CLINICAL PROTOCOL

Title:	A Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Enzastaurin Plus R-CHOP Versus R-CHOP in Treatment-Naïve Subjects with High-Risk Diffuse Large B-Cell Lymphoma Who Possess the Novel Genomic Biomarker DGM1 (ENGINE Study)
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IND Number:	IND 133358
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Version:	Version 6.0 US: Replaces Version 5.1 dated 27 February 2020 China: Replaces Version 5.0 dated 18 December 2019
Date:	8 July 2021

SPONSOR APPROVAL

Sponsor's Approval

The protocol has been approved by Denovo Biopharma LLC

Responsible Medical Officer: Guy Gammon, MBBS MRCP

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PROTOCOL SYNOPSIS

TITLE	A Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Enzastaurin Plus R-CHOP Versus R-CHOP in Treatment-Naïve Subjects with High-Risk Diffuse Large B-Cell Lymphoma Who Possess the Novel Genomic Biomarker DGM1 (ENGINE Study)
SPONSOR	Denovo Biopharma LLC
RATIONALE	Non-Hodgkin's Lymphoma (NHL) is the 7th most common cancer in the United States with 72,580 new cases predicted to occur in 2016 (SEER database). Approximately 20,150 people were predicted to die from this disease in 2016. Of these, slightly more than half, approximately 11,450 will be male, and 8,690 will be female. There are over a half million people with NHL living in this country. Diffuse Large B-Cell Lymphoma (DLBCL) is the most common of the NHLs, accounting for between 30%-40% of all cases. The incidence of DLBCL generally increases with age and roughly half of all patients are over the age of 60 at the time of diagnosis (Lymphoma Research Foundation, 2018). DLBCL is classified as an aggressive lymphoma meaning that its clinical course can progress rapidly to death. Nevertheless, patients with DLBCL can be cured with the appropriate treatment. The current standard of care treatment for DLBCL consists of rituximab added to the anthracycline-containing combination chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine and prednisone (NCCN Treatment Guidelines). This regimen is referred to as R-CHOP immunochemotherapy. For DLBCL as a whole, R-CHOP immunochemotherapy has resulted in cure rates of approximately 60%. However, for individual patients 5-year survival rates can range from 90% for low-risk DLBCL patients to less than 50% for high-risk DLBCL patients (Sehn et al., 2015, Zhou et al., 2014). Most important, for those subjects refractory to R-CHOP therapy less than 10% achieve a durable remission with secondary therapy (Sehn et al., 2015). Thus, while R-CHOP remains the standard treatment for high-risk, advanced stage DLBCL, approximately 30-40% patients fail front-line therapy with most not achieving complete response or with early relapse. An essential step to move forward and improve the outcomes of these patients is to increase the rate of complete response to front-line R-CHOP therapy (Chiapella et al., 2016). For this reason, there has been a great deal of effort placed on attempting to define disease characteristics that predispose patients to a poorer prognosis with R-CHOP therapy. Molecular and gene expression profiling of tumors and a variety of clinical prognostic indices have been used to identify patients at higher risk of failing R-CHOP immunochemotherapy. While this work has identified subgroups of patients who do not respond well to R-CHOP, to date these efforts have not resulted in substantial gains in response to front-line therapy. Denovo Biopharma (Denovo) has pioneered an alternative approach to this challenging problem. Denovo has developed a model that employs sophisticated pharmacogenomic testing to detect somatic biomarkers that identify those subjects who responded to a particular study treatment with

	the aim of re-studying the drug of interest, in this case enzastaurin, in an enriched population. Applying this technology to archived DNA samples from completed studies of enzastaurin in subjects with DLBCL, Denovo has identified a somatic biomarker that reliably identified subjects for whom the study treatment significantly prolonged survival. Enzastaurin is an oral serine/threonine kinase inhibitor, that targets the protein kinase C (PKC), and phosphoinositide 3-kinase (PI3K) and AKT pathways to inhibit tumor cell proliferation, induce tumor cell apoptosis, and suppress tumor-induced angiogenesis. The purpose of the current study is to prospectively assess the effect on overall survival (OS) of adding enzastaurin to R-CHOP immunochemotherapy in the front-line treatment of subjects with high-risk DLBCL (IPI ≥ 3). The detailed rationale for this study is provided in greater depth in Section 1.5.
STUDY DESIGN	This randomized, double-blind, placebo-controlled Phase 3 study intends to enroll approximately 235 treatment-naïve subjects with high-risk DLBCL. These subjects will be randomized 1:1 to R-CHOP plus enzastaurin or R-CHOP plus placebo. All subjects will receive up to 6 cycles (1 cycle = 21 days) of treatment during combination phase. PET-CT will be used for staging and to assess radiographic response at the end of treatment. Each subject's treatment assignment will be unblinded after combination phase tumor response assessment. Subjects randomized to the enzastaurin arm who have a complete response (CR) or partial response (PR) (at investigator's discretion) by the Lugano Classification (Cheson 2014) will have the opportunity to continue in the single-agent phase of the study and receive single-agent enzastaurin for up to 2 additional years.
PRIMARY OBJECTIVE	The primary objective of this study is to compare the effect of R-CHOP plus enzastaurin followed by enzastaurin or standard of care (SOC) versus R-CHOP followed by SOC on OS in treatment-naïve subjects with high-risk DLBCL who possess the DGM1 biomarker.
SECONDARY OBJECTIVES	• To determine the effect on OS of adding enzastaurin to R-CHOP in treatment naïve subjects with high-risk DLBCL regardless of DGM1 biomarker status. • To evaluate Event-free Survival (EFS), including EFS rate at 12 months (EFS12) and EFS rate at 24 months (EFS24), for all subjects, and for subjects who are DGM1 biomarker positive. • To compare the combination phase investigator assessed CR rate and objective response rate (ORR) in subjects with high-risk DLBCL who are DGM1 biomarker positive administered R-CHOP plus enzastaurin versus R-CHOP. • To further evaluate the safety profile of enzastaurin when administered in conjunction with R-CHOP.
EXPLORATORY OBJECTIVES	• To determine enzastaurin and enzastaurin metabolite(s) concentrations for incorporation into a subsequent population pharmacokinetics (PK) analysis.

	• To determine if the presence of other somatic or tumor biomarkers predicts improved efficacy in subjects taking enzastaurin. • To determine if chromaturia (orange/red discoloration of the urine) predicts improved efficacy in subjects taking enzastaurin. • To obtain samples urine for potential future analysis of enzastaurin metabolites. • To explore any relationship between subsequent DLBCL therapy(ies) and OS. • To assess regional similarities of primary and secondary efficacy measures between China and US.
NUMBER OF PATIENTS	Approximately 235 subjects randomized 1:1 to receive R-CHOP plus enzastaurin or R-CHOP plus placebo.
KEY ELIGIBILITY CRITERIA	**Inclusion Criteria** All inclusion criteria must be met for the subject to be considered for the study. 1. Male or female at least 18 years of age and able to provide informed consent. 2. Histologically confirmed diagnosis of CD20 positive DLBCL based on the WHO classification (2016); the diagnosis must be confirmed at the enrolling site. Note: Subjects with high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements, or high-grade B-cell lymphoma, NOS are eligible. 3. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2. 4. International Prognostic Index (IPI) score of at least 3. 5. Estimated life expectancy of at least 12 weeks. 6. Adequate organ function as follows (within 14 days prior to randomization): a. Hepatic: total bilirubin $\leq$ 1.5 times upper limit of normal (ULN) ($\leq$ 5 times ULN in the case of Gilberts Syndrome, liver or pancreatic involvement by lymphoma); alanine transaminase (ALT) and aspartate transaminase (AST) $\leq$ 2.5 times ULN ($\leq$ 5 times ULN if liver involvement) b. Renal: creatinine clearance of $\geq$ 40 mL/min by Cockcroft- Gault equation c. Bone marrow: platelets $\geq$ 75 x 10^9/L, absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L, hemoglobin $\geq$ 8 g/dL. (Platelets $\geq$ 50 x 10^9/L, ANC $\geq$ 1.0 x 10^9/L, hemoglobin $\geq$ 7.0 g/dL permitted if documented bone marrow involvement) 7. Male or female with reproductive potential, must be willing to use an approved contraceptive method (for example, intrauterine device (IUD), birth control pills, or barrier

	device) during and for 3 months after discontinuation of study treatment. Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to randomization. a. Men are considered of reproductive potential unless they have undergone a vasectomy and confirmed sterile by a post-vasectomy semen analysis. b. Women are considered of reproductive potential unless they have undergone hysterectomy and/or surgical sterilization (at least 6 weeks following a bilateral oophorectomy, bilateral tubal ligation, or bilateral tubal occlusive procedure that has been confirmed in accordance with the device's label) or achieved postmenopausal status (defined as cessation of regular menses for greater than 12 consecutive months in women at least 45 years of age). 8. Left ventricular ejection fraction ≥ 50% by echocardiography or nuclear medicine multi-gated scan. 9. Must be able to swallow tablets. 10. Must be able to comply with study protocol procedures. 11. Willing to consent to have blood stored for possible future biomarker and disease analysis. 12. Must have available and willing to submit pre-systemic treatment DLBCL tumor biopsy tissue/slides for central pathology review. **Exclusion Criteria** None of the exclusion criteria is met in order for the subject to be considered for the study. 1. Received treatment with an investigational drug within the last 30 days. 2. Receiving or has received radiation or any other systemic anticancer treatment for lymphoma (Up to 10 days of corticosteroids prior to randomization are permitted but should be administered after eligibility IPI determination and imaging scans). 3. History of indolent lymphoma or follicular Grade 3b lymphoma. 4. Primary mediastinal (thymic) large B-cell lymphoma. 5. B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma. 6. Burkitt lymphoma. 7. Pregnancy or breastfeeding. 8. Known central nervous system (CNS) involvement. 9. Any significant concomitant disorder based on the discretion of the investigator, including but not limited to active

