interrupt lenalidomide treatment and follow CBC weekly
Return to $\geq 50,000/\text{mcL}$	Resume lenalidomide at 5 mg less than the previous dose. Do not dose below 5 mg daily

5.5.4.2. Absolute Neutrophil counts (ANC)

Table 5. Neutropenia during treatment

When Neutrophils	Recommended Course
Fall to <1000/mcL for at least 7 days OR Fall to <1000/mcL with an associated temperature $\geq 38.5^{\circ}\text{C}$	Interrupt lenalidomide treatment and follow CBC weekly.
Fall to <500/mcL	Reduce lenalidomide dose by 5 mg. Do not dose below 5 mg daily. Follow CBC weekly. If persistent at 5 mg daily dose, discontinue lenalidomide dosing permanently.
Return to $\geq 1000/\text{mcL}$	Resume lenalidomide at 5 mg less than the previous dose. Do not dose below 5 mg daily.

5.5.4.3. Renal Impairment

For participants whose eGFR at baseline is 45–59 mL/min, the starting dose of lenalidomide should be 10 mg once daily. After discussion with the Medical Monitor, the dose may be escalated to 15 mg once daily after 2 cycles if the subject has tolerated therapy. For participants whose eGFR has dropped from $\geq 60\text{ mL/min}$ to 45–59 mL/min, reduce lenalidomide daily dose by 5 mg from the previous dose. For participants whose eGFR has dropped from $\geq 60\text{ mL/min}$ to 30–45 mL/min, reduce lenalidomide daily dose by 10 mg from the previous dose. For participants whose eGFR has dropped from 45–59 mL/min to 30–45 mL/min, reduce lenalidomide daily dose by 5 mg from the previous dose. Do not dose below 5 mg daily. If a subject's eGFR is <30 mL/min, permanently discontinue lenalidomide dosing. Contact the Medical Monitor for any specific renal dose modification questions.

5.5.4.4. Other Grade 3 or 4 Toxicities

For other Grade 3 or 4 toxicities considered to be related to lenalidomide, hold treatment and restart at the physician's discretion at next lower dose level when toxicity has resolved to Grade ≤ 2 .

5.5.5. Preparation and Dispensing

A qualified staff member will dispense the study intervention using unique container numbers via an IRT system and the blister cards provided, in quantities appropriate according to the SoE. A second staff member will verify the dispensing. The participant should be

instructed to maintain the product in the blister cards provided throughout the course of dosing and return the blister cards to the site at the next study visit.

5.6. Rituximab/Rituximab and Hyaluronidase Human

Refer to the rituximab and the rituximab and hyaluronidase human package inserts for detailed information on the description, preparation, administration, and storage of rituximab.

Biosimilars are allowed for subject use in this trial.

5.6.1. Description

All participants in this study will receive rituximab. Rituximab is a chimeric monoclonal antibody that recognizes CD20, a cell surface antigen typically found on B-lymphocytes and most B-cell lymphomas.

5.6.2. Method of Procurement

Commercially available rituximab will be provided by the study sites from their usual suppliers and will be reimbursed by the Sponsor or rituximab will be provided to sites through a local supplier if supply by site is not possible.

5.6.3. Dose and Administration

Rituximab 375 mg/m² will be administered either before or after administration of brentuximab vedotin on Cycle 1 Day 1 (±1 day) via IV infusion according to the package insert (RITUXAN Prescribing Information, Genentech Inc., Sep 2019) or institutional standard of care. If rituximab IV infusion is given after the brentuximab vedotin infusion, it should begin within approximately 60 to 90 minutes after the end of the brentuximab vedotin infusion.

If the Cycle 1 Day 1 rituximab IV infusion is well tolerated, participants may receive rituximab and hyaluronidase human 1400 mg via subcutaneous injection (RITUXAN HYCELA Prescribing Information, Genentech Inc., Mar 2021) on Day 1 of every cycle, starting at Cycle 2; or continue with rituximab IV infusion at 375 mg/m² on Day 1 of every cycle and then every 3 weeks. For all cycles, rituximab may be administered either before or after brentuximab vedotin/placebo. After Cycle 1, if the drugs are well tolerated, the time between infusion can be shortened per institutional guidelines for rituximab to a minimum of 30 minutes.

Additional premedications, including steroids, may be given prior to the rituximab infusion in accordance with the rituximab package insert (RITUXAN Prescribing Information, Genentech Inc., Sep 2019; RITUXAN HYCELA Prescribing Information, Genentech Inc., Mar 2021), institutional standard of care, or as clinically indicated.

5.6.4. Dose Modifications

Rituximab may continue to be administered if brentuximab vedotin or lenalidomide dosing is permanently discontinued due to toxicity. No dose reductions of rituximab are allowed; however, if unacceptable toxicity to rituximab develops, rituximab may be permanently

discontinued and brentuximab vedotin and lenalidomide dosing may continue. Rituximab may be held along with lenalidomide in the setting of significant cytopenias if, in the opinion of the investigator, it is felt that rituximab may be a potential contributing factor (see Table 3). Rituximab should be permanently discontinued in HIV-positive participants who have CD4+ counts ≤ 100 cells/mm³ (see Section 7.8.4).

Dose modifications as described in this section should continue to be followed during LTEP.

5.6.5. Preparation and Dispensing

See the package insert, or equivalent for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the preparation and dispensing.

5.7. Required Premedication and Postmedication

Routine premedication should not be administered for the prevention of infusion-related reactions prior to the first dose of brentuximab vedotin. However, participants who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent brentuximab vedotin infusions with premedication as described in Section 5.9.1. Participants who experience a Grade 3 or Grade 4 infusion-related reaction may potentially receive additional treatment with brentuximab vedotin at the discretion of the investigator after discussion with the sponsor.

Acetaminophen and an antihistamine should be given within 30 to 60 minutes prior to initiating the rituximab IV infusion on Cycle 1 Day 1. Additional premedications, including steroids, may be given prior to the rituximab infusion in accordance with the rituximab package insert (RITUXAN Prescribing Information, Genentech Inc., Sep 2019; RITUXAN HYCELA Prescribing Information, Genentech Inc., Mar 2021), institutional standard of care, or as clinically indicated.

Participants should be individually evaluated to assess the need for tumor lysis prophylaxis prior to the first dose of brentuximab vedotin. Participants should receive prophylaxis as appropriate per the institutional standards.

5.8. Concomitant Therapy

All concomitant medications, blood products, and radiotherapy administered will be recorded from Day 1 (predose) through the safety reporting period. Any concomitant medication given for a study protocol-related AE should be recorded from the time of informed consent.

5.8.1. Required Concomitant Therapy

All participants must take low-dose aspirin (at least 50 mg daily) as prophylactic anticoagulation, unless already receiving anticoagulation therapy. Participants may use warfarin, direct oral anticoagulants, antiplatelet agents, or low molecular weight heparin if intolerant to aspirin or per institutional guidelines. After the final OS analysis, for

participants continuing to LTTP, aspirin or other anticoagulation therapy is recommended for subjects receiving lenalidomide and may be continued per institutional guidelines and investigator-determined usual and customary clinical care.

Participants who have a history of past hepatitis B infection, namely those who are HBsAg negative but HBcAb positive, are at high risk of hepatitis B reactivation when receiving anti-CD20 therapy (ie, rituximab) or SCT. These participants are required to start anti-viral prophylaxis and should be continued for at least 12 months after the last dose of rituximab or SCT. Anti-viral therapies recommended for prophylaxis include entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide. Participants with appropriate anti-viral prophylaxis against hepatitis B reactivation may be enrolled without additional anti-viral prophylaxis.

Medications for infusion-related reactions during brentuximab vedotin and rituximab administration, such as epinephrine, antihistamines, and corticosteroids, should be available for immediate use.

5.8.1.1. Granulocyte-colony Stimulating Factors

G-CSF prophylaxis is required starting with Cycle 1 (filgrastim, pegfilgrastim, or filgrastim -biosimilars are acceptable). G-CSF prophylaxis should be administered starting 1 to 3 days after each brentuximab vedotin/placebo administration. The type of G-CSF formulation, dose, and duration used may be per institutional guidelines.

After the final OS analysis, for participants continuing to LTTP, administration of prophylactic G-CSF is recommended for patients receiving brentuximab vedotin and may be administered per institutional guidelines or investigator-determined usual and customary care.

5.8.2. Allowed Concomitant Therapy

Routine premedication for infusion reactions should not be administered prior to the first dose of brentuximab vedotin. However, participants who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent treatment with premedication as described in Section 5.9.1.

Co-administration of brentuximab vedotin with strong CYP3A4 inhibitors may increase exposure to MMAE. Participants who are receiving strong CYP3A4 inhibitors concomitantly with brentuximab vedotin/placebo should be closely monitored for adverse reactions. Examples of strong CYP3A4 inhibitors include clarithromycin, telithromycin, nefazodone, itraconazole, ketoconazole, atazanavir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir (see the FDA website for more examples: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>).

Participants who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent brentuximab vedotin/placebo infusions with premedication consisting of acetaminophen and diphenhydramine administered 30 to 60 minutes prior to each 30-minute infusion or according to institutional standards.

If anaphylaxis occurs, brentuximab vedotin/placebo administration should be immediately and permanently discontinued; lenalidomide and rituximab administration may continue.

Medications that aggravate cytopenias (eg, trimethoprim-sulfamethoxazole) should be avoided. All participants should be up-to-date on any recommended vaccinations prior to study entry. Additional vaccination(s) during each cycle of study treatment must be approved by the sponsor.

The administration of inactivated (non-live virus) vaccines are permitted including against influenza and/or COVID-19.

The use of thrombopoietic growth factors and blood product transfusions are allowed. Prednisone (or equivalent) ≤ 10 mg/day may be used for non-lymphomatous purposes.

Otherwise, all supportive measures consistent with optimal subject care should be provided throughout the study according to institutional standards.

5.8.3. Prohibited Concomitant Therapy

Participants must not receive other investigational drugs, live vaccines, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy during the treatment period. Prednisone (or equivalent) ≤ 10 mg/day may be used for non-lymphomatous purposes.

Erythropoietin-stimulating agents may not be administered to participants.

In addition, other prohibited concomitant therapies should be excluded in accordance with the approved prescribing information for each agent. Exceptions are noted in Section 5.8.2.

5.9. Management of Adverse Reactions

Management of AEs should occur per institutional standards. Additional information regarding treatment-emergent AEs for brentuximab vedotin, lenalidomide, rituximab, and rituximab and hyaluronidase human are available in Sections 5.4.3, 5.5.4, 5.6.4, and the respective package inserts.

5.9.1. Management of Infusion Reactions

Infusion-related reactions may occur during the infusion of brentuximab vedotin or rituximab. The infusion should be administered at a site properly equipped and staffed to manage anaphylaxis should it occur. All supportive measures consistent with optimal subject care should be given throughout the study according to institutional standards. Supportive measures may include extending the infusion time and/or administering medications for infusion-related reactions.

Participants who have experienced a Grade 1 or Grade 2 infusion-related reaction to brentuximab vedotin/placebo or rituximab should be premedicated for subsequent infusions.

If anaphylaxis occurs, administration of brentuximab vedotin should be immediately and permanently discontinued.

Infusion reactions related to rituximab should be managed according to the package insert (RITUXAN Prescribing Information, Genentech Inc., Sep 2019; RITUXAN HYCELA Prescribing Information, Genentech Inc., Mar 2021) and/or institutional standard of care.

5.9.2. Management of Allergic/Hypersensitivity Reactions

Allergic/hypersensitivity reactions are characterized by adverse local or general responses from exposure to an allergen (NCI CTCAE version 5.0). For purposes of this study, allergic/hypersensitivity reactions are differentiated from IRRs by being defined as occurring >24 hours after infusion of study intervention. Allergic/hypersensitivity reactions may manifest in the same manner as IRRs, i.e., a combination of signs or symptoms including fever, rigors, flushing, itching, various types of rashes, urticaria, dyspnea, nausea, vomiting, back or abdominal pain, and/or hypotension. All supportive measures consistent with optimal subject care should be given according to institutional standards.

5.9.3. Management of 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. See the IB for further details.

If PML is suspected, hold further brentuximab vedotin and rituximab dosing and undertake a diagnostic work-up including (but not limited to):

- Neurologic examinations, as warranted
- Brain radiologic features by magnetic resonance imaging (MRI)
- PCR analysis: John Cunningham virus DNA detectable in cerebrospinal fluid

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

5.9.4. Management of Overdose

Weight-based dosing for brentuximab vedotin is based on subject actual body weight (see Section 5.4.2), with the exception of participants weighing greater than 100 kg; doses will be based on 100 kg for these individuals. The maximum dose calculated per cycle in this study is 120 mg for participants receiving the 1.2 mg/kg dose level.

In the event of an overdose of brentuximab vedotin $\geq 10\%$, study personnel should:

- Care for and medically stabilize the subject until there is no immediate risk of complications or death, if applicable. There is currently no known antidote for an overdose of brentuximab vedotin.
- Notify the Medical Monitor as soon as they become aware of the overdose, to discuss details of the overdose (e.g., exact amount of brentuximab vedotin administered, subject weight) and AEs, if any.

- Document the quantity of excess dose as well as the duration of the overdose on the CRF (CRF entry not applicable once participants enter LTEP).

Overdose is reportable to Pfizer Safety **only when associated with an SAE**.

In the event of an overdose of lenalidomide, the event should be managed according to the product label and/or institutional standard of care, and promptly reported to the Sponsor.

In the event of an overdose of rituximab, the event should be managed according to the product label and/or institutional standard of care, and promptly reported to the Sponsor.

5.10. Treatment Compliance

Study drug administration will be performed by study site staff and documented in source documents and the CRF. In addition, participants will be provided with a diary in which they will be instructed to record details of lenalidomide dosing each day. Participants should complete the dosing diary every day until lenalidomide is permanently discontinued.

Following the final OS analysis and entry of remaining on-treatment participants into the LTEP, treatment administration data will no longer be collected in the CRFs / dosing diary. Refer to Section 8.1 for further details on LTEP data collection.

5.11. Continued Access to Study Intervention After the End of the Study

No intervention will be provided per protocol to study participants beyond the end of the study (end of LTEP).

6. STUDY ACTIVITIES

6.1. Schedule of Events

AEs and concomitant medications will be recorded from Day 1 (predose) through the safety reporting period (see Section 7.8.1.3). Any study protocol-related AE, as well as any concomitant medications given for treatment of the AE, should be recorded from the time of informed consent.

Clinical laboratory assessments (serum chemistry panel, complete blood count [CBC] with differential [manual differential if clinically indicated, see Section 7.8.2], serum β -HCG pregnancy test, and eGFR), physical exam, weight, performance status, and electrocardiogram (ECG) may be performed within 1 day prior to administration of study drug. The results from all relevant clinical laboratory assessments must be reviewed prior to dosing. Additional ECGs may be performed throughout the duration of the study, as clinically indicated.