	bacterial, fungal, or viral infection, incompatible with participation in the study. 10. A second primary malignancy (except adequately treated non-melanoma skin cancer); subjects who have had another malignancy in the past, but have been disease-free for more than 5 years, and subjects who have had a localized malignancy treated with curative intent and disease free for more than 2 years are eligible. 11. Use of a strong inducer or moderate or strong inhibitor of CYP3A4 (See Appendix A. Examples of Inhibitors and Inducers of CYP 3A4) within 7 days prior to start of study therapy or expected requirement for use on study therapy. 12. Personal or immediate family history of long QT syndrome, QTc interval > 450 msec (males) or > 470 msec (females) at screening (recommended that QTc be calculated using Fridericia correction formula, QTcF: see Section 6.2.1), or a history of unexplained syncope. 13. Use of any medication that can prolong the QT/QTc interval (See Appendix C. Drugs That Can Prolong the QT Interval) within 7 days prior to start of study therapy or expected requirement for use on study therapy. 14. History of severe allergic or anaphylactic reaction to monoclonal antibody therapy. 15. Confirmed diagnosis of progressive multifocal leukoencephalopathy. 16. Ongoing grade 2 or higher peripheral neuropathy. 17. Have any of the following cardiac disorders: uncontrolled hypertension, unstable angina, myocardial infarction within 8 weeks of randomization, New York Heart Association (NYHA) Grade 2 or higher congestive heart failure, ventricular arrhythmia requiring medication within 1 year of randomization, Fontaine Classification stage III or higher peripheral arterial disease. 18. Received a live vaccine within 28 days of randomization. 19. HIV positive. 20. Evidence of chronic hepatitis C infection as indicated by antibody to HCV with positive HCV-RNA. 21. Evidence of chronic hepatitis B infection as indicated by either: a) HBsAg+ or b) HBcAb+ with HBV-DNA+ (any detectable amount is considered positive)

TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION	Kinenza® (enzastaurin) 125 mg; matching placebo. Combination Phase (6 x 21-day cycles with R-CHOP) Subjects will receive a loading dose of 1125 mg (3 tablets TID) followed by 500 mg (4 tablets QD) of study drug (enzastaurin/placebo) daily. All four tablets will be taken together within 30 minutes after a meal and at approximately the same time daily to maintain steady-state concentrations. The tablets must not be crushed or broken for administration. Sigle-Agent Phase Following completion of up to 6 cycles of R-CHOP, subjects in the enzastaurin arm who have a CR, or PR (at investigator's discretion) may continue to take single-agent study drug (enzastaurin 500 mg) daily for up to 2 additional years.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Following screening (within 28 days), subjects will receive up to 6 cycles of R-CHOP immunochemotherapy (21-day cycles) plus study drug, during the combination phase. Note: for the R-CHOP regimen, subjects will receive a rituximab product, which may include Rituxan/MabThera or an FDA-approved rituximab biosimilar. However, for a given subject, Rituxan/MabThera or an FDA- approved rituximab biosimilar cannot be used interchangeably during the study; each subject must use the same rituximab product exclusively throughout the study treatment course. Following completion of the combination phase of the study, each subject's treatment assignment will be unblinded. Subjects randomized to the enzastaurin arm who have a CR or PR (at investigator's discretion) will be offered single-agent study drug for up to 2 additional years. All other subjects, including all subjects randomized to the placebo arm, will receive no further treatment on study, will receive standard of care based on their response assessment, and will go into the follow up phase and be evaluated for survival every 3 months until completion of the study or up to 5 years, whichever occurs first. The study is expected to take approximately 3.5 years to complete.
EFFICACY EVALUATIONS	The determination of response and progression will be based on standardized criteria: Lugano Classification (Cheson 2014). PET-CT should be performed during screening and at the end of the combination phase. A CT will be performed for an interim assessment which occurs after the completion of R-CHOP administration in Cycle 3 (PET-CT is acceptable per investigator's preference or local SOC, see Appendix D for details). The end of combination phase restaging tumor assessment (PET-CT) will be performed at least 4 weeks but preferably at 6 to 8 weeks after the completion of the last cycle of R-CHOP; weeks calculated from the last administration of rituximab product. Subjects will be seen or contacted at regular intervals in the single-agent and follow-up phases of the study to determine survival status.
SAFETY EVALUATIONS	Vital signs, physical exams, adverse events, ECGs, safety labs.

DATA MONITORING COMMITTEE	An independent Data Monitoring Committee (DMC) will meet during the study to review safety data and monitor study progress.
STATISTICAL PLAN	Study sample size was estimated for the primary efficacy objective. The primary outcome of this study is OS, with the primary analysis to be conducted in DGM1 biomarker positive subjects. Study subjects will be randomized 1:1 to R-CHOP + enzastaurin or R-CHOP + placebo. This will be an event driven study. 66 events are required to provide approximately 90% power to detect a HR of 0.45 for OS in subjects who are positive for the DGM1 biomarker, when using a stratified log-rank statistic having one-sided alpha of 0.0235 (Section 7.4). Statistical significance will be achieved with an estimated HR ≤ 0.613. Assuming control arm subjects have one-year survival of approximately 60% to 70% and median survival of approximately 24 to 30 months, the trial will have an approximate sample size of 200 DGM1 biomarker positive subjects. If the enrollment period is 12-18 additional months, approximately 12 to 24 additional months will be required for 66 events to occur. If approximately 15% of trial subjects will be DGM1 biomarker negative, the trial would enroll approximately 235 subjects, with 200 being biomarker positive and 35 being biomarker negative.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	adverse event
ALP	alkaline phosphatase
ALT	amino alanine transferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CNS	central nervous system
CR	complete response
CRA	clinical research associate
CRF	case report form
CRu	unconfirmed complete response
CT	computed tomography
CTCAE	Common Toxicity Criteria Adverse Events
DGM1	Denovo Genomic Marker 1
DLBCL	diffuse large B-cell lymphoma
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event free survival
EIAEDs	enzyme-inducing anti-epileptic drugs
GCP	Good Clinical Practice
GSK3β	glycogen synthase kinase 3 beta
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	hazard ratio
ICD	informed consent document
ICH	International Conference on Harmonization
ID	identification
IEC	Independent Ethics Committee
IPI	International Prognostic Index
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
LDH	lactate dehydrogenase
mOS	median overall survival
MRI	magnetic resonance imaging

MTD	maximum tolerated dose
MUGA	multiple gated acquisition
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
NOS	not otherwise specified
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PD	progressive disease (disease progression)
PET	positron emission tomography
PFS	progression free survival
P-gp	p-glycoprotein
PI	Principal Investigator
PI3K	phosphoinositide 3-kinase
PK	pharmacokinetics
PKC	protein kinase C
po	per os (oral administration)
PR	partial response
PT	Preferred Term
QD	once daily
R-CHOP	rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, and prednisone
RNA	ribonucleic acid
SAE	serious adverse event
SEC	US Securities and Exchange Commission
SNP	single-nucleotide polymorphism
SOC	standard of care
SOE	Schedule of Events
TEAE	treatment-emergent adverse event
TID	three times daily
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
WHO	World Health Organization

1 INTRODUCTION

1.1 DIFFUSE LARGE B-CELL LYMPHOMA

Non-Hodgkin's Lymphoma (NHL) is the 7th most common cancer in the United States with 72,580 new cases predicted to occur in 2016 (SEER database). Approximately 20,150 people were predicted to die from this disease in 2016. Of these, slightly more than half, approximately 11,450 will be male, and 8,690 will be female. There are over a half million people with NHL living in this country. Diffuse Large B-Cell Lymphoma (DLBCL) is the most common of the NHLs, accounting for between 30%–40% of all cases. The incidence of DLBCL generally increases with age and roughly half of all patients are over the age of 60 at the time of diagnosis (Lymphoma Research Foundation, 2018).

DLBCL is classified as an aggressive lymphoma meaning that its clinical course can progress rapidly to death. Nevertheless, patients with DLBCL can be cured with the appropriate treatment. The current standard of care treatment for DLBCL consists of rituximab added to the anthracycline-containing combination chemotherapy regimen of cyclophosphamide, doxorubicin, vincristine and prednisone (NCCN Treatment Guidelines). This regimen is referred to as R-CHOP immunochemotherapy. For DLBCL as a whole, R-CHOP immunochemotherapy has resulted in cure rates of approximately 60%. However, for individual patients 5-year survival rates can range from 90% for low-risk DLBCL patients to less than 50% for high-risk DLBCL patients (Sehn et al., 2015; Zhou et al., 2014).

Most important, for those subjects refractory to R-CHOP therapy less than 10% achieve a durable remission with secondary therapy (Sehn et al., 2015). Thus, while R-CHOP remains the standard treatment for high-risk, advanced-stage DLBCL, approximately 30−40% of patients fail front-line therapy with most not achieving Complete Response (CR) or with early relapse. An essential step to move forward and improve the outcomes of these patients is to increase the rate of complete response to front-line R-CHOP therapy (Chiapella et al., 2016).

For this reason, there has been a great deal of effort placed on attempting to define disease characteristics that predispose patients to a poorer prognosis with R-CHOP therapy. Molecular and gene expression profiling of tumors and a variety of clinical prognostic indices have been used to identify patients at higher risk of failing R-CHOP immunochemotherapy. While this work has identified subgroups of patients who do not respond well to R-CHOP, to date these efforts have not resulted in substantial gains in response to front-line therapy.

Denovo Biopharma (Denovo) has pioneered an alternative approach to this challenging problem. Denovo has developed a model that employs sophisticated pharmacogenomic testing to detect somatic biomarkers that identify those subjects who responded to a particular study treatment with the aim of re-studying the drug of interest, in this case enzastaurin, in an enriched population.

Applying this technology to archived DNA samples from completed studies of enzastaurin in subjects with DLBCL, Denovo has identified a somatic biomarker that reliably identified subjects for whom the study treatment significantly prolonged survival. Enzastaurin is an oral serine/threonine kinase inhibitor, that targets the PKC, and phosphoinositide 3-kinase (PI3K) and

AKT pathways to inhibit tumor cell proliferation, induce tumor cell apoptosis, and suppress tumor-induced angiogenesis.

The purpose of the current study is to prospectively assess the effect on survival of adding enzastaurin to R-CHOP immunochemotherapy in the front-line treatment of an enriched population of subjects with DLBCL. The detailed rationale for this study is provided in greater depth below.

1.2 ENZASTAURIN

Enzastaurin, an acyclic bisindolylmaleimide, is a potent and selective inhibitor of PKC-β. At plasma concentrations achieved clinically, enzastaurin and its metabolites suppress signaling not only through PKC, but also through the PI3K/AKT pathway; these pathways promote tumor-induced angiogenesis, as well as tumor cell survival and proliferation. Accordingly, inhibition of signaling pathways by enzastaurin suppresses the phosphorylation of glycogen synthase kinase 3 beta (GSK3β) at ser9, induces cell death (apoptosis), and suppresses proliferation in cultured cell lines from human colon cancers (Gokmen-Polar et al., 2001), glioblastoma (da Rocha et al., 2002), and lymphomas (Shipp et al., 2002). Oral dosing with enzastaurin to achieve exposure levels similar to that in human clinical studies suppresses vascular endothelial growth factor (VEGF)-induced angiogenesis and the growth of human colon cancer and glioblastoma xenografts. These studies have demonstrated that enzastaurin can suppress tumor growth through multiple mechanisms: the direct effect of inducing tumor cell death, suppressing tumor cell proliferation, and the indirect effect of suppressing tumor-induced angiogenesis.

Enzastaurin was developed by Eli Lilly and Company (Lilly). Lilly performed 51 clinical studies and 15 clinical pharmacology studies of enzastaurin: 39 single-agent studies (enzastaurin alone, or enzastaurin with drugs other than anti-cancer agents) and 27 combination studies (enzastaurin + another anti-cancer agent). As of September 2013, a total of 4,387 cancer patients and healthy subjects were enrolled in Lilly-sponsored clinical trials, of whom approximately 3,337 subjects received enzastaurin. Of the approximately 3,337 subjects who received enzastaurin, 3,149 were cancer patients and 188 were healthy subjects in 9 completed clinical pharmacology studies. In 2014, Denovo completed the transfer of ownership of enzastaurin to enable its further clinical development. Denovo has identified a unique subset of patients with DLBCL who responded favorably to enzastaurin in a prior trial of similar design to this current study.

1.3 SUMMARY OF RELEVANT PRIOR ANIMAL AND HUMAN STUDIES

1.3.1 Absorption, Metabolism and Drug Interactions

Food significantly increases exposures to enzastaurin and its metabolites in both healthy subjects and cancer patients. Patients are required to take enzastaurin in the fed state in order to maximize drug absorption.

Enzastaurin is primarily metabolized in the liver, with minimal renal elimination. However, when enzastaurin was given to cancer patients with mild, moderate, or severe hepatic impairment, exposures tended to be lower than exposures observed in patients with normal hepatic function in previous studies, and decreased with increasing severity of hepatic dysfunction. It is currently not recommended to administer enzastaurin to patients with moderate or severe hepatic impairment.

The human cytochrome P450 (CYP) 3A enzyme appears to be responsible for the observed routes of enzastaurin metabolism:

- Plasma exposures of enzastaurin were reduced significantly in patients receiving CYP3A enzyme-inducing anti-epileptic drugs (EIAEDs) compared to patients not receiving EIAEDs. Concomitant medications that are potent inducers of CYP3A are expected to significantly decrease enzastaurin exposures.
- Potent CYP3A inhibitors (eg, ketoconazole) resulted in significantly higher exposures to enzastaurin in healthy subjects. Concomitant medications that are potent inhibitors of CYP3A are expected to significantly increase enzastaurin exposures.
- In the presence of the weak CYP3A inhibitor cimetidine, the area under the curve (AUC) and maximum plasma concentration (C_{max}) of enzastaurin increased approximately 20%, but there was no appreciable effect of cimetidine on the AUC or C_{max} of the metabolite LSN326020. Concomitant medications that are weak CYP3A inhibitors are not expected to cause clinically significant changes in enzastaurin exposures.
- Enzastaurin is a moderate inhibitor of CYP3A in cancer patients and may increase exposures to orally administered drugs that are CYP3A substrates.
- In vitro studies suggest that enzastaurin and its major metabolite are inhibitors of CYP2C8, CYP2C9, and CYP2C19. If this inhibition occurs in vivo, exposures to drugs that are substrates of these enzymes may be increased. A warfarin interaction study in cancer patients indicates that enzastaurin is a weak inhibitor of CYP2C9 (area under the plasma concentration time curve from time zero to infinity ratio [$AUC_{0-\infty}$] of 1.28).
- In vitro data indicate that enzastaurin may be a P-glycoprotein (P-gp) inhibitor. However, in a drug interaction study with intravenous (IV) digoxin (a P-gp substrate), 500-mg daily doses of enzastaurin did not affect the exposures of digoxin in cancer patients; these results suggest that enzastaurin has no effect on P-gp activity in vivo.
- The administration of a proton pump inhibitor had no significant effect on the exposure to enzastaurin when enzastaurin was administered in the fed state.
- In mice, enzastaurin has been observed to produce an increase in hexobarbital-induced sleep, which suggests that enzastaurin may enhance the effect of anesthetic agents.

1.3.2 Preclinical and Clinical Toxicity

1.3.2.1 Liver

Liver tumors were noted in a 2-year rat carcinogenicity study; the relevance of this finding to humans is unknown.

Transient, mild increases in aspartate aminotransferase (AST) and alanine aminotransaminase (ALT) levels were observed in enzastaurin clinical trials.

1.3.2.2 Cataracts

Cataracts occurred in dogs in a 6-month study at approximately 3- to 5-fold the maximum human plasma exposures seen in cancer patients given 525 mg enzastaurin.

1.3.2.3 Retinal Findings

High doses of enzastaurin (1500 mg/kg) given to transgenic (Tg.rasH2) mice every day for 6 months caused hypertrophy of the retinal pigmented epithelium (RPE). These changes were not seen in mice given lower doses of enzastaurin for 6 months or in a 1-month study in mice given higher doses of enzastaurin. The relevance of this finding to humans is not clear. Some cases of blurred vision and also some rare but serious cases of retinal detachment/tear, blurred vision, and visual impairment have been reported in clinical trials.

1.3.2.4 Thrombocytopenia

Enzastaurin-related thrombocytopenia has been reported and is usually mild and reversible.

1.3.2.5 Hemorrhage

Hemorrhage, possibly related to enzastaurin, was observed, including reports of possibly related fatal cerebral hemorrhage in patients with glioblastoma multiforme.

1.3.2.6 QTc Prolongation

Nonclinical data suggest a potential for QT/QT interval corrected for heart rate (QTc) prolongation for both enzastaurin and its active metabolite, LSN326020. QTc prolongation has also been observed at steady state, following the administration of enzastaurin 500-mg daily doses to cancer patients, and a concentration-QT effect has been observed with higher doses. The protocol requires careful and frequent ECG monitoring.

1.3.2.7 Pregnant or Lactating Women

Enzastaurin has not been evaluated in pregnant or lactating women, as these subjects have been excluded from enzastaurin clinical studies. Therefore, women of childbearing potential must have a negative serum pregnancy test prior to taking enzastaurin.

1.3.2.8 Adverse Events

The most frequent (≥5%) AEs seen in single-agent Phase 1b and 2 enzastaurin studies in cancer subjects that were considered by the investigator to be possibly related to enzastaurin were fatigue (15.6%), chromaturia (12.3%), diarrhea (9.4%), nausea (9.3%), platelets decreased (7.4%), and transaminase elevated (6.4%). The most frequent adverse drug reactions reported in subjects receiving enzastaurin in the DLBCL Phase 3 maintenance study (PRELUDE; H6Q-MC-JCBJ) were diarrhea (20.1%), chromaturia (19.5%), limb edema (15.8%), and prolonged QTc interval (11.63%). In general, the events reported for subjects in combination studies occurred at frequencies that were not higher than those described for the anti-cancer agents used.

1.3.3 Pharmacokinetics in Humans

Pharmacokinetics (PK) of enzastaurin was evaluated in a Phase 1, non-randomized, open-label, dose-escalation trial (H6Q−MC−JCAD [JCAD]) with escalating oral doses of enzastaurin from 20 mg to 700 mg administered to 47 subjects with advanced or metastatic cancer. The data

showed that the maximum drug concentration in plasma (C_{max}) of enzastaurin was reached within 4 hours of dosing. The half-life of enzastaurin ranged from 12.3 to 26.7 hours and accumulated 1.5- to 3.0-fold upon daily dosing. There was temporal linearity since plasma concentrations from Day 1 dosing predicted Day 28 concentrations reasonably well. Dose escalation proceeded with only three dose-limiting toxicities (DLTs) of prolongation of QTc by >50 msec over baseline. One of these occurred at the 700-mg dose and two others at the 525-mg dose. Laboratory and non-laboratory National Cancer Institute (NCI) Common Toxicity Criteria (CTC; NCI 1998, CTC Version 2) Grade 3 or 4 toxicities were not observed at any dose level. The maximum tolerated dose (MTD) was not identified to be in the dose range 20 to 700 mg. No increase in mean plasma exposures was seen at 700 mg compared to 525 mg. The most commonly reported toxicities were fatigue and reddish discoloration of urine and feces (enzastaurin is red in color). Overall, enzastaurin was well tolerated in this study.