Participants still receiving clinical benefit and remaining on study intervention after the final OS analysis may continue receiving study intervention during the LTEP through December 2026. During this phase of the study, only pregnancies and SAEs will be collected by the Sponsor. All other assessments, including efficacy assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

A schedule of events is provided in Appendix A. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

6.2. Prescreening Visit

- CD30 Prescreening consent

6.3. Screening Visit (Day –28 to Day 1)

- Informed consent
- Study eligibility per inclusion/exclusion criteria
- Medical history
- Submit archived tumor tissue to central pathology laboratory for CD30
- Serology (HBsAg, HBcAb, anti-HCV, EBV)
- Participants who are positive for anti-HCV will need to have HCV PCR done. If the PCR is positive, then the subject is ineligible; if the PCR is negative despite a positive anti-HCV, then the subject is eligible.
- Hemoglobin A1C or fasting glucose
- CT/PET within 28 days prior to C1D1 (Section 7.2)
- Enroll subject in the US into lenalidomide REMS. Subject outside the US must follow their country specific risk minimization programs (GPPP)
- Serum pregnancy tests for participants of childbearing potential
- Two negative β -HCG pregnancy tests must be obtained prior to initiating therapy. The first test must be a serum β -HCG pregnancy test and the second test can either be a serum or urine β -HCG pregnancy test. The first test should be performed within 10 to 14 days and the second test within 24 hours prior to receiving lenalidomide therapy.
- HIV positive participants only: CD4 count

6.3.1. Baseline Visit (Day –7 to Day 1)

- Height and weight
- ECG
- Vital signs, including pulse oximetry and respiratory rate
- Physical examination

- ECOG Performance status ([Appendix B](#))
- Serum chemistry panel (fasting glucose required at baseline only)
- Serum pregnancy tests for participants of childbearing potential
- Two negative β -HCG pregnancy tests must be obtained prior to initiating therapy. The first test must be a serum β -HCG pregnancy test and the second test can either be a serum or urine β -HCG pregnancy test. The first test should be performed within 10 to 14 days and the second test within 24 hours prior to receiving lenalidomide therapy.
- CBC with differential (see Section [7.8.2](#))
- eGFR using the C-G formula

6.4. Treatment Period (Day 1 to Day 21)

6.4.1. Cycle 1 Day 1

- Results from clinical laboratory assessments must be reviewed prior to study drug administration.
- If Baseline Visit activities occur within 1 day prior to Cycle 1 Day 1, the following assessments do not need to be repeated at Cycle 1 Day 1:
 - Weight
 - Physical examination
 - Serum β -HCG pregnancy tests for participants of childbearing potential
 - A serum β -HCG pregnancy test must be administered weekly during the first month, then at least monthly thereafter in females with regular menstrual cycles or every 2 weeks in participants with irregular menstrual cycles.
 - Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected).
- Pregnancy testing will continue according to the schedule of events for participants of child-bearing potential during the LTEP.
 - ECOG performance status ([Appendix B](#))
 - Serum chemistry panel (see Section [7.8.2](#))
 - CBC with differential (see Section [7.8.2](#))
 - ECG
 - eGFR
- PRO assessments (see Section [7.6](#))

6.4.2. Day 1 of Each Cycle

- Vital signs, including pulse oximetry and respiratory rate (obtain prior to treatment)

- Subject outside the US must follow their country specific lenalidomide risk minimization programs (G-PPP)
- Cycles 1-4 only: PK/pharmacodynamic samples
- Serum chemistry panel (see Section 7.8.2)
- CBC with differential (see Section 7.8.2)
- Physical examination
- eGFR
- ECOG performance status
- Cycles 1-4 only: ADA and biomarker samples
- HIV positive participants only: CD4 count prior to each dose of rituximab
- Study treatment; administered after all assessments have been conducted
- Subject training on lenalidomide dosing and compliance. Ensure participants complete dosing diary (participants should complete the dosing diary every day until lenalidomide is permanently discontinued)
- Healthcare Utilization (see Section 7.6.2)

6.4.3. Days 2 to 21 of Each Cycle

- Study treatment administration
- Serum β -HCG pregnancy tests for participants of childbearing potential
 - Participants will be administered a serum β -HCG pregnancy test weekly during the first month, then at least monthly thereafter in females with regular menstrual cycles or every 2 weeks in participants with irregular menstrual cycles.
 - Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected)

6.4.4. Patient-reported Outcomes

Patient-reported outcomes (PROs) assessments (see Section 7.6) should be performed every 2 weeks while on treatment. If these assessments coincide with a study visit, these assessments should be performed first before any other study assessment. If Baseline Visit activities occur on the same day as Cycle 1 Day 1, it is acceptable that the PRO assessment is performed after lab assessment to confirm eligibility.

A legally acceptable representative, if applicable to this study, can assist with completing the PRO assessments.

6.4.5. Disease Response Assessment

Responses will be assessed as follows:

- CT scans of neck, chest, abdomen, and pelvis will be assessed at baseline, then every 6 weeks from randomization until Week 48 (± 7 days), then every 12 weeks (± 7 days) thereafter. A diagnostic quality CT-PET scan should also be performed at the time of suspected clinical progression. Participants who cannot tolerate contrast may have MRI scans instead.
- A PET scan is required at baseline and every 6 weeks from randomization until Week 48 (± 7 days), then every 12 weeks (± 7 days) thereafter. Once the PET is negative per the investigator, no further PET scans are required.
- Scans are encouraged to be performed before treatment during visits.
- Scans should continue until disease progression is documented radiographically, even if therapy had been previously discontinued or a subsequent anticancer therapy had been initiated.

6.5. End of Treatment Visit (30 to 37 Days After Last Dose of Study Drug)

End of treatment (EOT) visits should occur 30 to 37 days after the last dose of the final study drug unless delayed due to an AE. However, EOT evaluations must be performed before initiation of a new therapy. If EOT evaluations are completed before 30 days after the last study treatment, the subject will be contacted 30 to 37 days following the last treatment to assess for AEs.

- Physical examination
- Serum β -HCG pregnancy test for participants of childbearing potential
- CBC with differential (see Section 7.8.2)
- Brentuximab vedotin PK
- Brentuximab vedotin ADA and biomarker samples
- ECOG performance status (Appendix B)
- Serum chemistry panel (see Section 7.8.2)
- eGFR
- CT/PET scans
- For participants unable to tolerate contrast, an MRI scan should be performed.

- If the subject had a scan documenting their response after discontinuing treatment and within 4 weeks preceding EOT then an EOT visit scan is not required.
- Healthcare utilization (see Section 7.6.2)
- PRO assessments (see Section 6.4.4)

6.6. Safety Visit (110 days [+2 weeks] after last dose of rituximab, or 30 to 37 days after last dose of brentuximab vedotin or lenalidomide, whichever is later)

The final safety visit should occur 110 days (+2 weeks) after the last dose of rituximab or 30-37 days post last dose of brentuximab vedotin or lenalidomide (concurrent with the EOT visit), whichever is later. The following assessments will be performed:

- Physical exam
- Serum chemistry panel (Section 7.8.2)
- CBC with differential (Section 7.8.2)
- AEs and serious adverse events (SAEs)
- Record disease status, survival status, and any subsequent anticancer therapies received.

6.7. Follow-up

Participants will be followed every 3 months (± 1 week) after the EOT visit (a phone call or electronic medical record search) for Survival Status and Subsequent Therapies for the first year and then every 6 months (± 2 weeks) thereafter.

- Participants without radiographic disease progression should continue disease assessments in follow-up consistent with the schedule in Section 6.4.5
- Subject contact or in-person assessment of OS and/or disease recurrence, as well as collection of information regarding any additional anticancer therapies administered after completion of study treatment. Review of medical records, public records, or other public platforms may be used to obtain this information if reasonable efforts to contact subject are unsuccessful.
- Participants with AEs of treatment-emergent PN will have follow-up regarding the AE until the following:
 - Improvement back to study entry baseline, or
 - Resolution, or
 - Subject is considered lost to follow-up
- Subsequent therapy

6.8. Long-term Extension Phase (LTEP)

After the final OS analysis, participants still receiving benefit and remaining on treatment may continue receiving study intervention during the LTEP through December 2026. During this phase of the study, only pregnancies and SAEs will be collected by the Sponsor. All other assessments, including efficacy assessments, will be performed per institutional guidelines and investigator-determine usual and customary clinical care. Pregnancy testing will continue as outlined in the schedule of events for participants of child-bearing potential. Participants of child-bearing potential will continue to be counseled by clinical site staff about adequate contraception methods as outlined in Appendix B.

6.9. End of Study/End of Follow-up

Follow-up will continue until the final OS analysis which is expected to occur approximately 18 months after randomization of the last subject.

The study will end when the last LTEP participant has had their last study visit/contact.

The date the participant meets the criteria for study discontinuation and the reason for study discontinuation will be recorded in the medical record.

7. STUDY ASSESSMENTS

7.1. Screening/Baseline Assessments

Only participants who meet all inclusion and exclusion criteria specified in Section 4 will be enrolled in this study.

Physical examinations include assessments of the following body parts/systems: head and neck, cardiovascular and respiratory systems, lymph nodes, abdomen, extremities, skin, and neurological.

Tissue samples will be sent to the central pathology laboratory for evaluation of CD30 expression. The tissue to be submitted should be from the most recent biopsy specimen that demonstrates DLBCL.

Subject medical history includes a thorough review of significant past medical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant medications.

ECOG performance status will be assessed and recorded on the electronic CRF (eCRF).

Laboratory assessment(s) will be performed by local laboratories at scheduled timepoints during the course of the study are detailed in Section 7.8.2.

7.1.1. Prescreening Assessments

Tissue samples may be tested for CD30 expression prior to screening through a CD30 Prescreening program. Participants may provide consent for CD30 testing prior to providing consent for this study.

7.2. Response/Efficacy Assessments

The determination of antitumor activity will be based on response assessments made according to the Lugano Classification Revised Staging System for nodal non-Hodgkin and Hodgkin lymphomas (Cheson et al, 2014). Staging will be performed by PET/CT of diagnostic quality, with disease involvement determined by focal FDG uptake in nodal and extranodal (including spleen, liver, bone marrow, and thyroid) sites that is consistent with lymphoma, according to the pattern of uptake and/or CT characteristics. Up to 6 of the largest nodes, nodal masses, or other involved lesions that are measurable in 2 diameters should be identified as target lesions; if possible, they should be from disparate regions of the body and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved. Participants who have a contraindication to CT IV contrast may have MRI exams performed instead. MRI exams of the brain, neck, abdomen, and pelvis may be performed in lieu of CTs, but MRI exams of the chest are not recommended. In these cases, a non-contrast CT of the chest is strongly recommended to evaluate the thoracic anatomy.

Both PET and CT scanning will be required until site radiologist determines disease is PET negative; responses will then be followed by CT scan of diagnostic quality only. Progressive metabolic disease (PmD), no metabolic response, partial metabolic response, or complete metabolic response will be determined using PET-based response at each assessment after baseline. The PET scan metabolic uptake will be graded using the Deauville 5-point scale (Barrington et al, 2010; Biggi et al, 2013) with a score of ≤ 3 considered to represent a complete metabolic response. In addition to assessing metabolic response by Deauville, an evaluation of new lesions and bone marrow uptake will be included when evaluating PET/CT-based response (Cheson et al, 2014). If only CT-based assessment is performed, response will be categorized as PD, SD, PR, or CR. Evaluation of nonmeasured lesions, organ enlargement and new lesions will be included in the CT-based response assessment (Cheson et al, 2014). PmD/PD includes radiological evidence of progression per Lugano classification criteria. If clinical progression is determined by the investigator, radiographic staging must also be performed to determine response assessment per Lugano classification criteria. See Appendix A for details on scan timing.

Participants' clinical data must be available for CRF source verification. Copies of tumor images must be made available for review by the sponsor (or its designee).

During the LTEP, efficacy assessments will be performed per institutional guidelines and investigator-determined usual and customary clinical care and recorded in the participant's medical record.

7.3. Pharmacokinetic and Immunogenicity Assessments

Concentrations of brentuximab vedotin ADC and MMAE in serum or plasma will be measured at predose and end of infusion (C_{eoi}) in Cycles 1 and 2 and at predose in Cycles 3 and 4 (see Table 6). ADAs to brentuximab vedotin will also be measured predose at Cycles 1 through 4 and at EOT using an appropriate qualified assay.

PK parameters to be reported include concentration at the C_{eoi} and trough concentration (C_{trough}). The incidence of ADA to brentuximab vedotin will also be assessed.

Table 6 presents the PK, immunogenicity sample collection timepoints. All sampling times are relative to the start of brentuximab vedotin infusion, except for end of infusion. Refer to the Research Specimen Manual for information on collection, processing, storage, and shipment of samples.

Table 6. Pharmacokinetic and immunogenicity sampling time points

Cycles	Study Day	Time	Window	Relative Time ^a	PK	ADA
1 and 2	Day 1	Pre-dose	Within prior 24 hr	Start of infusion	X	X
		End of infusion (30 min)	Within 30 min post end of infusion	End of infusion	X	
3 and 4	Day 1	Pre-dose	Within prior 24 hr	Start of infusion	X	X
EOT ^b					X	X

^a Relative to infusion of brentuximab vedotin/placebo.

^b EOT sample not required for subjects entering LTEP.

7.4. Biomarker Studies

Blood samples will also be collected prior to the start of therapy, while on therapy, and at the EOT for the measurement of markers which may include selected cytokines in a multiplex panel, as well as other assays such as ctDNA analysis. The samples will be batched and analyzed at the end of the study, and the specific assays and cytokines to be included will be determined at a later date.

7.4.1. Characterization of Tumor Tissue

The most recent DLBCL biopsy specimen (obtained before Day 1) will be sent to a central laboratory for assessment of biomarkers including, but not limited to CD30 expression by IHC for visual assessment and computer-assisted imaging.

7.5. Biospecimen Repository

In the US only, for participants who provide additional consent, remaining de-identified unused blood and/or tissue will be retained by Pfizer and used for future research, including but not limited to the evaluation of targets for novel therapeutic agents, the biology of ADC sensitivity and resistance mechanisms, and the identification of pharmacodynamic biomarkers of ADCs. Blood and tissue samples donated for future research will be retained for a period of up to 25 years. If additional consent is not provided, any remaining biological samples will be destroyed after the study has been completed and all applicable regulatory obligations have been met.

7.6. Patient-reported Outcomes and Health Economics

7.6.1. Patient-reported Outcomes Analysis

PROs assessments using the EQ-5D-5L and NCCN FACT-Lym questionnaires will be analyzed to determine if response to therapy is accompanied by measurable changes in PROs. The analysis will be performed on summary scores as well as on subscales with specific analytical method to be described in a formal statistical analysis plan (SAP) developed prior to database lock. Investigation of missing data patterns and imputation, if appropriate, will be discussed in the SAP.