In Study H6Q-MC-JCAJ (JCAJ), a Phase 2 trial of enzastaurin as single-agent therapy in subjects with recurrent high-grade glioma, subjects on enzyme-inducing anti-epileptic drugs (EIAEDs) such as phenytoin and carbamazepine had significantly decreased enzastaurin exposures.

The pharmacokinetics of enzastaurin was evaluated in 25 native Chinese cancer patients who each received a fixed dose of 500 mg of enzastaurin. Twenty-one subjects were available for the PK analysis. The T_{max} was found to be approximately four hours and the half-life of enzastaurin was found to be approximately 14 hours. The mean AUC at steady state was 29,100 nmol.h/L for enzastaurin and 21,800 nmol.h/L for the active metabolite LSN326020. These results compare favorably with those from studies in other cancer patients in which the mean AUC_{ss} for enzastaurin ranged from 23,600 to 44,100 nmol.h/L and for LSN326020 from 15,000 to 23,000 nmo.h/L. Enzastaurin appeared to be safe and well tolerated in this population (Li, X et al., 2016).

Previous human studies have shown that 14 days of daily oral dosing is needed to achieve steady state exposures of enzastaurin.

1.3.4 Previous Human Studies of Patients With NHL

The Lilly Investigator's Brochure lists seven studies in 899 subjects in which enzastaurin was administered to patients with NHL. Of these, four studies administered enzastaurin to approximately 673 subjects with DLBCL. These seven studies are summarized in

Table 1 below.

Table 1. Summary of Prior Studies of Enzastaurin Performed in Subjects with NHL

Study ID/ Title	Enza Dose	Objective	Key I/E Criteria	# of Subjects	Results
H6Q-MC-JCAI A Multicenter, nonrandomized, open-label, single arm, Phase 2 study of enzastaurin in patients with relapsed/refractory DLBCL	500 mg/day 6 x 28-day cycles	Primary endpoint: clinical response rate	Relapse following < 4 prior treatment regimens at least one of which must have been CHOP	N = 55 (42 evaluable)	Clinical RR: 21.8% ORR: 4%
H6Q-MC-JCAO A Multicenter, nonrandomized, open-label, single arm, Phase 2 study of enzastaurin in patients with relapsed mantle cell lymphoma	500 mg/day 6 x 28-day cycles	FFP for ≥3 cycles; PFS	Relapse following < 5 prior treatment regimens	N = 59	FFP rate for ≥ 3 cycles: 35.6% A subset of subjects had extended stable disease with 6 free from progression for > 6 months and 3 remaining on study for at least 15 months. No objective complete or PR were observed in this study. Median PFS: 1.97 months
H6Q-MC-S011 A Phase 2 Study of Enzastaurin in Patients with Follicular Lymphoma	1125 mg loading dose D1 followed by 500 mg/d	ORR; PFS	Gr 1 or 2 follicular lymphoma; Stage III or IV disease; no more than one prior treatment regimen	N = 66 (53 evaluable)	ORR = 26.4% (3.8% CR). Median PFS = 551 days
H6Q-M-S013 An Open-Label, Single-Arm, Phase 2 study of Rituximab, Gemcitabine and Oxaliplatin plus Oral Enzastaurin as Treatment for Patients with Relapsed DLBCL	1125 mg loading dose D1 followed by 500 mg/d	PFS rate at 12 months	DLBCL ≥ 60 y.o. or if < 60 not eligible for ASCT	N = 68 treated	PFS rate at 12 months = 16.4%

Study ID/ Title	Enza Dose	Objective	Key I/E Criteria	# of Subjects	Results
H6Q-MC-S028 An Open-Label, Randomized, Phase 2 Study of R-CHOP Plus Enzastaurin versus R-CHOP in the First-Line Treatment of Patients with Intermediate and High-Risk Diffuse Large B-Cell Lymphoma	6 x 21-day cycles of R-CHOP plus enzastaurin or R-CHOP enzastaurin dose: 1125 mg loading dose followed by 500 mg/day. Maintenance enzastaurin 500 mg/d for up to 3 years	PFS, RR, OS	Chemo naïve adults with histologically confirmed DLBCL	N = 101 (100 evaluable); 57 enzastaurin, 43 placebo	Median PFS: for R-CHOP/enzastaurin 36.2 months (95% CI: 20.2, NE; range 1-55 months); R-CHOP 23 months (95% CI: 9, NE; range 1-46.2 months; HR, 0.73; p = 0.151) High risk (IPI score > 2) R-CHOP/enzastaurin PFS when compared to R-CHOP: HR, 0.5; p = 0.037). Safety profile similar to control with slight increase in febrile neutropenia in enzastaurin arm. PK demonstrated no relevant drug-drug interactions between enzastaurin and CHOP components
H6Q-MC-S057 A Multicenter, Open-Label, Noncomparative Study of Enzastaurin in Patients with Non-Hodgkin's Lymphomas	1125 mg loading dose D1 followed by 250 mg BID	ORR	Relapsed subjects with TCL, or IBCL, or ABCL	N = 57	ORR: CTCL = 18.2%; SLL=14.3% and follicular grade 1 & 2 = 12.5%; Follicular grade 3a & 3b = 20.0% and history of IBCL = 10.0%. All responses were PR, except 1 CTCL patient had a CRu.
H6Q-MC-JCBJ A Phase 3 Study to Investigate the Prevention of Relapse in Lymphoma Using Daily Enzastaurin (PRELUDE)	500 mg/d for up to 3 years	DFS	DLBCL, CR or CRu after 6−8 cycles R-CHOP, stage 3 or 4 disease or bulky stage 2 disease	N = 758 randomized; 742 treated; Enzastaurin 493; placebo 249	Investigator-assessed DFS HR 0.92 (p = 0.54) Safety profile: TEAEs 93.1% enzastaurin vs 92.4% placebo; Gr 3/4 QTc prolongation: 3.4% enzastaurin vs 2.4% placebo; all but one = Gr 3

Abbreviations: ABCL, aggressive B-cell lymphoma; ASCT, autologous stem cell transplant; BID, twice daily; CR, complete response; CRu, unconfirmed complete response; CTCL, cutaneous T-cell lymphoma; DFS, disease free survival; DLBCL, diffuse large B-cell lymphoma; FFP, freedom from progression; Gr, grade; HR, hazard ration; IBCL, indolent B-cell lymphoma; IPI, International Prognostic Index; NE, non-estimable; ORR, objective response rate; OS, overall survival; PK, pharmacokinetic; PFS, progression free survival; PR, partial response; RR, response rate; SLL, small lymphocytic lymphoma; TCL, T-cell lymphoma; TEAE, treatment-emergent adverse event

1.4 DISCOVERY AND VALIDATION OF DGM1 BIOMARKER

As noted in the introduction, Denovo has pioneered an alternative approach to improving the response of patients with DLBCL to first line therapy with R-CHOP. Denovo has developed a model that employs sophisticated pharmacogenomic testing to detect somatic biomarkers that identify those subjects who responded to a particular study treatment with the aim of re-studying the drug of interest, in this case enzastaurin, in an enriched population.

The first such test of this model was applied to the Prelude trial. This was a multinational, randomized, double-blind, placebo-controlled study of high-risk DLBCL (IPI ≥ 3) patients with a histologic diagnosis of diffuse large B-cell lymphoma (DLBCL) and a CR or CRu, or a negative FDG-PET scan after 6–8 cycles of R-CHOP. Patients were randomly assigned in a 2:1 ratio to receive either enzastaurin 500 mg daily or an identical placebo as maintenance therapy, for a planned treatment duration of 3 years. The primary endpoint was DFS, defined as lack of disease progression or death. Data were analyzed three years after the last enrolled subject initiated treatment.

The study enrolled 758 subjects (enzastaurin, n = 504; placebo, n = 254). Median age at enrollment was 64 years (range 21–89); at diagnosis, 65% of patients had stage IV disease, 48% had B symptoms, and 25% had a mass >10 cm; baseline disease and patient characteristics were well balanced between treatment arms. Fifty-seven percent had a negative PET scan following completion of R-CHOP. Median follow-up time for all patients was 48 months (range 0.03–80). At the time of analysis, 209 events had occurred. The DFS HR for enzastaurin vs placebo was 0.92 (95% CI: 0.69, 1.22; 2-sided log-rank p = 0.54). DFS at 24 and 48 months were 79% and 70% for the enzastaurin arm, and 75% and 71% for placebo, respectively. OS at 24 and 48 months was 87% and 81% for enzastaurin, and 89% and 82% for placebo; HR for enzastaurin vs placebo was 1.04 (95% CI: 0.74, 1.47; 2-sided log-rank p = 0.81) (Crump et al., 2013).

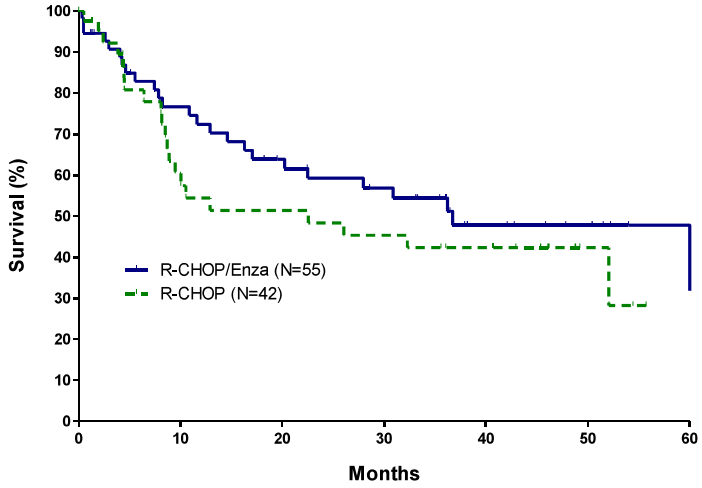
DNA samples extracted from blood of patients enrolled in the Prelude trial were genotyped using whole genome single nucleotide polymorphism (SNP) arrays. Approximately 5 million SNPs were analyzed. It was found that a specific configuration for two SNPs located on chromosome 8, Reference SNP ID 309605 (rs309605) and Reference SNP ID 309604 (rs309604), was strongly associated with survival in the enzastaurin arm. The p-value for this association was 5.8×10^{-9} (Note, given the multiple comparisons performed in exploratory pharmacogenomic research, a p-value smaller than 5×10^{-8} is usually considered the threshold for genome-wide significance.). This biomarker is now referred to as the Denovo Genomic Marker 1 (DGM1).

To confirm these findings from the Prelude trial, an analysis of the DGM1 biomarker was performed using archived DNA samples extracted from blood specimens from the P2 study of enzastaurin added to R-CHOP therapy in the front-line treatment of patients with intermediate or high-risk DLBCL. In this study, 101 subjects were randomized 3:2 to receive R-CHOP plus enzastaurin or R-CHOP as first line therapy for intermediate or high-risk DLBCL (enzastaurin-58 subjects, control-43 subjects). Following the initial treatment period, subjects in the enzastaurin group received maintenance enzastaurin for up to 3 years or until disease progression. The median PFS for patients in the enzastaurin arm was 36.2 months vs 22.6 months for in the control arm (HR = 0.73; p = 0.151). After adjusting for imbalances in baseline IPI score (≤ 2 vs > 2) and Eastern Cooperative Oncology Group (ECOG) PS (0 vs 1 or 2), the

HR was 0.59 (95% CI: 0.32, 1.09; one sided p-0.048) (Hainsworth et al., 2016). In a post-hoc subgroup analysis, subjects with an IPI score > 2 had a median PFS that was not evaluable in the enzastaurin arm compared to 8.9 months in the control arm (HR = 0.50). The 2-year OS was 75% and 69% in favor of enzastaurin in the overall population and 71% and 55% in favor of enzastaurin in the subset of subjects with an IPI score > 2. Conversely, in the post-hoc subgroup analysis, subjects with intermediate risk (IPI score 2) had an estimated increase in mortality from the addition of enzastaurin; approximately 90% of patients with IPI score 2 in the enzastaurin arm were DGM1 positive.

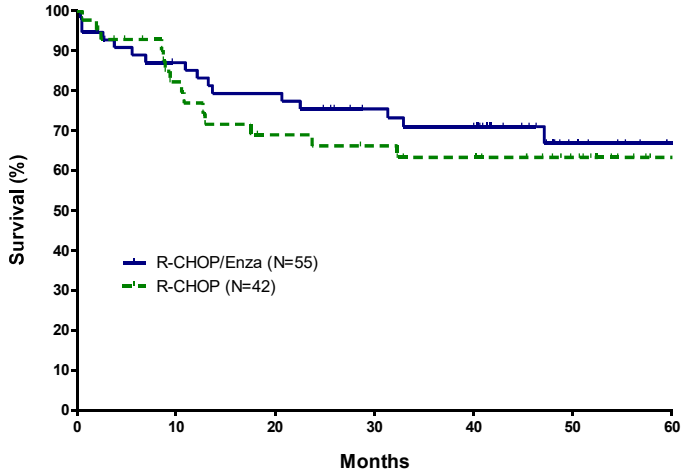
The Kaplan-Meier curves for PFS (Figure 1) and OS (Figure 2) are shown below.

Figure 1. Progression Free Survival R-CHOP/Enzastaurin vs R-CHOP



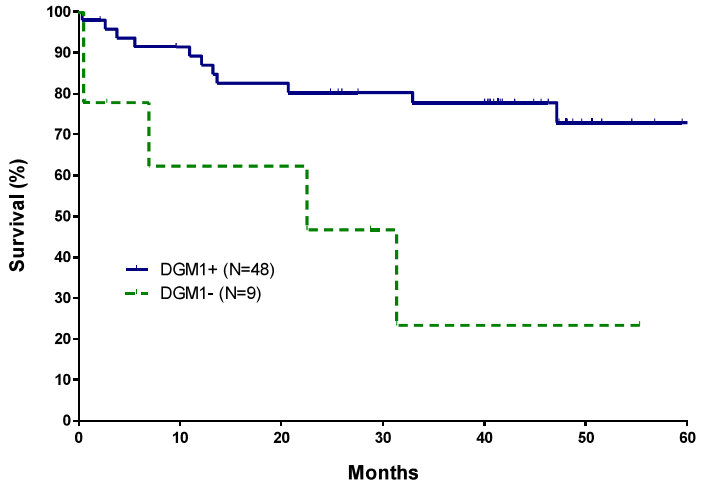
The mOS was not reached in either group. The HR for survival was 0.81 (0.39–1.67), p = 0.33.

Figure 2. Overall Survival R-CHOP/Enzastaurin vs R-CHOP



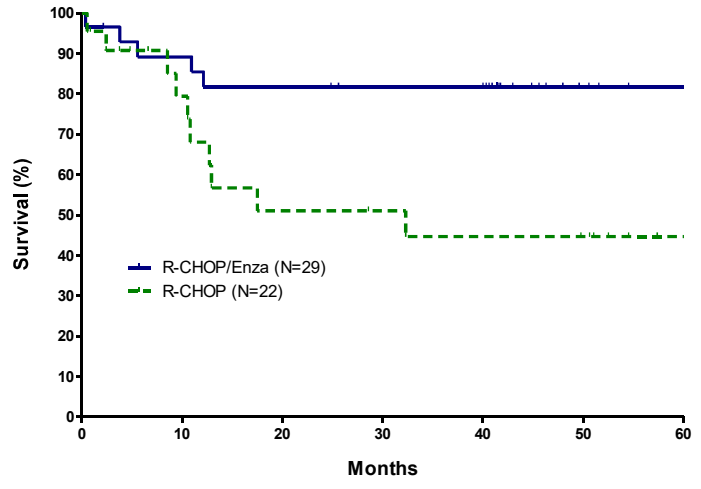
Analyzing these data based on the presence or absence of the DGM1 biomarker yields the following results (Figure 3). In the R-CHOP/enzastaurin arm, mOS for those with the DGM1 biomarker was not reached and for those lacking the biomarker was 22.5 months. The HR was 0.1 (0.02–0.49) (Note: HR: hazard ratio and 95% confidence interval).

Figure 3. Overall Survival R-CHOP/Enzastaurin Arm Based on Presence or Absence of DGM1 Biomarker



As discussed earlier, a subgroup analysis showed that addition of enzastaurin to R-CHOP had more favorable efficacy in high-risk DLBCL subjects and this efficacy is also observed in subjects who possess the DGM1 biomarker (Figure 4). The mOS for DGM1 positive, high-risk DLBCL (IPI ≥ 3) subjects in the R-CHOP/enzastaurin arm was not reached compared to 32.3 months for DGM1 positive, high-risk DLBCL subjects in the R-CHOP arm. The HR was 0.28 (0.1, 0.81).

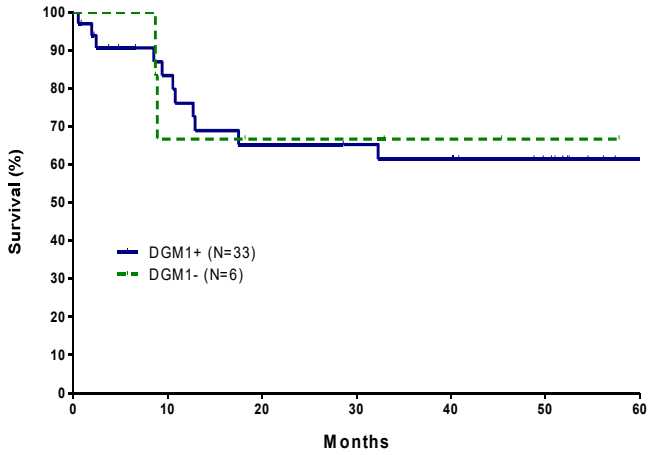
Figure 4. Overall Survival for DGM1 Positive, High-Risk DLBCL (IPI ≥ 3) Subjects R-CHOP/Enzastaurin vs R-CHOP



The question arises as to whether the DGM1 biomarker is a predictive or prognostic biomarker. This question can best be answered by performing the same biomarker analysis on subjects in the

R-CHOP control arm. When survival in the control arm (R-CHOP only) was analyzed, no improvement in survival was observed for subjects who possessed the DGM1 biomarker. The HR for survival in those subjects with the DGM1 biomarker was 1.02 (0.23–4.63) compared to those subjects who lacked the biomarker. These data are shown in Figure 5. These data demonstrate that in subjects with DLBCL, the DGM1 biomarker is a predictor of improved survival in the presence of enzastaurin, but does not confer a better prognosis for subjects who carry this biomarker.