7.6.2. Health Economic Analysis Using Healthcare Utilization and Utility

Information derived from EQ-5D-5L and healthcare utilization data will be used for health economic modeling and cost estimates, if appropriate. Healthcare utilization, defined as all medical care encounters related to lymphoma, treatment for lymphoma, or lymphoma-related assessments, will be collected for all participants.

7.7. Long-term Survival Status Follow-up

Lymphoma assessment and imaging will be performed until radiographic disease progression (for participants who discontinued treatment for reasons other than radiographic disease progression). After radiographic disease progression, follow-up contact may be limited to telephone contact. Follow-up data will include survival status, and poststudy treatment for lymphoma and response.

Participants will be followed on this schedule until end of study, as defined in Section 6.9.

7.8. Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of AEs including SAEs, recording of concomitant medication, and measurements of protocol-specified physical examination findings and laboratory tests.

Only pregnancies and SAEs will be collected by the Sponsor during the LTTP. All other assessments, including additional safety assessments, will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue as outlined in the schedule of events for participants of child-bearing potential.

7.8.1. Adverse Events

7.8.1.1. Definitions

Adverse Event

According to the International Council for Harmonisation (ICH) E2A guideline Definitions and Standards for Expedited Reporting, and 21 CFR 312.32, Investigational New Drug (IND) Safety Reporting, an AE is any untoward medical occurrence in a subject or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events and Pre-existing CRF:

- From the time of informed consent through the day prior to study Day 1, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All medical conditions present or ongoing predose on study Day 1 should be recorded.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (during and post-dose) through the end of the safety reporting period (see Section 7.8.1.3). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs whether or not the procedure was protocol mandated.
- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety reporting period should be recorded.
- New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study, should be recorded.
- In general, an abnormal laboratory value should not be recorded as an AE unless it worsens from baseline, is considered clinically significant in the medical and scientific judgement of the investigator, is associated with clinical signs or symptoms, requires an intervention, results in a SAE, or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded (e.g., record “anemia” rather than “low hemoglobin”).
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction should be recorded.
- Signs, symptoms, or the sequelae of a suspected overdose of either study intervention or a concomitant medication should be recorded. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

The following events DO NOT meet the AE definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.

- Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day to day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Serious Adverse Events

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death
Life threatening:	The AEs placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE resulted in hospitalization or prolonged an existing in subject hospitalization. In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs. Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
Disabling/incapacitating:	An AE that resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria but could have jeopardized the subject and might have required medical or surgical intervention to prevent 1 of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent. Potential drug-induced liver injury (DILI) also is considered a medically significant event (see Section 7.8.1.2 for the definition of potential DILI.)

Adverse Event Severity

AE severity should be graded using the NCI CTCAE version 5.0. These criteria are provided in the study manual.

AE severity and seriousness are assessed independently. ‘Severity’ characterizes the intensity of an AE. ‘Serious’ is a regulatory definition and serves as a guide to the sponsor for defining regulatory reporting obligations (see definition for SAEs, above).

Relationship of the Adverse Event to Study Treatment

As this is a double-blind study, the investigator will provide the relationship assessment to each study treatment. If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as “related to study intervention” for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the PSSA and in accordance with the SAE reporting requirements.

The relationship of each AE to each study treatment (brentuximab vedotin + lenalidomide + rituximab, or placebo + lenalidomide + rituximab) should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: • A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) • One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
Unrelated:	Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment, or a causal relationship is considered biologically implausible

Outcome Assessment

Record the appropriate outcome of the event in relation to the participant’s status:

- **Fatal:** The termination of life as a result of an AE.
- **Not Recovered/Not Resolved:** One of the possible results of an adverse event AE outcome that indicates that the event has not improved or recuperated.
- **Recovered/Resolved:** One of the possible results of an AE outcome that indicates that the event has improved or recuperated.
- **Recovered/Resolved with Sequelae:** One of the possible results of an AE outcome where the participant recuperated but retained pathological conditions resulting from the prior disease or injury.

- Recovering/Resolving: One of the possible results of an AE outcome that indicates that the event is improving.
- Unknown: Not known, not observed, not recorded, or refused.

7.8.1.2. Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during subject questioning, discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

During the LTEP, only pregnancies and SAEs will be reported to the sponsor using the PSSA and will not be recorded within the CRF.

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the Adverse Events CRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Diagnosis versus Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate AE.

Important exceptions for this study are adverse reactions associated with the infusion of study drug. Record each sign or symptom as an individual AE in addition to the IRR term. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its level of severity.

Recording Serious Adverse Events

For SAEs, record the event(s) on the CRF and report the SAE to Pfizer Safety using PSSA.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.
- During the LTEP, SAEs will be reported to the Sponsor using the PSSA and will not be recorded within the CRF, following the same reporting guidelines as outlined in this section.

Progression of the Underlying Malignancy

Since progression of underlying malignancy is being assessed as an efficacy variable, it should not be reported as an AE or SAE. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. The terms “Disease Progression”, “Progression of Disease”, or “Malignant disease progression” and other similar terms should not be used to describe an AE or SAE. However, clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. In addition, complications from progression of the underlying malignancy should be recorded as AEs or SAEs in the CRF (CRF entry not applicable once participants enter LTEP).

Lack of Efficacy

Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an SAE if they fulfil the definition of an SAE. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

Exposure During Pregnancy

An EDP occurs if:

- A participant is found to be pregnant while receiving or after discontinuing study intervention.
- A participant who is receiving or has discontinued study intervention inseminates a partner.
- A nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
 - A family member or healthcare provider reports that they are pregnant after exposure to study intervention, for example, by ingestion, inhalation, or skin contact.
 - A family member or healthcare provider who has been exposed to the study intervention, for example, by ingestion, inhalation, or skin contact and then inseminates their partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner after the start of study intervention and until 12 months after the last dose of the last study intervention, the investigator must report this information to Pfizer Safety on the PSSA regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 12 months after the last dose of the last study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety via PSSA. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed PSSA is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE.
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to their partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to their partner.

Exposure during Breastfeeding

An EDB occurs if:

- A participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (i.e., environmental exposure). An example of environmental EDB is a family member or healthcare provider who reports breastfeeding after having been exposed to study intervention by, for example, ingestion, inhalation, or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the PSSA. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed PSSA is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accordance with authorized use. However, if the Infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the PSSA regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed PSSA must be maintained in the investigator site file.

Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the AE Page of the CRF	Reported via PSSA to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the CRF (CRF entry not applicable once participants enter LTEP).

In the event of a medication dosing error, the sponsor should be notified within 24 hours. Medication errors should be reported to Pfizer Safety within 24 hours via PSSA **only when associated with an SAE**.

Potential Drug-induced Liver Injury

Hy's Law can be used to estimate severity and the likelihood that a study drug may cause an increased incidence of severe hepatotoxicity.

The absence of hepatotoxicity in clinical trials provides a limited predictive value for DILI in the clinical setting(s) being studied. However, finding 1 Hy's Law case in clinical trials is ominous; finding 2 cases is highly predictive of a potential for severe DILI.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values.

Participants with AST/ALT and T bili baseline values within the normal range and who subsequently present with:

1. Aminotransferase (ALT and/or AST) elevation ≥ 3 x ULN

AND

2. Total bilirubin ≥ 2 x ULN, with no evidence of hemolysis and an alkaline phosphate value < 2 x ULN or not available

AND

3. No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

For participants with baseline AST OR ALT OR T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

- Pre-existing AST or ALT baseline values above the normal range: AST or ALT values ≥ 2 times the baseline values AND ≥ 3 x ULN; or ≥ 8 x ULN (whichever is smaller).
- Pre-existing values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥ 1 x ULN or if the value reaches ≥ 3 x ULN (whichever is smaller).

All participants presenting with abnormal laboratory tests as outlined above and/or suspicious of DILI, must be discussed with the medical monitor.

Reporting Requirements

Any potential Hy's Law case should be handled as a serious adverse event (SAE) and reported promptly to the Sponsor.

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

Reporting should include all available information and should initiate close follow-up until complete resolution of the problem and completion of all attempts to obtain supplementary data.

Follow-up for Abnormal Laboratory Results Suggesting Potential DILI

In general, an increase of serum ALT or AST to $>3 \times$ ULN should be followed by repeat testing within 48 to 72 hours of serum ALT, AST, alkaline phosphatase, and total bilirubin, to confirm the abnormalities and to determine whether they are worsening.

Appropriate medical assessment should be initiated to investigate potential confounding factors and alternative causes of hepatotoxicity. During this investigation, consider withholding study drug.

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, eosinophils (%), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over the counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

7.8.1.3. Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Day 1 (predose) through 110 days after the last dose of rituximab or 30 days after the last dose of brentuximab vedotin or lenalidomide, whichever is later. However, all study protocol-related AEs are to be recorded from the time of informed consent. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has concluded study participation, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using PSSA.

SAEs will be followed until significant changes return to baseline, the event stabilizes (recovering/resolving) or is no longer considered clinically significant by the investigator, or the subject dies or withdraws consent. All non-serious AEs will be followed through the safety reporting period. Certain non-serious AEs of interest may be followed until resolution, return to baseline, or study closure.

If a participant begins a new anticancer therapy, SAEs occurring during the safety reporting period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note

that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for purposes of SAE reporting. If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started.

7.8.1.4. Serious Adverse Events Require Immediate Reporting

All SAEs occurring in a participant during the safety reporting period are reported to Pfizer Safety on the PSSA immediately upon awareness and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

For initial SAE reports, available case details are to be recorded on an SAE form. At a minimum, the following should be included:

- Subject number
- Date of event onset
- Description of the event
- Study treatment, if known
- Investigator causality assessment

It is not acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Report Form/AE or SAE CRF page. There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

SAE Reporting to Pfizer Safety via an Electronic DCT

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (PSSA).
- If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic DCT (PSSA) or paper form (as applicable) as soon as the data become available.
- After the study is completed at a given site, the electronic DCT will be taken off line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off line, then the

site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the backup method to transmit this information to Pfizer Safety in case PSSA is unavailable for more than 24 hours.
- In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.

Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

7.8.1.5. Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs to the sponsor (see Section 7.8.1.4). The sponsor will report all SAEs, including suspected unexpected serious adverse reactions to regulatory authorities as required per local legislation or regulatory reporting requirements. An investigator who receives SUSARs or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

7.8.2. Clinical Laboratory Tests

Local laboratory testing will include institutional standard tests for evaluating safety and making clinical decisions. The following laboratory assessment(s) will be performed by local laboratories at scheduled timepoints (see Appendix A) during the course of the study and the results (no blood) will be sent to ICON iRIS:

- The serum chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, eGFR, chloride, glucose, LDH, phosphorus, potassium, sodium, total bilirubin, amylase, lipase, thyroid stimulating hormone (TSH) with reflex to free T4, and uric acid.
- The CBC with differential is to include the following tests: white blood cell count with 5-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), platelet count, hemoglobin, and hematocrit.
- The eGFR should be calculated using the CG formula as applicable, with Scr reported in mg/dL.

$$\text{GFR (mL/min)} = ([140 - \text{age}] \times \text{weight [kg]} \times 0.85 [\text{if female}]) / (\text{Scr} \times 72)$$

- A serum β -HCG pregnancy test for participants of childbearing potential with sensitivity of at least 25 mIU/mL.

- During LTEP, pregnancy testing will continue for subjects of child-bearing potential receiving lenalidomide, at least monthly in participants with regular menstrual cycles or every 2 weeks in participants with irregular menstrual cycles and according to Section 6.4.1. During the LTEP, pregnancy reporting should continue and will be collected by the Sponsor using the PSSA. See Section 7.8.1.1. for further details on pregnancy reporting requirements.

Following the final OS analysis, local laboratory testing, with the exception of pregnancy testing, will be performed per institutional guidelines and investigator-determined usual and customary clinical care.

7.8.3. Physical Examination

Physical examinations should include assessments of the following body parts/systems: abdomen, extremities, head, heart, lungs, neck, and neurological. Measurements of height obtained within the prior 12 months may be utilized.

7.8.4. Additional Monitoring for HIV-Positive Participants

Monitoring and management of HIV viral load should be performed according to institutional standard of care. At a minimum, CD4+ counts will be assessed in HIV-positive participants at screening and prior to each dose of rituximab. Rituximab should be permanently discontinued in HIV-positive participants who have CD4 counts ≤ 100 cells/mm³. Such participants may continue to receive brentuximab vedotin and lenalidomide until development of unacceptable toxicity or disease progression, irrespective of the CD4 count.

7.9. Appropriateness of Measurements

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications.

Response will be assessed by the investigator according to Lugano Criteria for Response Assessment (Cheson et al, 2014) which are standardized criteria for evaluating response in DLBCL. The intervals of evaluation in this protocol are considered appropriate for disease management.

Immunogenicity is commonly assessed for biologics; therefore, standard tests will be performed to detect the possible presence of specific antibodies to brentuximab vedotin. PK assessments are also common in clinical studies to help characterize dose-exposure-response relationships.

8. DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1. Site Training and Monitoring Procedures

A study manual with instructions for study compliance and CRF completion will be provided. Prior to the enrollment of participants at the site, Pfizer or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current IB/package insert
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- Institutional review board/independent ethics committee (IRB/IEC) review and approval process
- Informed consent process
- Good clinical practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing and record keeping
- Subject coding and randomization (if applicable)
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Pfizer representative will typically review regulatory documentation, CRFs, source documentation, and investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study participants, and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is

suitable for inspection by Pfizer or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

Following the final OS analysis and entry of remaining on-treatment participants into the LTEP, data will no longer be collected in CRFs. Only pregnancies and SAEs will be collected by the sponsor during the LTEP using the PSSA. See Section 7.8.1.1 for further details on pregnancy and SAE reporting requirements.

8.2. Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- CRFs will be reviewed for accuracy and completeness during monitoring visits to the study centers and/or by centralized monitoring. Any discrepancies will be resolved with the investigator or designees as appropriate.
- During the LTEP, CRFs will not be collected.

9. DATA ANALYSIS METHODS

9.1. Determination of Sample Size

Approximately 225 participants will be enrolled in order to provide sufficient power to compare OS between the treatment arms. The null hypothesis of no difference in OS between the experimental and control arms will be tested in the ITT population at a 2-sided alpha of 0.05 using a stratified log-rank test. Assuming median OS of 9 months in the control arm and a hazard ratio (HR) of 0.62, the median OS for the experimental arm is approximately 14.5 months under the exponential model assumption.

The final analysis of OS will be performed after approximately 170 OS events have occurred. An interim analysis of OS for both efficacy and futility will be performed at approximately 128 OS events (0.75 information fraction). A non-binding futility criteria of $HR > 1.1$ will be used at the interim analysis. Efficacy boundaries at the interim and final OS analysis will be determined using an alpha spending approach with an O'Brien-Fleming boundary in order to maintain type I error control at a 2-sided alpha level of 0.05. Example boundaries for each analysis are presented in Table 7 below. Boundaries at the interim and final analysis will be revised to reflect the actual information available as well as any previous alpha spending.