Figure 5. Overall Survival by Presence or Absence of DGM1 Biomarker R-CHOP Arm



1.5 STUDY RATIONALE

The purpose of this study is to prospectively confirm the biomarker analysis results of the Phase 2 (study H6Q-MC-S028) study of enzastaurin in subjects with newly diagnosed high-risk DLBCL. The primary objective will be to analyze the effect on OS of adding enzastaurin to R-CHOP therapy in high-risk DLBCL (IPI $\geq$ 3) subjects who possess the DGM1 biomarker. This study aims to determine whether there is markedly improved survival in this enriched population compared to the current standard of care, R-CHOP alone. This study will be conducted in the United States, China and possibly other countries with an appropriate incidence of biomarker positive patients. The range of biomarker-positive subjects is approximately 68% for subjects of African ancestry living in the Southwest United States, approximately 90% for subjects of European ancestry, to approximately 95% of subjects living in Beijing, China. (International Genome Sample Resource-1000 Genomes Project).

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to compare the effect of R-CHOP plus enzastaurin followed by enzastaurin or standard of care (SOC) versus R-CHOP followed by SOC on OS in treatment naïve subjects with high-risk DLBCL who possess the DGM1 biomarker.

2.2 SECONDARY OBJECTIVES

- To determine the effect on OS of adding enzastaurin to R-CHOP in treatment-naïve subjects with high-risk DLBCL regardless of DGM1 biomarker status
- To evaluate Event-free Survival (EFS), including EFS12 and EFS24, for all subjects, and for subjects who are DGM1 biomarker positive.
- To compare the combination phase investigator assessed CR rate and objective response rate (ORR) in subjects with high-risk DLBCL who are DGM1 biomarker positive administered R-CHOP plus enzastaurin versus R-CHOP.
- To further evaluate the safety profile of enzastaurin when administered in conjunction with R-CHOP.

2.3 EXPLORATORY OBJECTIVES

- To determine enzastaurin and enzastaurin metabolite(s) concentrations for incorporation into a subsequent population pharmacokinetics (PK) analysis.
- To determine if the presence of other somatic or tumor biomarkers predicts improved efficacy in subjects taking enzastaurin.
- To determine if chromaturia (orange/red discoloration of the urine) predicts improved efficacy in subjects taking enzastaurin.
- To obtain samples urine for potential future analysis of enzastaurin metabolites.
- To explore any relationship between subsequent DLBCL therapy(ies) and OS.
- To assess regional similarities of primary and secondary efficacy measures between China and US.

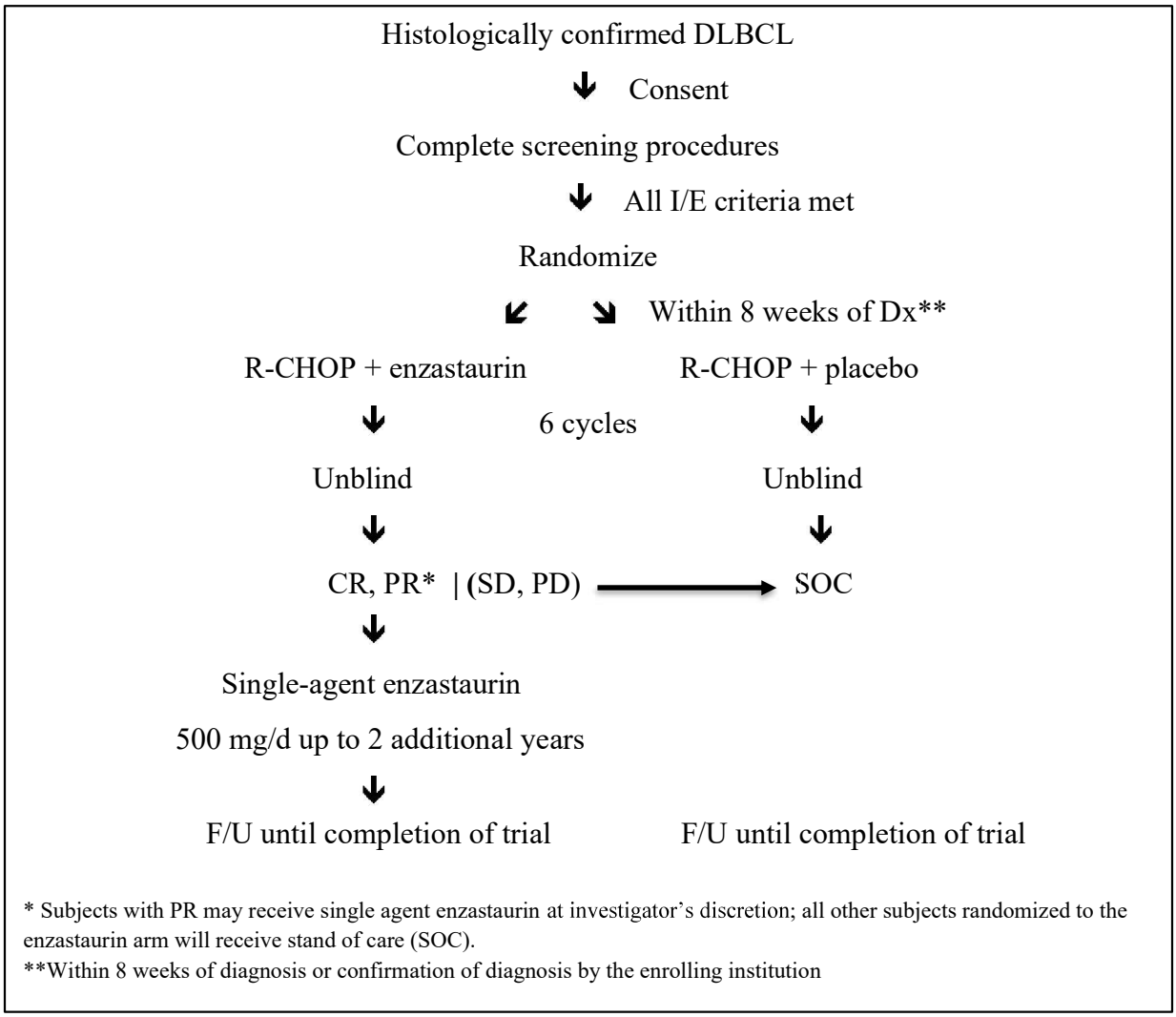
3 INVESTIGATIONAL PLAN

This is a multinational, multicenter, randomized, placebo-controlled Phase 3 study of enzastaurin added to R-CHOP in the treatment of treatment naïve subjects with high-risk DLBCL. The trial will enroll approximately 235 subjects with treatment-naïve DLBCL. For purposes of ensuring diagnostic consistency across participating centers and regions, and as a measure of quality assurance, the diagnosis of DLBCL will be reviewed and confirmed by an expert pathologist prior to final study analysis. Within 8 weeks of diagnosis or confirmation of diagnosis by the enrolling institution, subjects who meet all the inclusion and none of the exclusion criteria will be randomized 1:1 to receive R-CHOP plus enzastaurin or R-CHOP plus placebo for up to six, 21-day cycles (combination phase). R-CHOP will be administered in standard doses. Enzastaurin or placebo will be administered as an 1,125 mg loading dose (3 tablets TID within 30 minutes after a meal) on the first day after completion of R-CHOP administration in Cycle 1 and then 500 mg/day (4 tablets once daily within 30 minutes after a meal) thereafter. High-risk DLBCL subjects will be defined as those with an IPI score of at least 3.

After completion of the combination phase of treatment, subjects will be reassessed using PET-CT and subsequently each subject's treatment assignment will be unblinded. Subjects randomized to the enzastaurin arm who have a CR or PR at investigator's discretion by the Lugano Classification (Cheson 2014) will be offered single-agent enzastaurin at 500 mg/day (4 tablets once daily) continuously for up to 2 additional years. All other subjects on the enzastaurin arm and subjects randomized to the placebo arm will receive no further study treatment and transition into the follow up phase of the study; these subjects will receive standard of care based on their response assessment.

During follow up, all subjects will be followed for survival every 3 months until completion of the study, or 5 years, whichever comes first. The study is expected to take approximately 3.5 years to complete. The study schema is shown below in Figure 6.

Figure 6. Study Schema



* Subjects with PR may receive single agent enzastaurin at investigator's discretion; all other subjects randomized to the enzastaurin arm will receive stand of care (SOC).
**Within 8 weeks of diagnosis or confirmation of diagnosis by the enrolling institution

3.1 DISCUSSION OF STUDY DESIGN

This study is designed to confirm the biomarker analysis results of the Phase 2 (H6Q-MC-S028) study that suggested improved efficacy by adding enzastaurin to standard R-CHOP therapy in subjects with high-risk DLBCL who possess the DGM1 biomarker. Consequently, most of the features of that trial have been maintained in the current protocol. In order to minimize the potential for bias, the study will utilize a blinded, placebo-controlled design during the combination phase. In order to ensure that subjects are able to make an informed decision on their care, the treatment assignment of all subjects will be unblinded following completion of the combination phase and subsequent tumor assessment.

While a number of prognostic indices have been developed for patients with DLBCL, the Phase 2 study of enzastaurin used the "standard" International Prognostic Index, and therefore the same index will be used in the current study. This index defines 5 variables: age (> 60), tumor stage (III or IV), number of extranodal sites (> 1), ECOG performance status (> 1) and serum lactate dehydrogenase (LDH) (> 1 times upper limit of normal). One point is assigned for each variable and subjects with 3 points are classified as high-intermediate risk, and subjects with 4 or 5 points are classified as high-risk DLBCL. Subjects must have at least 3 points in order to be eligible for this study (See Appendix B. International Prognostic Index).

Because of the small number of biomarker negative subjects exposed to enzastaurin in Phase 2, biomarker negative subjects, as well as biomarker positive subjects, will be enrolled in this study.