Table 7. Projected OS Efficacy and Futility Boundaries

Analysis	Planned OS Events	Futility Boundary (HR)	Efficacy Boundary P-value (HR)*
Interim	128	1.1	0.0196 (0.662)
Final	170		0.0442 (0.734)

* 2-sided p-value. HR based on planned OS events at analysis

Under the assumptions above there is approximately 87% power to reject the null hypothesis of no difference in OS in the ITT population. Assuming a 10% risk of drop out from OS follow-up over 12 months, 225 participants are expected to allow for accumulation of approximately 170 OS events within approximately 18 months of the last subject randomized.

The key secondary endpoints of PFS and ORR will be tested per Lugano 2014 by investigator in the ITT population sequentially using a fixed sequence approach if the null hypothesis associated with the primary endpoint is rejected. In order to provide strong control of the familywise error rate an alpha spending approach with a Pocock boundary will be used for hypothesis testing for PFS and testing of ORR will be based on the first interim analysis. Details of hypothesis testing and multiplicity are presented in Section 9.3.1.5 and the SAP.

Approximately 155 PFS are expected to have occurred at the time of the interim analysis and 170 events are expected at the time of the final analysis. Assuming a HR of 0.62 and applying an alpha spending approach at a 2-sided alpha of 0.05 with a Pocock boundary there is approximately 86% power to reject the null hypothesis of no difference in PFS between the treatment arms.

Assuming an ORR of 30% for the control arm and 50% for the experimental arm (equivalent to a common odds ratio of approximately 2.35) and a 2-sided alpha of 0.05 there is approximately 87% power to reject the null hypothesis of no difference in ORR between the treatment arms.

See Section 9.3.1.5 for details on multiple testing and Section 9.3.1.9 for details on the timing of the analyses.

9.2. Study Endpoint Definitions

9.2.1. Primary Endpoint: Overall Survival (OS)

OS is defined as the time from the date of randomization to date of death due to any cause; specifically, $OS = \text{Date of death} - \text{Date of randomization} + 1$.

Participants that have not died will be censored at the last date the subject is known to be alive (ie, date of last contact). Participants lacking data beyond the date of randomization will have their survival time censored on the date of randomization.

Detailed methodology, including sensitivity analysis of OS, will be described in the SAP.

9.2.2. Key Secondary Endpoints

9.2.2.1. Progression-free Survival (PFS) per Lugano 2014 by Investigator

PFS is defined as the time from the date of randomization to the date of first documentation of PD or death due to any cause, whichever occurs first. Assessment of PD will be performed by the investigator based on the Lugano Criteria for Response Assessment ([Cheson et al, 2014](#)).

If PD is not documented and the subject is alive at the time of the data cutoff or has withdrawn from the study, PFS will be censored at the date of the most recent tumor assessment. Additional censoring rules include:

- If there is no radiographic postbaseline tumor assessment, PFS will be censored at the date of randomization.
- If a PFS event occurs immediately after missing 2 or more consecutive scheduled tumor assessments PFS will be censored at the most recent evaluable tumor assessment prior to the first of the consecutively missed assessments.
- If a subject has initiated new anticancer therapy subsequent to study treatment and prior to experiencing a PFS event they will be censored at the most recent evaluable tumor assessment prior to the initiation of new anticancer therapy.

Detailed methodology, including additional sensitivity analyses for the analysis of PFS, is provided in the SAP. Sensitivity analyses of PFS may include PFS by blinded independent central review (BICR) assessment.

9.2.2.2. Objective Response Rate (ORR) per Lugano 2014 by Investigator

ORR is defined as the proportion of participants with best response of CR or PR according to investigator assessment per the Lugano Criteria for Response Assessment ([Cheson et al, 2014](#)). Only responses occurring prior to documentation of PD or initiation of new anticancer therapy will be considered in the derivation of best response. Participants whose disease response cannot be assessed will be counted as non-responders for calculating the ORR. Sensitivity analyses of ORR based on BICR assessment may also be performed.

9.2.3. Other Secondary Endpoints

9.2.3.1. Complete Response (CR) Rate per Lugano 2014 by Investigator

CR rate is defined as the proportion of participants with best response of CR according to investigator assessment per the Lugano Criteria for Response Assessment ([Cheson et al, 2014](#)). Only responses occurring prior to documentation of PD or initiation of new anticancer therapy will be considered in the derivation of best response. Participants whose disease response cannot be assessed will be counted as non-responders for calculating the CR rate. Sensitivity analyses of CR rate based on BICR assessment may also be performed.

9.2.3.2. Duration of Response (DOR) per Lugano 2014 by Investigator

DOR is defined as the time from start of the first documentation of objective tumor response (CR or PR) to the first documentation of tumor progression by investigator assessment per the Lugano Criteria for Response Assessment (Cheson et al, 2014) or death due to any cause, whichever occurs first. If PD is not documented and the subject is alive at the time of the data cutoff or has-withdrawn from the study, DOR will be censored at the date of the most recent tumor assessment. Additional censoring rules for duration of response will be similar to those specified for PFS. DOR will only be calculated for participants achieving a CR or PR. Sensitivity analyses of DOR based on BICR assessment may also be performed.

9.3. Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the SAP. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment. The SAP will be finalized prior to database lock for the interim analysis of OS.

9.3.1. General Considerations

Tabular summaries and analyses will be presented by treatment arm unless otherwise specified. Participants enrolled in the open label safety run-in will be summarized separately unless otherwise specified.

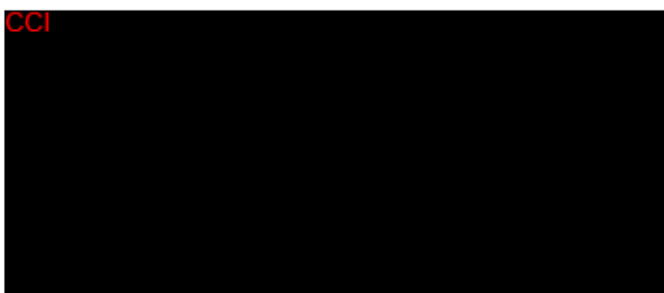
9.3.1.1. Randomization and Blinding

This is a randomized, double-blind, placebo-controlled, active-comparator, multicenter phase 3 study designed to evaluate the efficacy of brentuximab vedotin or placebo in combination with lenalidomide and rituximab for the treatment of participants with relapsed or refractory DLBCL. The study will enroll approximately 225 participants and participants will be randomized in a 1:1 manner to either of the treatment arms.

The randomized portion of the study described above was preceded by an unblinded, nonrandomized safety run-in.

The sponsor's study team will be blinded at the study level to aggregate efficacy data according to a prespecified blinding procedure until the blind is broken.

Randomization will be stratified by:



Randomization will be performed centrally using a system that will assign a unique subject randomization number but will not specify the actual treatment assignment.

9.3.1.2. Adjustments for Covariates

Stratified analyses will include adjustment for the stratification factors as recorded at randomization (described in Section 9.3.1.1). Strata levels may be combined for stratified analyses if too few participants are included in certain strata levels; details for combining strata will be provided in the SAP. Covariates may be considered for adjustment in exploratory analyses.

9.3.1.3. Handling of Dropouts and Missing Data

Missing data generally will not be imputed, with the exception of AE start dates for calculating duration of events. Participants with missing values of a variable other than the timeto-event endpoints (eg, PFS and OS) will be excluded from the analysis of that endpoint unless otherwise specified. Censoring rules will be applied to the estimation of the distribution of the timetoevent endpoints.

9.3.1.4. Multicenter Studies

There are multiple centers in this study, however it is not anticipated that any center will accrue enough participants to warrant an analysis by center. Accordingly, no analysis by center is planned.

9.3.1.5. Multiple Comparisons and Multiplicity

Multiple hypothesis tests will be performed in this study to compare the treatment arms for the following endpoints and populations:

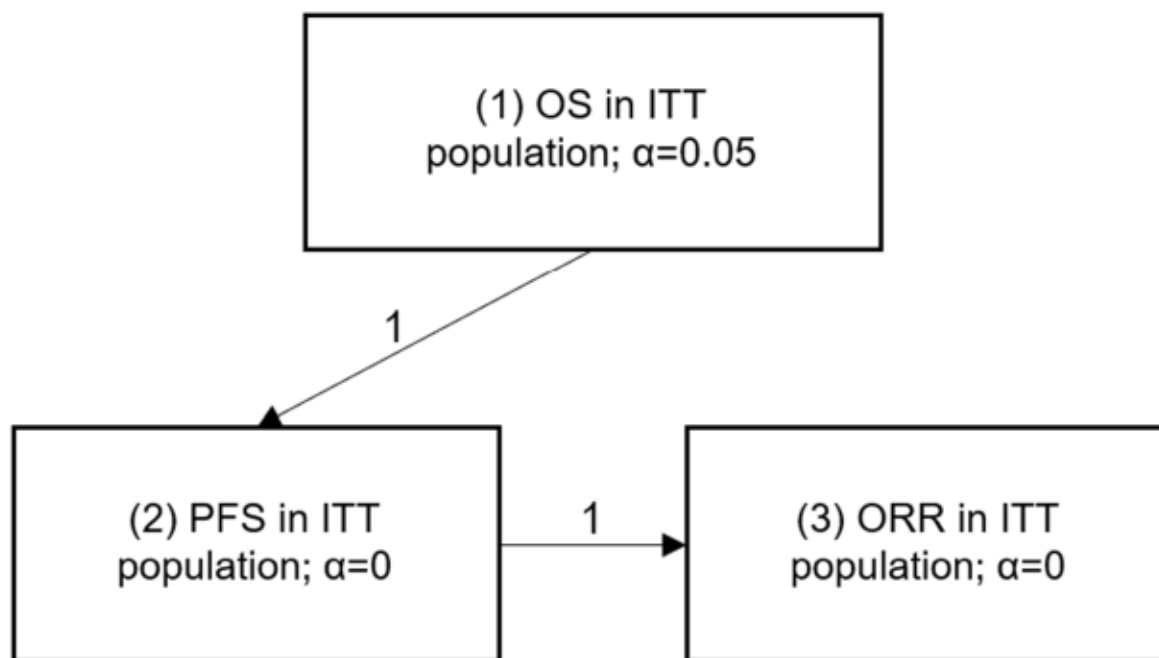
- OS in the ITT population
- PFS per Lugano 2014 by investigator in the ITT population
- ORR per Lugano 2014 by investigator in the ITT population

A graphical approach (Bretz et al, 2009) is used to represent initial alpha allocation to hypothesis testing for each endpoint, with arrows connecting endpoints to indicate reallocation of initial alpha allocation when hypotheses are rejected. Since an interim and final analysis is planned the following additional considerations will be applied to hypothesis testing to control the overall type I error rate at the 2-sided alpha level of 0.05:

- OS will be tested using an alpha spending approach with an O'Brien-Fleming boundary
- PFS will be tested at the time OS is statistically significant using an alpha spending approach with a Pocock boundary
- ORR will be tested based on the results at the interim analysis of OS

The graphical representation of the testing strategy is presented in Figure 2 and further details are described below; additional details will be included in the SAP.

Figure 2: Graphical representation of hypothesis testing in study C5691003/SGN35-031



- (1) Test OS in the ITT population at initial alpha allocation 0.05.
- (2) Test PFS in the ITT population when OS is significant.
- (3) Test ORR in the ITT population when PFS is significant.

1. Test OS in the ITT population based on a stratified log-rank test at a 2-sided alpha level 0.05. Type I error is controlled using a group sequential alpha spending approach with an O'Brien-Fleming efficacy boundary. A non-binding futility criteria for OS of HR >1.1 will also be used at the interim analysis.
 - a. Perform the interim analysis at approximately 128 events (0.75 information fraction). If the O'Brien-Fleming null hypothesis of no difference in OS between the treatment arms is rejected then proceed to test PFS in step 2; the final OS analysis will be descriptive. If the null hypothesis is not rejected and the study is not stopped due to futility then proceed to the final analysis of OS.
 - b. Perform the final analysis of OS at approximately 170 events. If the null hypothesis of no difference in OS between the treatment arms is rejected then proceed to test PFS in step 2.

2. Test PFS per Lugano 2014 by investigator in the ITT population based on a stratified log-rank test. Type I error is controlled using a group sequential alpha spending approach with a Pocock boundary based on a total planned event count of 170.
 - a. Test the null hypothesis of no difference in PFS between the treatment arms. If the null hypothesis of no difference in PFS between the treatment arms is rejected then proceed to test ORR in step 3.
3. Test ORR per Lugano 2014 by investigator in the ITT population based on the Cochran-Mantel-Haenszel test. In order to control the familywise error rate the hypothesis test is performed using the data cutoff from the interim analysis of OS. No further hypothesis testing is performed after this step.

Analyses not described in this section will be considered descriptive and no hypothesis testing will be performed; any corresponding nominal p-values may be presented for descriptive purposes only.

9.3.1.6. Data Transformations and Derivations

Time variables based on 2 dates (eg, start date and end date) will be calculated as (end date – start date + 1 [in days]).

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

9.3.1.7. Analysis Sets

ITT analysis set: the ITT analysis set will include all randomized participants. Participants will be included in the treatment arm assigned at randomization regardless of the actual treatment received. The analysis of the primary and key secondary efficacy endpoints will be based on the ITT analysis set.

Safety analysis set: the safety analysis set will include all participants who were randomized and received any amount of study drug (brentuximab vedotin, lenalidomide, or rituximab). Treatment arms will be determined using the actual treatment received, regardless of the randomization treatment assignment. Participants receiving any dose of brentuximab vedotin will be grouped into the experimental group. Participants who do not receive brentuximab vedotin but receive any dose of lenalidomide or rituximab will be grouped into the control group.

Safety run-in analysis set: the safety run-in analysis set will include all participants who were enrolled and received any amount of study drug (BV, lenalidomide, or rituximab) in the safety run-in part of the study.

Additional analysis sets may be defined in the SAP.

9.3.1.8. Examination of Populations

Analyses of the CD30-positive population will be performed for the OS endpoint. Additional exploratory analyses (e.g., subgroup analyses based on CD30 expression status) may be conducted for selected endpoints. Detailed methodology will be provided in the SAP.

9.3.1.9. Timing of Analyses

The interim analysis of OS will be performed when approximately 128 OS events have occurred (0.75 information fraction). It is expected that 128 OS events will occur approximately 3 months after randomization of the last subject. The final analysis of OS will be performed after approximately 170 OS events have occurred. It is expected that 170 OS events will occur approximately 18 months from randomization of the last subject.

If the interim analysis of OS is statistically significant then other analyses will be performed at that time, including hypothesis testing of the key secondary endpoints. Other analyses will also be performed at the time of the final analysis of OS.

The estimated duration of the study is approximately 4 years from the randomization of the first subject (including approximately 2.5 years of enrollment and an approximate additional 18 months of follow-up to reach the final analysis of OS).