4 STUDY POPULATION

Unless otherwise noted below, all eligibility criteria must be assessed within 28 days prior to randomization; tests performed as standard of care qualify for eligibility assessment if performed within this timeframe. Eligibility labs may be re-performed to meet eligibility if it is within the specified timeframe prior to randomization. IPI score (including LDH), and imaging scans should be performed before corticosteroids.

4.1 INCLUSION CRITERIA

All inclusion criteria must be met for the subject to be considered for the study.

1. Male or female at least 18 years of age and able to provide informed consent.
2. Histologically confirmed diagnosis of CD20 positive DLBCL based on the WHO classification (2016); the diagnosis must be confirmed at the enrolling site.
   Note: Subjects with high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements, or high-grade B-cell lymphoma, NOS are eligible.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2.
4. International Prognostic Index (IPI) score of at least 3.
5. Estimated life expectancy of at least 12 weeks.
6. Adequate organ function as follows (within 14 days prior to randomization):
   a. Hepatic: total bilirubin $\leq$ 1.5 times upper limit of normal (ULN) ($\leq$ 5 times ULN in the case of Gilberts Syndrome, liver or pancreatic involvement by lymphoma); alanine transaminase (ALT) and aspartate transaminase (AST) $\leq$ 2.5 times ULN ($\leq$ 5 times ULN if liver involvement)
   b. Renal: creatinine clearance of $\geq$ 40 mL/min by Cockcroft- Gault equation
   c. Bone marrow: platelets $\geq$ 75 x 10^9/L, absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L, hemoglobin $\geq$ 8 g/dL. (Platelets $\geq$ 50 x 10^9/L, ANC $\geq$ 1.0 x 10^9/L, hemoglobin $\geq$ 7.0 g/dL permitted if documented bone marrow involvement)
7. Male or female with reproductive potential, must be willing to use an approved contraceptive method (for example, intrauterine device (IUD), birth control pills, or barrier device) during and for 3 months after discontinuation of study treatment. Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to randomization.
   a. Men are considered of reproductive potential unless they have undergone a vasectomy and confirmed sterile by a post-vasectomy semen analysis.
   b. Women are considered of reproductive potential unless they have undergone hysterectomy and/or surgical sterilization (at least 6 weeks following a bilateral oophorectomy, bilateral tubal ligation, or bilateral tubal occlusive procedure that has been confirmed in accordance with the device's label) or achieved postmenopausal status (defined as cessation of regular menses for greater than 12 consecutive months in women at least 45 years of age).
8. Left ventricular ejection fraction $\geq$ 50% by echocardiography or nuclear medicine multi-gated scan.
9. Must be able to swallow tablets.
10. Must be able to comply with study protocol procedures.
11. Willing to consent to have blood stored for possible future biomarker and disease analysis.

12. Must have available and willing to submit pre-systemic treatment DLBCL tumor biopsy tissue/slides for central pathology review.

4.2 EXCLUSION CRITERIA

None of the exclusion criteria is met in order for the subject to be considered for the study.

1. Received treatment with an investigational drug within the last 30 days.
2. Receiving or has received radiation or any other systemic anticancer treatment for lymphoma (Up to 10 days of corticosteroids is permitted but should be administered after eligibility IPI determination and imaging scans).
3. History of indolent lymphoma or follicular Grade 3b lymphoma.
4. Primary mediastinal (thymic) large B-cell lymphoma.
5. B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma.
6. Burkitt lymphoma.
7. Pregnancy or breastfeeding.
8. Known central nervous system (CNS) involvement.
9. Any significant concomitant disorder based on the discretion of the investigator, including but not limited to active bacterial, fungal, or viral infection, incompatible with participation in the study.
10. A second primary malignancy (except adequately treated non-melanoma skin cancer); subjects who have had another malignancy in the past, but have been disease-free for more than 5 years, and subjects who have had a localized malignancy treated with curative intent and disease free for more than 2 years are eligible.
11. Use of a strong inducer or moderate or strong inhibitor of CYP3A4 (See Appendix A. Examples of Inhibitors and Inducers of CYP 3A4) within 7 days prior to start of study therapy or expected requirement for use on study therapy.
12. Personal or immediate family history of long QT syndrome, QTc interval > 450 msec (males) or > 470 msec (females) at screening (recommended that QTc be calculated using Fridericia correction formula, QTcF: see Section 6.2.1), or a history of unexplained syncope.
13. Use of any medication that can prolong the QT/QTc interval (See **Appendix** C. Drugs That Can Prolong the QT Interval) within 7 days prior to start of study therapy or expected requirement for use on study therapy.
14. History of severe allergic or anaphylactic reaction to monoclonal antibody therapy.
15. Confirmed diagnosis of progressive multifocal leukoencephalopathy.
16. Ongoing grade 2 or higher peripheral neuropathy.
17. Have any of the following cardiac disorders: uncontrolled hypertension, unstable angina, myocardial infarction within 8 weeks of randomization, New York Heart Association (NYHA) Grade 2 or higher congestive heart failure, ventricular arrhythmia requiring medication within 1 year of randomization, Fontaine Classification stage III or higher peripheral arterial disease.
18. Received a live vaccine within 28 days of randomization.
19. HIV positive.

20. Evidence of chronic hepatitis C infection as indicated by antibody to HCV with positive HCV-RNA.
21. Evidence of chronic hepatitis B infection as indicated by either:
    a) HBsAg+ or
    b) HBcAb+ with HBV-DNA+ (any detectable amount is considered positive)

4.3 RATIONALE FOR KEY EXCLUSION CRITERIA

This study is designed to confirm the biomarker analysis results of the Phase 2 (H6Q-MC-S028) study that demonstrated improved efficacy by adding enzastaurin to standard R-CHOP therapy in subjects with high-risk DLBCL who possess the DGM1 biomarker. Consequently, most of the features of that trial have been maintained in the current protocol. Because the number of DGM1 biomarker negative subjects treated in that study was too small to definitively assess their response to enzastaurin, both biomarker positive and negative subjects will be enrolled in the current study.

Because enzastaurin can prolong the QT interval, patients with a personal or immediate family history of long QT syndrome QTc interval > 450 msec (males) or 470 msec (females) at screening, a history of ventricular arrhythmias requiring medication within 1 year of randomization or a history of unexplained syncope, are excluded from participating in the study.

Because of the risk of cardiac dysfunction in subjects receiving anthracycline-based chemotherapy, the protocol excludes subjects with clinical or laboratory evidence of left ventricular dysfunction. An increase in the frequency of left ventricular cardiac function assessment is recommended in subjects who have received doxorubicin in the past, particularly as the cumulative dose exceeds 300 mg/m^2.

Although subjects with chronic hepatitis B infections may be treated with R-CHOP in conjunction with antiviral medication, the lack of PK or safety data with such combinations has prompted the exclusion of patients with chronic hepatitis B and C infections from this study.

4.4 WITHDRAWAL OF SUBJECTS

4.4.1 Discontinuation of Study Treatment

Subjects must discontinue study treatment for any of the following reasons:

1. The subject withdraws consent or requests to discontinue treatment on study.
2. The subject refuses to comply with the requirements for study evaluations/visits.
3. The subject develops an intercurrent illness or other substantial change in the subject's condition or circumstances that prevents further administration of study treatment or would place the subject at unacceptable risk, as determined by the Investigator in consultation with the Medical Monitor.
4. Investigator's decision.
5. Progressive disease that requires institution of a non-study therapy.

6. The subject becomes pregnant. Pregnant subjects should be followed for the duration of the pregnancy and the outcome of the pregnancy should be documented.
7. The subject cannot tolerate the study treatment despite dose delay and modification and appropriate supportive care.
8. Subject develops QTc prolongation >500 msec with life-threatening signs and symptoms (eg, arrhythmia, chronic heart failure, hypotension, shock, syncope) or torsade de pointes (CTCAE Grade 4).
9. Discontinuation of the study by the Sponsor, relevant regulatory agencies, or Institutional Review Board (IRB)/Independent Ethics Committee (IEC).
10. The subject dies.

All randomized subjects who discontinue from the study treatment should undergo the applicable End of Treatment (EOT) procedures and, unless consent is withdrawn, followed for survival as indicated in the Schedule of Events (SOE) in Table 6.

4.4.2 Withdrawal from Follow-Up

Subjects may withdraw or may be withdrawn from study follow-up, for any of the following reasons:

1. The subject withdraws consent or requests to be withdrawn from the study.
2. The subject dies.
3. The study concludes.

4.5 TERMINATION OF THE STUDY

The Sponsor retains the right to terminate the study at any time.

5 TREATMENT

5.1 TREATMENTS ADMINISTERED

Subjects will be randomly assigned to receive one of the following: R-CHOP plus enzastaurin (Arm A) or R-CHOP plus placebo (Arm B). There are two treatment periods: combination and single agent. Study treatment should be initiated within 3 days of randomization. For the R-CHOP regimen, subjects will receive a rituximab product, which may include Rituxan/MabThera or an FDA-approved rituximab biosimilar. However, for a given subject, Rituxan/MabThera or an FDA-approved rituximab biosimilar cannot be used interchangeably during the study; each subject must use the same rituximab product exclusively throughout the study treatment course.

5.1.1 Pre-randomization Treatment

Subjects may receive up to 10 days of treatment with corticosteroids prior to randomization. Such pre-randomization treatment should not be administered until after the subject's imaging scans, and IPI determination (including LDH) have been completed. Eligibility CBC must be assessed before or > 14 days after transfusion.

5.1.2 Combination

During the combination phase of the study, all subjects will receive R-CHOP in standard doses for up to six, 21-day cycles. Subjects in the enzastaurin arm (Arm A) will receive a 1125 mg loading dose on the first day following completion of R-CHO administration in Cycle 1 followed by 500 mg daily. Subjects in the placebo arm (Arm B) will take an identical number of tablets. These treatments are summarized in Table 2 and Table 3.