9.3.2. Subject Disposition

An accounting of subject disposition will be tabulated by treatment arm. The number of participants in each analysis population will be summarized by treatment arm. Participants who discontinue study treatment and participants who withdraw from the study will be summarized by treatment and reason for discontinuation or withdrawal and listed.

9.3.3. Subject Characteristics

Demographics, other baseline characteristics, and concomitant medications will be summarized by treatment arm and listed. Details will be provided in the SAP.

9.3.4. Treatment Compliance

The dose administered at each cycle for each treatment agent will be summarized. Dose intensity will also be summarized. Details will be provided in the SAP.

9.3.5. Efficacy Analyses

9.3.5.1. Primary Efficacy Analysis

Kaplan-Meier methods will be used to estimate OS. The stratified log-rank test will be used in the primary evaluation of OS differences between the experimental arm and the control arm. The primary endpoint of OS will be tested in the ITT population at a 2-sided alpha of 0.05. All events entered in the database by the time of data cutoff will be included in the analysis of OS, even if there are more than the prespecified number of events.

An interim and final analysis of OS are planned. The interim analysis of OS will initially be performed by an IDMC; the sponsor will perform the analysis of OS if the IDMC

recommends the sponsor should be unblinded based on meeting the pre-specified criteria for efficacy or futility. If the study is not unblinded at the interim analysis then the sponsor will not perform the analysis of OS until the final analysis. Details of the IDMC role in the interim analysis are specified in the IDMC charter.

Kaplan-Meier curves depicting OS in the 2 arms will be generated, with median OS reported by treatment arm. The 2-sided 95% confidence intervals (CI) for the median will be calculated using the complementary log-log transformation method (Collett, 1994). OS rates and 95% CIs will be presented by time from randomization. Detailed methodology is provided in the SAP.

9.3.5.2. Secondary Efficacy Analyses

PFS per Lugano 2014 by investigator will be analyzed using Kaplan-Meier methodology and Kaplan-Meier plots will be provided by treatment arm using the ITT analysis set. Hypothesis testing of PFS will be performed according to Section 9.3.1.5. The median PFS and its 2-sided 95% CI using the complementary log-log transformation method (Collett 1994) will be calculated by treatment arm.

ORR per Lugano 2014 will be summarized by treatment arm using the ITT analysis set. The difference in ORR as well as the common odds ratio will be presented with the corresponding 95% CIs. Hypothesis testing of ORR will be performed according to Section 9.3.1.5. ORR for each arm will also be presented with the exact 95% CI using the Clopper-Pearson method. Similar summaries will be presented for CR rate per Lugano 2014 by investigator.

DOR per Lugano 2014 will be analyzed using methodology similar to OS and PFS for participants achieving a CR or PR in the ITT Population.

An analysis of OS in the CD30-positive population will also be performed. Methods will be similar to the analysis of OS in the ITT population.

9.3.6. Pharmacokinetic and Immunogenicity Analyses

CCI

9.3.7. Biomarker Analyses

CCI

9.3.8. Patient-reported Outcomes Analyses

CCI

9.3.9. Safety Analyses

9.3.9.1. Extent of Exposure

Duration of treatment, number of cycles, total dose and dose intensity will be summarized by treatment arm using the safety analysis set. Dose modifications will also be summarized.

Details will be provided in the SAP.

9.3.9.2. Adverse Events

An overview of AEs will provide a tabulation of the incidence of all treatment emergent AEs, treatment-related AEs, Grade 3 and higher AEs, SAEs, treatment-related SAEs, deaths, and AEs leading to study treatment discontinuation. AEs will be defined as treatment emergent if they are newly occurring or worsen following study treatment. AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be listed and summarized by MedDRA preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in 1 subject, the AE will be counted once. The incidence of AEs will be tabulated by preferred term and treatment arm. AEs leading to study treatment discontinuation will be summarized and listed in the same manner.

9.3.9.3. Deaths and Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

9.3.9.4. Clinical Laboratory Results

For laboratory results, summary statistics for actual values and for change from baseline may be tabulated as appropriate by treatment arm and scheduled visit. Laboratory values will be listed by treatment arm with grade per NCI CTCAE version 5.0 and flagged when values are outside the normal reference range.

9.3.10. Interim Analyses

An interim analysis of OS is planned after approximately 128 OS (ie, 0.75 information fraction) events have occurred. If the study is unblinded based on the results of the OS interim analysis additional analyses, including specified hypothesis of the key secondary endpoints, will be performed. Details of the interim analysis are discussed in relevant sections of this protocol and will be further specified in the SAP.

9.3.11. Safety Monitoring Committee

The SMC evaluated the safety data from the run-in period. The SMC is composed of the study medical monitor, study biostatistician, drug safety representative, and study site investigators.

9.3.12. Independent Monitoring Committee

An Independent Data Monitoring Committee (IDMC) consisting of independent expert physicians and biostatisticians will periodically monitor the trial for safety and will review expedited SAEs as they arise. The IDMC will also oversee the interim analysis of OS and provide a recommendation to the sponsor whether the efficacy or futility criteria have been met at the time of the interim analysis. The IDMC conduct of ongoing safety reviews and the interim analysis of OS will be described in the IDMC Charter.

10. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations

10.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP that the investigator becomes aware of.

10.2. Financial Disclosures

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant or their legally authorized representative and answer all questions regarding the study. The investigator may not delegate obtaining consent to a local healthcare professional. The participant or their legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (if allowed by local regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH GCP guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or their legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant or their legally authorized representative must be informed that their personal study related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant or their legally authorized representative.

The participant or their legally authorized representative must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or their legally authorized representative is fully informed about his or her right to access and correct their personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants or their legally authorized representative must be reconsented to the most current IRB/EC version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant or their legally authorized representative (if allowed by local regulations).

Participants who are rescreened are required to sign a new ICD.

10.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant specific numerical code. Any participant records or datasets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.5. Committees Structure

10.5.1. Independent Data Monitoring Committee (IDMC)

Please see Section 9.3.12 for information on the independent data monitoring committee.

This study will use an IDMC. The IDMC is independent of the Pfizer study team and includes only external members. The IDMC charter describes the role of the IDMC in more detail.

The IDMC will be responsible for ongoing monitoring of the efficacy and safety of participants in the study according to the charter. The recommendations made by the IDMC will be forwarded to the appropriate authorized Pfizer personnel for review and final decision. Pfizer will communicate such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data, to regulatory authorities and investigators, as appropriate.

10.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer sponsored interventional studies in accordance with the format and timelines set forth by EU requirements following the end of the study globally.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant level data or full CSRs for the purposes of “bona fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or onsite monitoring), are provided in the Data Management Plan and clinical monitoring plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data. Records and documents, including signed ICDs, pertaining to

the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.8. Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source document and its origin can be found in Source Document Locator, which is maintained by the Sponsor.

Description of the use of computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source record) that supports the information entered in the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH GCP guidelines, and all applicable regulatory requirements.

10.9. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be reidentified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), and participant contact information (eg, telephone/fax number, email address).
- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).
- There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.10. Study and Site Start and Closure

The study start date is the date of the first participants first visit.

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

If the sponsor decides to terminate the study for a reason unrelated to the safety of brentuximab vedotin, lenalidomide, or rituximab, participants may continue to receive study intervention(s) per the investigator's judgment and protocol-specified safety assessments will continue to be performed for these participants until the end of the study as defined in Section 6.9.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.11. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study intervention or Pfizer related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. When applicable, editorial or technical support provided by a third party and paid for by Pfizer, or provided by a Pfizer employee, may be a reportable transfer of value under the Sunshine Act for US

licensed physicians or other healthcare professionals. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication. The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

10.12. Sponsor's Medically Qualified Individual

The sponsor will designate a medically qualified individual (MQI, also known as the medical monitor) to advise the investigator on study-related medical questions. The contact information for the study medical monitor is documented in the Study Team Contact List located in the Investigator Site File or equivalent.

Participants are provided with a Pfizer study information card at the time of informed consent, which includes contact information for their investigator in case of study-related medical questions. The study information card contains, at a minimum, (a) study number, (b) participant's study identification number, and (c) principal investigator contact information.

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APPENDIX A: SCHEDULE OF EVENTS

The SoE table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoE table, in order to conduct evaluations or assessments required to protect the well being of the participant.

		Prescreening	Screening/Baseline		Day of 21-Day Combination Treatment Cycle			EOT visit	Safety follow-up visit	Long-term F/U				LTEP
										Months after EOT visit				
										3	6	9	≥12	
Day		Prior to D-28	D -28 to 1	D -7 to 1	D1 ^a	D2 to 21	Between D15 to 21	30-37 days post last dose ^d	110 days [+2 weeks] after last dose of rituximab, or 30-37 days after last dose of brentuximab vedotin or lenalidomide, whichever is later	±1 week			Every 6 months ±2 weeks	
Visit Window					-2 d ^j									
	CD30 Prescreening consent ^f	X												
Screening/Baseline Assessments	Informed consent		X											
	Inclusion/exclusion		X											
	Enrollment in Randomization and Trial Supply Management			X ^e										
	Medical history		X											
	Physical exam			X	X			X	X					X ^o
	Tumor Biopsy for Central lab ^a		X											
	HgbA1c or fasting glucose		X											
	Height			X										
	Weight			X	X									X ^o
	Electrocardiogram ^g			X										
	Vital signs (including pulse oximetry and respiratory rate)			X	X									X ^o

		Prescreening	Screening/Baseline		Day of 21-Day Combination Treatment Cycle			EOT visit	Safety follow-up visit	Long-term F/U				LTEP
										Months after EOT visit				
										3	6	9	≥12	
Day		Prior to D-28	D-28 to 1	D-7 to 1	D1 ^a	D2 to 21	Between D15 to 21	30-37 days post last dose ^d	110 days [+2 weeks] after last dose of rituximab, or 30-37 days after last dose of brentuximab vedotin or lenalidomide, whichever is later	±1 week			Every 6 months ±2 weeks	
Visit Window					-2 d ^j									
	Serology (HBsAg, HBcAb, anti-HCV, ^k and EBV)		X											
	Pregnancy test by serum β-HCG ^b		X	X	X	X	X	X						X
	ECOG performance status			X	X			X						X ^o
	Lenalidomide REMS/risk minimization programs (G-PPP)		X		X									X
Treatment	Study treatment administration – brentuximab vedotin or placebo				X									X
	Study treatment administration – lenalidomide				X	X								X
	Study treatment administration – rituximab				X									X
ADA/PK	Samples for ADA/PK				See Table 6									
Biomarkers	Samples for biomarkers				Collections same as ADA timepoints (see Table 6)									
Response Assessment	CT ^c (neck, chest, abdomen, pelvis) PET ^c (Whole body) Lugano 2014 Response Assessment		X		See Section 6.4.5 for details.									X ^o
	Disease status								X					X ^o

		Prescreening	Screening/Baseline		Day of 21-Day Combination Treatment Cycle			EOT visit	Safety follow-up visit	Long-term F/U				LTEP
										Months after EOT visit				
										3	6	9	≥12	
Day		Prior to D-28	D -28 to 1	D -7 to 1	D1 ^a	D2 to 21	Between D15 to 21	30-37 days post last dose ^d	110 days [+2 weeks] after last dose of rituximab, or 30-37 days after last dose of brentuximab vedotin or lenalidomide, whichever is later	±1 week		Every 6 months ±2 weeks		
Visit Window					-2 d ^j									
	Survival status and subsequent treatment								X	X ^d	X ^d	X ^d	X ^d	
Safety Assessments	Serum chemistry ^f			X	X			X	X					X ^o
	CBC with differential ^g			X	X ^g			X	X					X ^o
	CD4 count for HIV positive participants ⁱ		X		X									
	Estimated glomerular filtration rate			X	X			X						X ^o
	Concomitant meds and AEs		Collect any related to study protocol procedures		Collect from Day 1 (predose) through 110 days after the last dose of rituximab or 30 days after the last dose of brentuximab vedotin or lenalidomide, whichever is later									X ^{o,p}
PRO/MRU	Healthcare Utilization				X									
	NCCN FACT-Lym ^b				X			X						
	EQ-5D-5L ^b				X			X						

a. Tumor specimen must be submitted for central pathology review before randomization to confirm CD30 expression. **CCI**

b. Participants of childbearing potential must avoid pregnancy for at least 4 weeks before beginning lenalidomide therapy, during therapy, during dose interruptions, and for at least 12 months after completing therapy.

- d. Once a subject experiences PD per investigator assessment, survival status is required every 3 months after the EOT visit for the first year and then every 6 months thereafter until death or study closure, whichever comes first. After 30 months, the window for the assessment is ±1 month. Collect information regarding subsequent anticancer therapies. If the subject had a scan documenting their response after discontinuing treatment and within 4 weeks preceding EOT then an EOT visit scan is not required
- e. Randomization to occur after eligibility is determined and within 3 business days of planned first dose of study treatment.
- f. The chemistry panel is to include the following tests: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, eGFR, chloride,

	Prescreening	Screening/Baseline		Day of 21-Day Combination Treatment Cycle			EOT visit	Safety follow-up visit	Long-term F/U				LTEP
									Months after EOT visit				
									3	6	9	≥12	
Day	Prior to D-28	D-28 to 1	D-7 to 1	D1 ^m	D2 to 21	Between D15 to 21	30-37 days post last dose ^d	110 days [+2 weeks] after last dose of rituximab, or 30-37 days after last dose of brentuximab vedotin or lenalidomide, whichever is later	±1 week		Every 6 months ±2 weeks		
Visit Window				-2 d ^j									

Participants must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of birth control (see [Appendix C](#)), beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions, and continuing for 12 months following discontinuation of study drug (brentuximab vedotin, rituximab, or lenalidomide). Two negative β -HCG pregnancy tests must be obtained prior to initiating therapy. The first test must be a serum β -HCG pregnancy test and the second test can either be a serum or urine β -HCG pregnancy test. The first test should be performed within 10 to 14 days and the second test within 24 hours prior to receiving lenalidomide therapy. Afterwards, a serum β -HCG pregnancy test must be administered weekly during the first month, then at least monthly thereafter in females with regular menstrual cycles or every 2 weeks in participants with irregular menstrual cycles. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). If sexually active in a way that could result in pregnancy, participants of childbearing potential and participants who can father children and have partners of childbearing potential must agree to use 2 effective contraception methods (see [Appendix C](#)) during the study and for 12 months following the last dose of study drug. Additionally, participants of childbearing potential should be counselled on adequate contraception methods as outlined in [Appendix C](#).

- c. A combined CT/PET may be obtained to satisfy the requirements for CT and PET scanning, as long as a diagnostic quality CT scan is obtained; PET scans may also be obtained any time during the study if clinically indicated. Diagnostic-quality CT scans of neck, chest, abdomen and pelvis, will be assessed at baseline, then every 6 weeks from randomization until Week 48 (± 7 days), then every 12 weeks (± 7 days) thereafter (see [Section 6.4.5](#)). A diagnostic quality CT-PET scan should also be performed at the time of suspected clinical progression. Participants who cannot tolerate contrast may have magnetic resonance imaging (MRI) scans instead. A PET scan is required at baseline and every 6 weeks from randomization until Week 48 (± 7 days), then every 12 weeks (± 7 days)

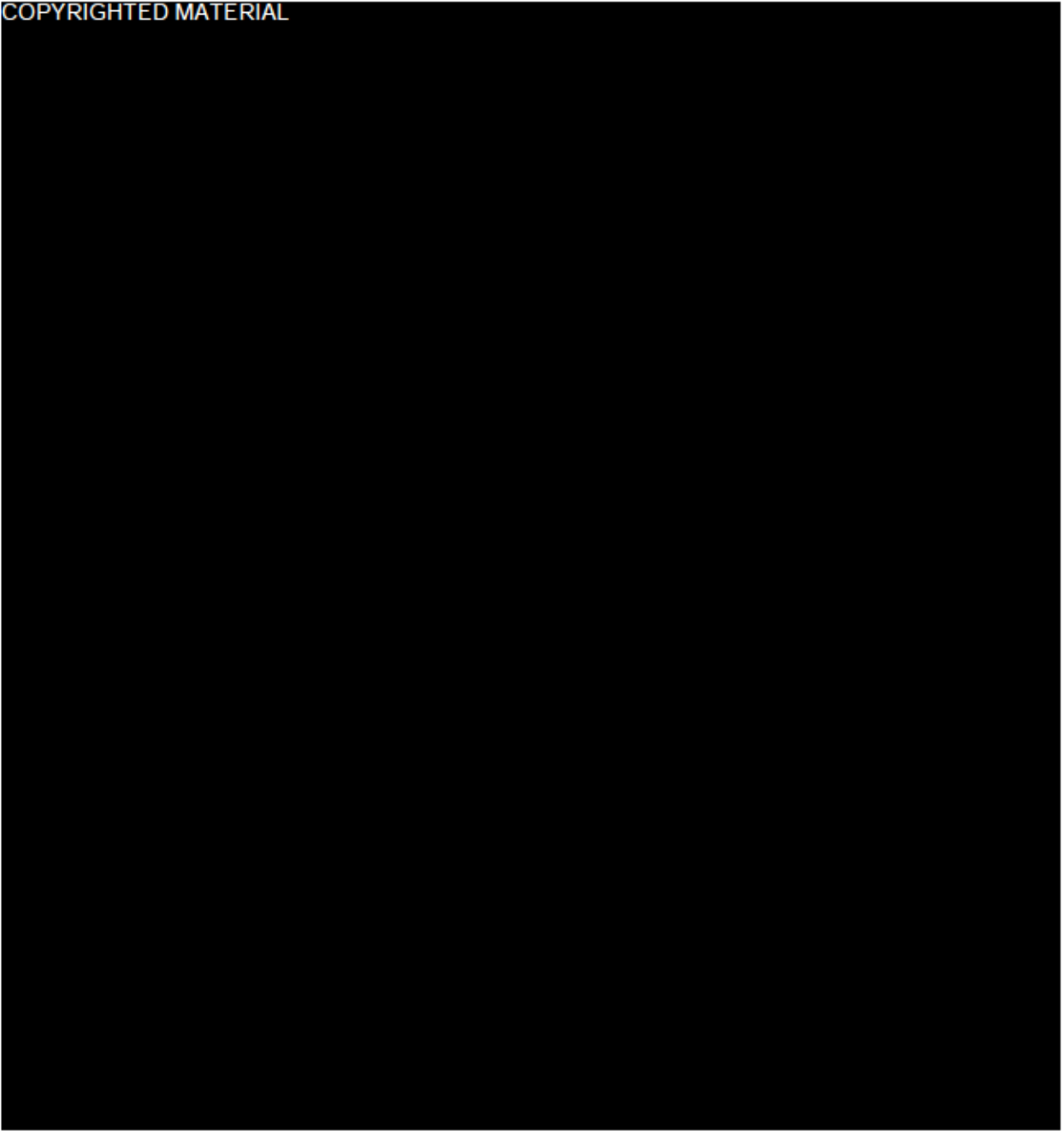
- glucose, LDH, phosphorus, potassium, sodium, total bilirubin, amylase, lipase, TSH with reflex to free T4, and uric acid.
- g. If ANC drops below 500/mcL, follow CBC weekly.
 - h. PRO assessments should be performed every 2 weeks while on treatment. If these assessments coincide with a study visit, these assessments should be performed first before any other study assessment.
 - i. Monitoring of CD4 counts will be done at screening, prior to each dose of rituximab, and should be performed according to institutional standard of care (see [Section 7.8.4](#)).
 - j. This 2-day window applies only to Cycles 2 and beyond.
 - k. Participants who are positive for anti-HCV will need to have HCV PCR done as a reflex test. If the PCR is positive, then the subject is ineligible; if the PCR is negative despite a positive anti-HCV, then the subject is eligible.
 - l. CD30 prescreening consent can be signed prior to screening.
 - m. If Baseline Visit activities occur within 1 day prior to Cycle 1 Day 1, the following assessments do not need to be repeated at Cycle 1 Day 1: weight, physical examination, Serum β -HCG pregnancy test, ECOG performance status, serum chemistry panel, CBC with differential, ECG, and eGFR.
 - n. Additional ECGs may be performed throughout the duration of the study, as clinically indicated.
 - o. During the LTEP, safety and efficacy assessments that include determination of disease progression will be performed per institutional guidelines and investigator-determined usual and customary clinical care. Pregnancy testing will continue for participants of child-bearing potential.
 - p. Only SAEs and pregnancy collected by the sponsor.

	Prescreening	Screening/Baseline		Day of 21-Day Combination Treatment Cycle			EOT visit	Safety follow-up visit	Long-term F/U				LTEP
									Months after EOT visit				
									3	6	9	≥12	
Day	Prior to D-28	D-28 to 1	D-7 to 1	D1 ^a	D2 to 21	Between D15 to 21	30-37 days post last dose ^d	110 days [+2 weeks] after last dose of rituximab, or 30-37 days after last dose of brentuximab vedotin or lenalidomide, whichever is later	±1 week		Every 6 months ±2 weeks		
Visit Window				-2 d ^j									

thereafter. Once the PET is negative per the investigator, no further PET scans are required. Scans are encouraged to be performed before treatment during visits. Scans should continue until disease progression is documented radiographically, even if therapy had been previously discontinued or a subsequent anticancer therapy had been initiated. Participants who have a contraindication to CT IV contrast may have MRI exams performed instead. MRI exams of the brain, neck, abdomen, and pelvis may be performed in lieu of CTs, but MRI exams of the chest are not recommended. In these cases, a non-contrast CT of the chest is strongly recommended to evaluate the thoracic anatomy.

APPENDIX B: PERFORMANCE STATUS SCALES CONVERSION

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APPENDIX C: GUIDANCE ON CONTRACEPTION

For the purposes of this guidance, complete abstinence, if consistent with the subject's preferred lifestyle, is an acceptable form of contraception. Complete abstinence is defined as abstinence starting from the time of informed consent and continuing throughout the study and until the end of systemic exposure (at least 12 months after the final dose of study drug; see Section 4.1).

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Postmenopausal with 1 of the following conditions:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

For individuals with permanent infertility due to a medical cause other than the above (e.g., mullerian agenesis, androgen insensitivity), investigator judgement will determine childbearing status and study eligibility.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

- Postmenopausal female:

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Female participants who are of childbearing potential and who are sexually active in a way that could lead to pregnancy may choose any two of the following: one of the following

highly effective and one effective methods (must use at least one method of highly effective birth control):

Acceptable methods for highly effective birth control (preventing conception)

• Hormonal methods of contraception (excluding progestin-only pills; method must be associated with inhibition of ovulation), unless contraindicated
• Intrauterine device with failure rate <1%
• Tubal ligation
• Vasectomy (at least 90 days from the date of surgery with a semen analysis documenting azoospermia)

Acceptable methods for effective birth control

• Barrier method/s (male condom with or without spermicide, cervical cap with or without spermicide, diaphragm with or without spermicide) ^a
• Male participants who are sexually active in a way that could lead to pregnancy must use male condom with or without spermicide.
• The female partner should consider using an acceptable method of effective birth control such as: hormonal IUD, intrauterine hormonal release system, female barrier method (diaphragm, cap, sponge)
a A barrier method should only be used with a highly effective birth control method that is not a barrier method. Barrier methods alone, including a double-barrier method, are not considered highly effective contraceptive measures (see unacceptable methods of contraception). • Acceptable combinations of contraceptive methods: • Hormonal method and vasectomy • Hormonal method and barrier method • Intrauterine device and vasectomy • Intrauterine device and barrier method • Tubal ligation and vasectomy • Tubal ligation and barrier method

Acceptable methods for preventing secondary exposure to seminal fluid

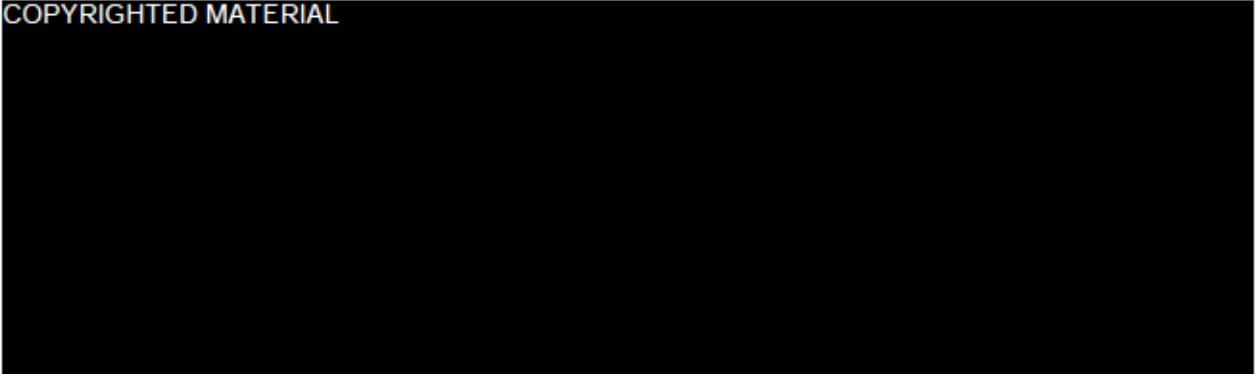
Participants born male and who are sexually active with a pregnant or breastfeeding person, must use the contraceptives in Option 1 or 2:
• Option 1: Male condom (with or without spermicide) and cervical cap
• Option 2: Male condom (with or without spermicide) and diaphragm

Unacceptable methods of contraception

• Periodic abstinence	• Spermicide only
• No method	• Progestin-only pills
• Withdrawal	• Concomitant use of female and male condoms
• Rhythm	• Barrier methods alone, including double-barrier methods

APPENDIX D: NEW YORK HEART ASSOCIATION CLASSIFICATION

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Online source: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp

APPENDIX E : COUNTRY-SPECIFIC REQUIREMENTS

European Union

This study will be conducted in compliance with Regulation (EU) No 536/2014. The recruitment plans for each EU Member State concerned are included in the respective Recruitment and Informed Consent Procedure documents.

The sponsor will notify EU Member States concerned of the following:

- Any SUSAR via reporting to the EudraVigilance database
- Any unexpected event that affects the benefit risk-profile of the study, but are not SUSARs, no later than 15 days of becoming aware of that event
- Any serious breach, as described in Section 10.1.1, no later than 7 days of becoming aware of that breach
- Any urgent safety measure, as described in Section 10.1.1, no later than 7 days of the measure being taken
- Any inspection report of a third-country authority concerning the study

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 25 years or longer if required by other European Union law.

France

Contract Unique

1. GCP Training

Before enrolling any participants, the investigator and any subinvestigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and subinvestigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Study Intervention

No participants or third-party payers will be charged for study intervention.

3. Urgent Safety Measures

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

4. Termination Rights

Pfizer retains the right to discontinue development of brentuximab vedotin at any time.

Netherlands

Netherlands only: The sponsor will communicate safety data (ie, SAEs) to the Medical Research Ethics Committee (MREC) on a periodic basis; SAE reports will not be expedited to MREC.

Switzerland

For all advanced therapy medicinal products (ATMPs) including oncological ATMPs investigated in a clinical trial, all cases of death that occur during the clinical trial in Switzerland must be reported to Swissmedic.

In order to comply with this requirement, all deaths (including fatal disease progression) for all ATMPs in this study that occur during the active reporting period must be reported to Pfizer Safety within 24 hours.

APPENDIX F: DOCUMENT HISTORY**Summary of Changes for Prior Global Amendments****Summary of Changes in Amendment 1**

Section(s)	Change	Rationale
3.1, Synopsis	Updated to state that safety data from 6 participants and PK data from 3 participants will be evaluated during the safety run-in.	Clarification
3.1 and Synopsis	Added "At least 200 CD30-positive participants will be enrolled in this study."	Clarification
3.2, 3.2.2	Updated dose rationale to reference recent phase 1 study.	Correction
4.1, Synopsis	Inclusion criterion #1: Included the DLBCL subtypes eligible for enrollment.	Clarification
4.1, Synopsis	Inclusion criterion #1: Changed minimum subject age from 12 to 18 Inclusion criterion #13: removed ICF criteria for minors.	The small number of adolescent participants may lead to challenges in obtaining clinically meaningful results.
4.1, Appendix C	Updated Appendix C and inclusion criterion #9 and added an additional inclusion criterion #10 to further define subject eligibility for participants of childbearing potential and those who can father children.	Subject safety
4.3	Added section defining participants who have childbearing potential or can father children.	Clarification
5.2.3	Added "For Grade 3 or 4 electrolyte abnormalities that last longer than 72 hours, are clinically complicated, don't resolve spontaneously, or don't respond to conventional medical interventions, discuss with Medical Monitor before the next dose."	Subject safety
5.3.2	Updated lenalidomide procurement.	Clarification
5.3.4.2	Updated dose modifications for lenalidomide based on ANC <500/mcL to be reduced by 5 mg, follow CBC weekly, and if persistent at 5 mg daily dose, discontinue lenalidomide permanently.	Subject safety
5.3.4.3	Added dose modifications for lenalidomide based on renal impairment.	Patient safety
5.4.2	Updated rituximab procurement.	Clarification
5.6.1.1 and Synopsis	Participants now must receive primary G-CSF prophylaxis.	Subject safety
5.6.2	Added guidance about P-gp inhibitor use.	Subject safety
5.6.3	Added erythropoietin-stimulating agents as prohibited medications.	Subject safety
5.8, 6.3.1	Added instructional text for patient diary.	Clarification
6.3.1, 6.4	Removed lymphoma assessments.	Correction

Section(s)	Change	Rationale
6.3.3, Appendix A	Broke out PROs into separate section and added instructional text and added footnote "h" in Appendix A.	Correction and clarification
6.3.4, 6.4, Appendix A	Added that scans will continue until disease progression is documented, even if therapy had been previously discontinued.	Clarification
6.5	Updated follow-up assessments for peripheral neuropathy.	Correction
6.6	Added "Follow-up will continue until the final OS analysis, which is expected to occur no later than 5 years after enrollment of the first subject."	Clarification
7.2, Appendix A	Updated so that participants who show progressive disease by PET and/or CT imaging will be discontinued from study treatment, thus allowing alternative treatment options.	Subject safety
9.1	Added "The decision to conduct the ORR analysis will be made prior to completion of enrollment; details will be provided in the SAP and the decision will be documented by Seattle Genetics. If the ORR analysis is not performed no alpha will be allocated to this analysis; the full alpha 0.05 will be used for testing the PFS and OS endpoints."	Clarification
9.3.1.2 and Synopsis	Added "Strata levels may be combined for stratified analyses if too few participants are included in certain strata levels; details for combining strata will be provided in the SAP."	Clarification
9.3.1.9	Added "Determination whether to perform the interim analysis based on ORR will be made prior to completion of enrollment and documented by Seattle Genetics; further details will be provided in the SAP."	Clarification
Appendix A	Corrected footnote on "30-37 days post last dose" from "e" to "d".	Correction
Appendix A	Corrected cross-reference from Section 7.2 to Section 6.3.4.	Correction
Appendix A	Added footnotes "f" and "g" for consistency with protocol body.	Clarification
Appendix B	Removed Lanksy scale.	No longer enrolling minor participants in study
Throughout	Minor administrative edits and corrections.	Corrections

Summary of Changes in Amendment 2

Section(s)	Change	Rationale
Title Page	Added EudraCT number.	Update for European countries
Synopsis	Merged all study treatments underneath one header.	Clarification
Synopsis, 3.1, 6.3.5, Appendix A	Updated scan schedule for first year to be until Week 48 and added scan window of ± 7 days for first year and beyond.	Correction
4.1	k. DLBCL arising from transformed ~~follicular lymphoma or marginal zone lymphoma~~ indolent lymphomas/leukemias	Clarification
5.3.1	Removed lenalidomide dosing levels	Clarification
5.3.2	Updated text to state that commercially available lenalidomide will be provided by the Sponsor.	Update to the study supply
5.3.4.3	Changed creatinine clearance to eGFR	Clarification
6.2.1, 6.3.2, 6.4, Appendix A	Added CD4 count for HIV positive participants only.	Correction
6.3.1	Moved Cycle 1 Day 1 assessments out to a separate section.	Clarification
6.3.5, Appendix A	Added "Scans are encouraged to be performed before treatment during visits."	Clarification
7.2, Appendix A	Added: "Participants who have a contraindication to CT IV contrast may have MRI exams performed instead. MRI exams of the brain, neck, abdomen and pelvis may be performed in lieu of CTs, but MRI exams of the chest are not recommended. In these cases, a noncontrast CT of the chest is strongly recommended to evaluate the thoracic anatomy."	Subject safety
7.3	Removed pharmacodynamic assessments	Correction
7.4.1, Appendix A	Added "Bone marrow biopsies and FNA samples are not permitted for central pathology assessment of CD30."	Clarification
7.6.2	Added "Healthcare utilization is defined as all medical care encounters related to lymphoma, treatment for lymphoma, or lymphoma-related assessments will be collected for all patients."	Clarification
7.8.4	Added EOT assessment of CD4 count for HIV participants.	Subject safety
Appendix A	Removed "Eligibility documentation submitted to sponsor prior to study start; randomization" and added row for Enrollment in Randomization and Trial Supply Management.	Correction
Appendix A	Added row for CD4 count for HIV positive participants and footnote "i".	Correction

Section(s)	Change	Rationale
Appendix A	Changed footnote “e” to 3 business days.	Allow flexibility for sites
Appendix A	Added footnote “j”: “This ± 2 day window applies only to Cycles 2 and beyond.”	Clarification
Appendix C	Changed acceptable methods for highly effective birth control to include barrier methods only in combination with non-barrier methods. A list of acceptable combinations of contraceptive methods has been included. The list of unacceptable methods was revised to include barrier methods alone, including double-barrier methods.	To align with Clinical Trials Facilitation and Coordination Group (CTFG) guidance on contraception in clinical trials
Throughout	Minor administrative edits and corrections.	Corrections

Summary of Changes in Amendment 3

Section(s)	Change	Rationale
Title Page	Added study name "ECHELON-3"	Study name
Throughout	Changed "Seattle Genetics, Inc." to "Seagen Inc." and changed "Seattle Genetics" to "Seagen"	Sponsor update
Synopsis, 2	Removed "prognostic" from exploratory objective: "To explore the relationship between ~~prognostic~~ molecular phenotype markers and clinical responses to brentuximab vedotin, lenalidomide, and rituximab"	Clarification
Synopsis, 3.1, 3.2.1, 9.3.11	Changed safety run-in period to past tense and added no new safety signals or concerns.	Safety run-in period ended and SMC reviewed data.
Synopsis, 3.1, 4.1	Criterion 4: added the text "Biopsies containing bone material, including bone marrow biopsies, as well as all liquid aspirates, are not permitted for central pathology assessment of CD30 expression."	Clarification
3.1	Changed Figure 1 PET*/CT description from "Scan at baseline then every 6 weeks thereafter and then every 12 weeks until Week 48 (± 7 days)..." to "Scan at baseline, then every 6 weeks from randomization until Week 48 (± 7 days)..."	Correction
4	Added "Subject re-screening is allowed for this study."	Clarification
4.1	Criterion 3e: modified the text to "Unable to receive CAR-T therapy due to financial, geographic, ~~or insurance, or~~ manufacturing issues."	Clarification
4.1	Criterion 8a: added the text "Absolute neutrophil count (ANC) $\geq 1000/\mu\text{L}$. If recent G-CSF has been used, the ANC result must be ≥ 14 days after last dose of pegylated G-CSF or ≥ 7 days after last dose of G-CSF."	Subject safety
4.1	Changed Inclusion Criterion 8b to Platelet count $\geq 50,000/\mu\text{L}$ at least 7 days after last treatment for DLBCL with no platelet transfusion during this 7 day period. ~~or growth factor support in the 28 days prior to Day 1.~~	Clarification
4.1	Added Inclusion Criterion 8c "For participants whose last therapy was CAR-T therapy, the ANC and platelet count requirements must be met at least twice during screening, with the measurements at least 7 days apart."	Subject safety

Section(s)	Change	Rationale
4.1	Added Inclusion Criterion 8d “hemoglobin ≥ 8.0 g/dL and have not received a transfusion in the 7 days prior to testing.”	Request from the Taiwan health authority
4.1, 6.2.1, 7.8.2	Changed “eGFR using Modification of Diet Renal Disease (MDRD)” to “eGFR using CockcroftGault- (C-G)”	Product label is in mL/min
4.1, Appendix A (Footnote b)	Criterion 9a: modified the text to “Must avoid pregnancy for at least 4 weeks before beginning lenalidomide therapy, during therapy, during dose interruptions, and for at least 12 months after completing therapy. Participants must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of ~~reliable~~ birth control simultaneously: one highly effective form of contraception – tubal ligation, intrauterine device (IUD), hormonal (birth control pills, injections, hormonal patches, vaginal rings, or implants), or partner’s vasectomy, and 1 additional effective contraceptive method – male latex or synthetic condom, diaphragm, or cervical cap (see Appendix C), beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions, and continuing for 12 months following discontinuation of study drug (brentuximab vedotin, rituximab, or lenalidomide).”	Subject safety
4.1, 6.2, 6.2.1, Appendix A	Changed “Two negative serum beta human chorionic gonadotropin (β -HCG) pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10 to 14 days and the second test within 2448 hours prior to receiving lenalidomide therapy.”	Correction
4.1	Criteria 9d and 10b: removed the text highly effective.	Clarification
4.1	Criteria 11: added “The following requirements for participants who are known to be human immunodeficiency virus (HIV)-positive.”	Clarification

Section(s)	Change	Rationale
4.1, 5.3.3	Removed Inclusion Criterion 12 and modified text to "Participants in the US must be registered into the mandatory lenalidomide REMS® program. Participants outside the US must follow their country specific Risk Minimization Program (Global Pregnancy Prevention Program [G-PPP]). ~~risk minimization programs and be willing to comply with its requirements.~~ Per standard lenalidomide REMS/risk minimization programs (G-PPP) requirements, all physicians who prescribe lenalidomide for research participants enrolled into this trial, ~~must be registered in, and~~ must comply with, all requirements of the lenalidomide REMS/risk minimization programs.	Clarification
4.2	Added Criterion #8 "Any contraindication to associated study treatments."	Subject safety
4.2	Criterion #9: Added "Participants who are HBsAg negative but HBcAb positive are eligible, but should start hepatitis B prophylaxis therapy prior to receiving the first dose of rituximab." Criterion #9: Added "Known to be positive for hepatitis C infection (either confirmed positive by polymerase chain reaction [PCR] or on antiviral therapy for hepatitis C within the last 6 months)."	Clarification
4.2	Criterion #13: added "pulmonary embolism,"	Request from the Taiwan health authority
5.3.4	Added "A 5 mg increase in lenalidomide dose after a prior dose reduction will be permitted only after discussion with the Medical Monitor."	Clarification
5.3.4.3	Changed "For participants ~~with~~ whose eGFR has dropped to 45–60 mL/min/1.73 m ² , reduce lenalidomide daily dose ~~to 10~~ by 5 mg from the previous dose. For participants whose eGFR has dropped from >60 mL/min to 30–45 mL/min, reduce lenalidomide daily dose by 10 mg ~~daily~~ from the previous dose. For participants whose eGFR has from 40–45 mL/min to 30–45 mL/min, reduce lenalidomide daily dose by 5 mg from the previous dose. Do not dose below 5 mg daily. If a subject's eGFR is <30 mL/min/1.73 m ² , permanently discontinue lenalidomide dosing. Contact	Subject safety

Section(s)	Change	Rationale
	the Medical Monitor for any specific renal dose modification questions.	
5.4.3	Added "Rituximab 375 mg/m ² will be administered either before or after administration of brentuximab vedotin on Cycle 1 Day 1 (±1 day) via IV infusion according to the package insert (RITUXAN Prescribing Information, Genentech Inc., Sep 2019) or institutional standard of care. ~~The~~ If rituximab IV infusion is given after the brentuximab vedotin infusion, it should ~~will~~ begin within approximately 60 to 90 minutes after the end of the brentuximab vedotin infusion. If the Cycle 1 Day 1 rituximab IV infusion is well tolerated, participants may receive rituximab 1400 mg and hyaluronidase human via subcutaneous injection on Day 1 of every cycle, starting at Cycle 2. For all cycles, rituximab may be administered either before or after brentuximab vedotin/placebo."	Investigator flexibility
5.6.1	Changed "All participants must take low-dose aspirin (at least 50 ~~81~~ mg daily)"	Clarification
5.6.1	Added anti-viral prophylaxis text: "Participants who have a history of past hepatitis B infection, namely those who are HBsAg negative but HBcAb positive, are at high risk of hepatitis B reactivation when receiving anti-CD20 therapy (ie, rituximab) or SCT. These participants are required to start anti-viral prophylaxis and should be continued for at least 12 months after the last dose of rituximab or SCT. Anti-viral therapies recommended for prophylaxis include entecavir, tenofovir disoproxil fumarate, and tenofovir alafenamide. Participants with appropriate anti-viral prophylaxis against hepatitis B reactivation may be enrolled without additional anti-viral prophylaxis."	Subject safety
5.6.2	Removed P-gp language for brentuximab vedotin	Consistency with product label.
5.6.3	Changed "Participants ~~may~~ must not receive other investigational drugs, live vaccines...."	Clarification
6.2, Appendix A	Added "Serology (~~hepatitis B~~ [HBsAg], HBcAb, anti-HCV, EBV) Added "Participants who are positive for anti-HCV will need to have HCV PCR done. If the PCR is positive, then	Clarification

Section(s)	Change	Rationale
	the subject is ineligible; if the PCR is negative despite a positive anti-HCV, then the subject is eligible.”	
6.2, 6.3.2, Appendix A	Changed “Enroll subject in the US into lenalidomide REMS./ Subject outside the US must follow their country specific risk minimization programs (GPPP).” Changed “ ~~Registration into lenalidomide~~ Lenalidomide REMS/risk minimization programs (GPPP)”	Clarification
6.3.1	Changed “Results from clinical laboratory assessments must be reviewed and must confirm eligibility prior to study drug administration”	Clarification
6.4, Appendix A	Removed “HIV positive participants only: CD4 count prior to each dose of rituximab” at EOT visit	Clarification
6.5, Appendix A	Added a safety follow-up visit and disease status assessment	Subject safety
7.3	Changed “All sampling times are relative to the start or end of brentuximab vedotin infusion, except for end of infusion.”	Clarification
7.3	Added “/placebo” to end of Footnote a of Table 5: Pharmacokinetic and immunogenicity sampling time points	Correction
7.8.1.3, Appendix A	Updated end of reporting period from “30 days after the last study treatment, whichever is later” to “110 days after the last dose of rituximab or 30 days after the last dose of brentuximab vedotin or lenalidomide, whichever is later”	Subject safety
7.8.1.5	Added a Sponsor Safety Reporting to Regulatory Authorities section	Clarification and regulatory compliance
7.8.2	Added “The following laboratory assessment(s) will be performed by local laboratories at scheduled timepoints (see Appendix A) during the course of the study and the results (no blood) will be sent to ICON iRIS:”	Clarification
7.8.2, Appendix A (Footnote f)	Added “thyroid stimulating hormone (TSH) with reflex to free T4,” to serum chemistry panel	Subject safety
9.3.1.5, 11	Replaced the Siegel 2013 reference with the Ye 2013 reference. Added Ye 2013 reference into References section	To add the correct citation.
Appendix A (Footnote k)	Added footnote “k”: “Participants who are positive for anti-HCV will need to have HCV PCR done as a reflex test. If the PCR is positive, then the subject is	Clarification

Section(s)	Change	Rationale
	ineligible; if the PCR is negative despite a positive anti-HCV, then the subject is eligible"	
Appendix A	Added time point for Lenalidomide REMS/risk minimization programs (G-PPP)	Subject safety
Appendix C	Updated guidance to mandate use of 1 highly effective method of birth control for females of childbearing potential and usage of male condom for males who engage in sexual activity that could result in pregnancy Moved footnote "a" text to text body.	Subject safety
Throughout	Minor administrative edits and corrections.	Correction

Summary of Changes in Amendment 4

Section(s)	Change	Rationale
Synopsis, 3.1	Removed "or have declined"	Per FDA patients must be ineligible and "declined" can be interpreted as a subjective term
Synopsis, 3.1, Appendix A (footnote)	Removed references to Ber-H2 Antibody Receptors	Specific details related to the biopsy processing and CD30 testing requirements belong in the laboratory manual not in the protocol.
3.1	Added: "The local lab must provide the CD30 expression result as a percentage value."	To aid with CD30 stratification to reduce the potential discordance with local and central results.
3.1, 4.1, Appendix A (footnote)	Added: "CCI [REDACTED]"	Clarification
3.1	Added: "The same DLBCL biopsy specimen used by the local lab for CD30 testing and stratification should be sent to the central pathology lab"	Clarification
4.1	Added "For participants with transformed DLBCL (subtype k), at least the last systemic therapy used must have been for DLBCL."	Clarification
4.1	Added: "PET, CT imaging, and labs performed prior to consent but within 28 days of Day 1 can be used."	Clarification
4.1	Changed eGFR to ≥ 45	Correction; allows participants with lower renal function to be eligible when using lower lenalidomide dosing.
4.1, 6.2, 6.3.1, Appendix A (footnote)	Modified: Two negative serum β -HCG pregnancy tests must be obtained prior to initiating therapy. The first test must be a serum β -HCG pregnancy test and the	Correction

Section(s)	Change	Rationale
	second test can either be a serum or urine β -HCG pregnancy test. The first test should be performed within 10 to 14 days and the second test within 24 hours prior to receiving lenalidomide therapy.	
4.1, 6.4.1, 6.4.3, Appendix A (footnote)	Added: "at least" monthly	Clarification
4.2	Added: "Previous treatment with other vedotin-based ADCs is permitted if the last dose is at least 6 months prior to Day 1."	Clarification
5.4.3	Added: "If brentuximab vedotin, rituximab, or both are held at a cycle and Lenalidomide is being continued, the cycle is considered to have begun. If the patient can be treated with either or both drugs within 7 days of the delay, the dose should be given for that cycle. If not, the drugs should be eliminated for that cycle and would be administered at the next cycle once the reason for the hold has resolved. The minimum time between doses of either brentuximab vedotin or rituximab is 14 days. If all drugs at a cycle are being held the entire cycle should be delayed until treatment resumes. Visits occurring between cycles would be considered unscheduled visits. The following cycle visit date would be calculated from the start of the delayed cycle, not C1D1."	Added clarification regarding dose delays to allow better instructions for study sites
5.5.3, 5.5.4.3	Added: For participants whose baseline eGFR is 45-59 mL/min, the lenalidomide starting dose will be 15 mg orally once daily.	Clarification
5.6.2	Added: or rituximab will be provided to sites through a local supplier if supply by site is not possible.	Clarification
5.6.3	Added: If the Cycle 1 Day 1 rituximab IV infusion is well tolerated, participants may receive rituximab ~~1400 mg~~ and hyaluronidase human 1400 mg via subcutaneous injection (RITUXAN HYCELA Prescribing Information, Genentech Inc., Mar 2021) on Day 1 of every cycle, starting at Cycle 2; or continue with rituximab IV infusion at 375 mg/m ² on Day 1 of every cycle and then every 3 weeks. For all cycles, rituximab may be administered either before or after brentuximab vedotin/placebo. After Cycle 1, if the	Provide clarity for study sites regarding the waiting time before starting rituximab when administered after BV

Section(s)	Change	Rationale
	drugs are well tolerated, the time between infusion can be shortened per institutional guidelines for rituximab to a minimum of 30 minutes.	
6.2, 7.1.1	Added: CD30 Prescreening Consent	Update
6.3	Modified: CT/PET within 28 days prior to C1D1 to Baseline Visit	Correction
6.4.2	Added pulse oximetry and respiratory rate to vital signs assessment	Sites have not been completing these assessments, added to increase clarity for study sites
6.4.4	Added: "If Baseline Visit activities occur the same day than Cycle 1 Day 1, it is accepted that the PRO assessment is performed after lab assessment to confirm eligibility. A legally acceptable representative, if applicable to this study, can assist with completing the PRO assessment."	The protocol allows the combination of baseline and C1D1 the following text has been added
7.1	Added: "The tissue to be submitted should be from the most recent biopsy specimen that demonstrates DLBCL." Removed: "Recent biopsies (≤ 4 weeks) are preferred if medically feasible to obtain. If a recent biopsy is not feasible or appropriate, contact the Medical Monitor."	Clarification; since all participants are eligible with regards to CD30 expression level, this change allows participants otherwise eligible to be enrolled using CD30 results from older biopsy specimens
7.1.1	Added new subheading "7.1.1 Prescreening Assessments Tissue samples may be tested for CD30 expression prior to screening through a CD30 Prescreening program. Participants may provide consent for this CD30 testing by the local pathology lab prior to providing consent for this study. The CD30 IHC results and other data will be collected on a prescreening CRF."	Added New Prescreening Assessments information to aid in enrollment
7.4.1	The most recent DLBCL biopsy specimen tumor tissue (obtained before Day 1)	Clarification
7.4.1	Removed: "Bone marrow biopsies and fine-needle aspiration samples are not permitted for central pathology assessment of CD30."	This detail belongs in the lab manual
7.8.1.2	Changed: the sponsor's Drug Safety Department within 24 48 hours of becoming aware of a pregnancy	Correction, per Safety time should be 24 hours
9.3.1	Removed: "per central assessment"	Method used for stratification was not specified in other sections of the protocol
Appendix A	Added CD30 prescreening and updated Vital signs to included pulse oximetry and respiratory rate	To assist clinical sites with completing these assessments, added to increase clarity for study sites
Throughout	Minor administrative corrections and edits	Correction

Summary of Changes in Amendment 5

Section(s)	Change	Rationale
Synopsis Section 2 (Objectives)	- Changed primary objective to OS - Changed key secondary objectives to include PFS, ORR, CR - Changed other secondary objectives to include CR and DOR per Lugano 2014 by investigator - Added key secondary objective of OS in the CD30-positive population - CCI [REDACTED] - Changed response assessment from "per BICR" to "per investigator" - Added clarifications to objectives and corresponding endpoints - Reduced planned number of participants to 225 (approximately 113 per arm) - Added new statistical considerations for updated study design, including interim futility and final analysis for OS - Additional minor clarifications provided throughout	- Change in overall study design to OS in ITT population as primary endpoint - Clarification
3.1 (Summary of Study Design)	- CCI [REDACTED] - Removed requirement for biopsies containing bone material - Added clarifications for sample submission and biomarker evaluations	- Change in overall study design to OS in ITT population as primary endpoint - Clarification
3.2 (Discussion and Rationale for Study Design)	- Provided additional text and references for rationale of the updated study design - Revised previous text for rationale	- Added rationale for the updated study design - Clarification
3.2.3 (Blinding and Unblinding)	Provided clarification for unblinding procedures	Clarification
4.1 (Inclusion Criteria)	Added Criterion #11: "Follicular lymphoma Grade 3b"	Updated based on literature

Section(s)	Change	Rationale
5.3.3 (Dose and Administration) 5.3.4.3 (Renal Impairment)	Provided lenalidomide dose modification guidance for patients with renal impairment	Alignment with global reference safety information
5.6.1 (Required Concomitant Therapy)	Provided clarification for required anticoagulation prophylaxis	Clarification
5.6.2 (Allowed Concomitant Therapy)	Added guidance on the use of inactivated vaccines for influenza and COVID-19	Addition for the management and treatment of COVID-19
6.4.1 (Cycle 1 Day 1) Appendix A: Schedule of Events (footnote m)	Removed "Height" from the assessments that do not need to be repeated at Cycle 1 Day 1 and added "eGFR."	Correction
6.4.2 (Day 1 of Each Cycle) Appendix A: Schedule of Events (footnote m)	Added bullet point "ECOG performance status"	Clarification
6.4.2 (Day 1 of Each Cycle) 6.5 (End of Treatment Visit (30 to 37 Days After Last Dose of Study Drug))	Modified bullet point by adding "and biomarker"	Clarification
6.4.5 (Disease Response Assessment) Appendix A: Schedule of Events (footnote c)	Clarified on-study response assessment procedures	Clarification
6.7 (Follow-up)	- Added clarifying text for on-study response assessment procedures - Added text regarding follow-up for OS and subsequent treatment	Clarification and consistency with Section 6.4.5
6.8 (End of Study/End of Follow-up)	Clarified duration of follow-up	Change in overall study design to OS in ITT population as primary endpoint

Section(s)	Change	Rationale
7.1.1 (Prescreening Assessments)	Clarified prescreening CD30 tissue sample testing requirements	Clarification
7.2 (Response/Efficacy Assessments)	Removed text to clarify radiographic requirements for determination of disease progression	Clarification
7.4 (Biomarker Studies) 7.4.1 (Characterization of Tumor Tissue)	Clarified biomarker analyses for blood samples collected on study	Clarification
7.7 (Long-term Survival Status Follow-up)	Added clarifying text for on-study response assessments and follow-up procedures	Clarification
7.8.1.5 (Sponsor Safety Reporting to Regulatory Authorities)	Added language for the Netherlands only that the sponsor will communicate safety data (ie, SAEs) to MREC on a periodic basis	Clarification
9.1 (Determination of Sample Size)	- Modified text regarding determination of sample size - Added text for the statistical considerations for the planned futility and final analyses of OS - Removed previous text - Clarifications added throughout	3. Change in study design to OS in ITT population as primary endpoint 4. Clarification
9.2.1 (Primary Endpoint: Overall Survival (OS))	- Provided definition for OS - Added text for censoring rules and methodology in the SAP	5. Change in study design to OS in ITT population as primary endpoint 6. Clarification
9.2.1 (Progression-free Survival (PFS) per Lugano 2014 by Investigator)	- Clarified assessment of PD according to investigator - Clarified text for censoring rules and methodology in the SAP - Added sensitivity analyses for PFS by BICR	7. Change in study design 8. Clarification
9.2.2.2 (Objective Response Rate (ORR) per Lugano 2014 by Investigator)	- Provided definition for ORR according to investigator - Added sensitivity analyses for ORR by BICR	9. Change in study design 10. Clarification
9.2.3.1 (Complete Response (CR) Rate per Lugano 2014 by Investigator)	- Provided definition for CR according to investigator - Removed previous inapplicable text for ORR - Added sensitivity analyses for CR by BICR	11. Change in study design 12. Clarification

Section(s)	Change	Rationale
9.2.3.2 (Duration of Response (DOR) per Lugano 2014 by Investigator)	• Provided definition for DOR according to investigator • Added clarifying text for censoring rules • Added sensitivity analyses for DOR by BICR	13. Change in study design 14. Clarification
9.3 (Statistical and Analytical Plans)	Clarified the SAP will be finalized prior to the interim analysis of OS	Change in study design
9.3.1 (General Considerations)	Provided clarifying text regarding consideration of participants in tabular summaries	Clarification
9.3.1.1 (Randomization and Blinding)	• Modified the planned number of participants to 225 • CCI [REDACTED] • Removed text to clarify blinding requirements	15. Change in study design to OS in ITT population as primary endpoint 16. Clarification
9.3.1.3 (Handling of Dropouts and Missing Data)	Clarified handling of missing data	Clarification
9.3.1.4 (Multicenter Studies)	Clarified plans for analyses by center	Clarification
9.3.1.5 (Multiple Comparisons and Multiplicity)	• Removed previous statistical language • Specified PFS and ORR analyses according to investigator assessment • Added graphical approach for alpha allocation according to endpoints • Provided statistical considerations and graphical representation of hypothesis testing • Added statistical considerations and methodologies for interim and final analyses	17. Change in study design to OS in ITT population as primary endpoint 18. Clarification
9.3.1.7 (Analysis Sets)	• Provided clarifications to the ITT and Safety analysis sets • Added text for the Safety run-in analysis set	Clarification

Section(s)	Change	Rationale
9.3.1.8 (Examination of Populations)	Provided clarifications for CD30-positive population analysis	Clarification
9.3.1.9 (Timing of Analyses)	- Removed previous language regarding timing of analyses - Added text for timing of the interim and final analyses - Added text for the estimated duration of the study	19. Change in study design to OS in ITT population as primary endpoint 20. Clarification
9.3.5.1 (Primary Efficacy Analysis)	- Modified primary efficacy analysis text from PFS to OS - Added text to clarify the planned interim analysis by the IDMC - Added text on the procedures for unblinding following the interim analysis	21. Change in study design to OS in ITT population as primary endpoint 22. Clarification
9.3.5.2 (Secondary Efficacy Analyses)	- Modified secondary efficacy analysis text from OS to PFS by investigator - Modified secondary efficacy analysis text for ORR - Added text for the planned analyses for DOR - Added text for the planned analysis of OS in the CD30-positive population	23. Change in study design to OS in ITT population as primary endpoint 24. Clarification
9.3.9.2 (Adverse Events)	Provided clarifications for consistency	Clarification
9.3.10 (Interim Analyses)	- Removed previous interim analysis text - Added interim analysis plans for OS - Added text for planned analyses of secondary endpoints in the case of unblinding	Change in study design
9.3.12 (Independent Monitoring Committee)	Added text to clarify the IDMC will oversee the interim analysis of OS	Change in study design
Appendix A: Schedule of Events	Removed Physical Exam "X" from "D-28 to 1" and "D1"	Correction
Appendix A: Schedule of Events	Removed Electrocardiogram "X" from "D1"	Correction

Section(s)	Change	Rationale
Appendix A: Schedule of Events	Added row for biomarker samples to indicate that collections are the same as ADA timepoints	Clarification
Appendix A: Schedule of Events	Removed “±” in front of 2 days from footnote j	Correction
Appendix A: Schedule of Events	Removed “Bone marrow biopsies and fine-needle aspirations samples are not permitted for central pathology assessment of CD30” from footnote “a”	Clarification
Appendix A: Schedule of Events	Added “eGFR” and “ECG” to footnote “m”	Clarification
Throughout	Minor administrative corrections and edits	Correction

Summary of Changes in Amendment 6

Section(s)	Change	Rationale
Synopsis	Updated the study design section	To align closely with Section 3.1 and footnote ‘a’ of Appendix A
6.1 (Schedule of Events)	Clinical laboratory assessments (serum chemistry panel, complete blood count [CBC] with differential [manual differential if clinically indicated, see Section 7.8.2], serum β -HCG pregnancy test, and eGFR), physical exam, weight, and performance status, and ECG may be performed within 1 day prior to administration of study drug.	Updated text to align with footnote “m” in Appendix A
6.3.1 (Baseline Visit (Day -7 to Day 1))	Moved CD4 count assessment from Section 6.3.1 Baseline Visit (Day -7 to Day 1) to Section 6.3 Screening Visit (Day -28 to Day 1)	CD4 count assessment should be conducted during the Screening Visit (Day -28 to Day 1)
7.8.4 (Additional Monitoring for HIV-Positive)	Changed ‘baseline’ to ‘screening’	To align with CD4 count assessment being conducted during the Screening Visit (Day -28 to Day 1)
Appendix A		
9.2.3.2 (Duration of Response (DOR) per Lugano 2014 by Investigator)	~~Duration of response~~ DOR will only be calculated for participants achieving a CR or PR. Sensitivity analyses of ~~CR rate~~ DOR based on BICR assessment may also be performed.	Correction