Table 2. Summary of Combination Dosing Regimens

	Arm A	Arm B
R-CHOP*	Up to six 21-day cycles	Up to six 21-day cycles
Enzastaurin[a]	Day 2[b]: 1125 mg (3 tablets TID); Subsequent doses: 500 mg (4 tablets) QD	
Matching Placebo[a]		Day 2[b]: 3 tablets TID; Subsequent doses: 4 tablets QD

*See details in Table 3 below.

[a] Taken within 30 minutes after a meal

[b] If R-CHO given over 2 days, the loading dose will be given on Day 3.

Table 3. R-CHOP Regimen

Drug	Dose/Mode	Day of Cycle
Rituximab***	375 mg/m^2 IV*	Day 1**
Cyclophosphamide	750 mg/m^2 IV	Day 1
Doxorubicin	50 mg/m^2 IV	Day 1
Vincristine	1.4 mg/m^2 i.v. (2 mg max)	Day 1
Prednisone	100 mg po	Days 1–5

Abbreviations: IV, intravenous; po, per os (oral administration)

*Premedicate with acetaminophen and antihistamine. First infusion: start at 50 mg/hr and increase by no more than 50 mg/hr every 30 minutes until a maximum of 400 mg/hr. Subsequent infusions: start at 100 mg/hr and increase by no more than 100 mg/hr every 30 minutes until a maximum of 400 mg/hr. If the subject did not experience a Gr 3 or 4 infusion reaction during Cycle 1, a 90-minute infusion can be administered with a glucocorticoid-containing chemotherapy regimen for subsequent infusions. Please consult full rituximab prescribing information for details.

**Cycle 1, at investigator's discretion, rituximab may be given alone on Day 1 with other components of CHOP given on Day 2. Prednisone would then be given Days 2–6 and enzastaurin loading dose would be given on Day 3. Although it is preferred that the entire R-CHOP regimen is administered on Day 1 in subsequent cycles, investigators may administer R-CHOP over two days in the same manner as Cycle 1 in subsequent cycles. Flexibility with R-CHOP schedule is allowed per local institutional practice.

*** A rituximab product (Rituxan/MabThera or an FDA-approved rituximab biosimilar) may be used. However, for a given subject, Rituxan/MabThera or an FDA-approved rituximab biosimilar cannot be used interchangeably during the study; each subject must use the same rituximab product exclusively throughout the study treatment course.

The investigator or his/her designee is responsible for explaining the correct use of the investigational agent(s) to subjects, verifying that instructions are followed properly, maintaining accurate records of study drug dispensing and collection, and returning all unused medication to Denovo or its designee at the end of the study, unless it is the site's policy to destroy or dispose of unused investigational product (IP) on site.

Subjects will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drug.

At the completion of the combination phase, a restaging tumor assessment will be performed at least 4 weeks but preferably at 6 to 8 weeks after the last combination cycle of R-CHOP; weeks calculated from the last administration of rituximab product. Enzastaurin/placebo will continue to be taken daily until unblinding determines transition to either the follow up phase or single-agent phase (see Section 5.1.3). Unblinding to treatment assignment will occur after the post-combination phase tumor response assessment is determined and documented.

5.1.3 Single-Agent

Following completion of 6 cycles of combination therapy and restaging via PET-CT, the treatment assignment for each subject will be unblinded. Subjects in the enzastaurin arm who have achieved a CR or PR (at investigator's discretion) will have the opportunity to continue in the single-agent phase of the study. These subjects will receive single agent enzastaurin at 500 mg/day for up to 2 additional years. Subjects who discontinue R-CHOP plus enzastaurin therapy before 6 cycles but otherwise meet these response criteria will also be allowed to continue to single-agent enzastaurin therapy at the investigator's discretion; these subjects must also undergo end of combination phase tumor assessment (at least 4 weeks but preferably 6 to 8 weeks after

the last combination cycle of R-CHOP) with response documented before unblinding. All other subjects will receive no further study treatment and will transition into the follow up phase; these subjects will receive standard of care based on their response assessment. The post-combination treatments are summarized in Table 4.

Table 4. Summary of Post-Combination Treatments

	Arm A	Arm B
CR, PR*	500 mg (4 tablets) QD with food for up to 2 additional years	Standard of Care
SD, PD	Standard of Care	Standard of Care

Abbreviations: CR, complete response; PD, disease progression; PR, partial response; QD, once daily; SD, stable disease
*Investigator's discretion

5.2 MATERIALS AND SUPPLIES

5.2.1 Enzastaurin (Kinenza®)/Placebo

Enzastaurin will be supplied by Denovo as enzastaurin monohydrochloride tablets containing 125 mg of active drug. The tablets must not be crushed or broken for administration.

The drug will be supplied in bottles containing 96 tablets. A separate bottle containing 9 tablets will be supplied for the loading dose.

Room temperature storage condition is recommended for the tablet drug product. The pharmacist or designee will dispense the correct number of tablets for each dosing cycle.

If a patient vomits within 30 minutes of taking a dose of enzastaurin, the enzastaurin dose should be repeated one time only, that same day, if nausea/vomiting is tolerable (at the discretion of the investigator).

Enzastaurin should be taken at approximately the same time every day, within approximately 30 minutes after a meal, preferably breakfast or lunch.

Matching placebo will be supplied for the combination phase of the study and should be taken in the same fashion as enzastaurin.

5.2.2 Rituximab Product

Rituximab product, which may include Rituxan/MabTheraor an FDA-approved rituximab biosimilar, will be supplied locally and should be prepared according to the package insert or local institutional practice.

Premedication consisting of acetaminophen and diphenhydramine may attenuate infusion reactions and should be given approximately 30–60 minutes before each infusion. A glucocorticoid may also be administered prior to rituximab product infusion if that is the local standard of care.

On Day 1 of each 21-day cycle, rituximab product is given as a slow intravenous infusion at a dose of 375 mg/m^2. **Rituximab product should never be administered as an intravenous push or bolus**, as severe infusion reactions may occur. These reactions typically occur during the first infusion with a time to onset of 30–120 minutes.

First Infusions

The subject must be afebrile at the time of the first infusion. Rituximab product should not be mixed or diluted with other drugs. The initial infusion rate should be 50 mg/hr. If the subject tolerates this infusion, the rate can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If an infusion reaction develops, the infusion should temporarily be slowed or interrupted. Upon improvement of the subject's symptoms, the infusion may be resumed at one-half the previous rate.

For Cycle 1, at the investigator's discretion, rituximab product may be given alone on Day 1 with other components of CHOP given on Day 2. Prednisone would then be given Days 2–6 and enzastaurin loading dose or placebo would be given on Day 3. Additionally, investigator may choose to administer rituximab product over 2 days at the beginning of each cycle per local practice. Although it is preferred that the entire R-CHOP regimen is administered on Day 1 in subsequent cycles, investigators may administer R-CHOP over two days in the same manner as Cycle 1 in subsequent cycles.

Subsequent Infusions

If the subject tolerated the first infusion well, subsequent infusions of rituximab product can be administered at an initial rate of 100 mg/hr and increased in 100 mg/hr increments at 30-minute intervals to a maximum of 400 mg/hr. If the subject did not tolerate the first infusion well, subsequent infusions should follow the guideline for first infusion above. If the subject did not experience a Grade 3 or 4 infusion reaction during Cycle 1, a 90-minute infusion can be administered with a glucocorticoid-containing chemotherapy regimen for subsequent infusions. Please consult full rituximab prescribing information for details.

5.2.3 Cyclophosphamide

Cyclophosphamide will be supplied locally and should be prepared according to the package insert or local institutional practice. Cyclophosphamide 750 mg/m^2 will be given intravenously on Day 1 of each 21-day cycle. If the investigator elects to give R-CHOP over 2 days, cyclophosphamide will be given on Day 2.

5.2.4 Doxorubicin

Doxorubicin will be supplied locally and should be prepared according to the package insert or local institutional practice. Doxorubicin 50 mg/m^2 will be given intravenously on Day 1 of each 21-day cycle. If the investigator elects to give R-CHOP over 2 days, doxorubicin will be given on Day 2.

5.2.5 Vincristine

Vincristine will be supplied locally and should be prepared according to the package insert or local institutional practice. Vincristine 1.4 mg/m^2 (2 mg max) will be given by intravenous push

on Day 1 of each 21-day cycle. If the investigator elects to give R-CHOP over 2 days, vincristine will be given on Day 2.

5.2.6 Prednisone

Prednisone will be supplied locally. Prednisone 100 mg will be given orally from Day 1 through Day 5 of each 21-day cycle. If the investigator elects to give R-CHOP over 2 days, prednisone will be given on Day 2 through Day 6.

5.3 METHOD OF ASSIGNMENT TO TREATMENT

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized through a web-based (IWRS) or voice-activated (IVRS) randomization system. Randomization will be stratified by IPI score: 3 vs 4, 5, and by region.

5.4 RATIONALE FOR SELECTION OF DOSES IN THE STUDY

As discussed previously, the purpose of this study is to confirm the results of the Phase 2 study, H6Q-MC-S028. The dose of enzastaurin used in the Phase 2 study was 500 mg/day following an 1125 mg loading dose. This dose has been administered to over 600 subjects with DLBCL. In the completed Phase 2 study, when combined with R-CHOP, this dose was found to have a safety profile similar to that of the R-CHOP control arm.

R-CHOP is still considered the standard of care for subjects with DLBCL and will be administered in the recommended doses.

5.5 DOSE MODIFICATIONS

5.5.1 Enzastaurin

5.5.1.1 During Combination Therapy

Subjects should be supported by initiation of colony stimulating factors and/or platelet transfusions. If a subject experiences any of the following events that are considered related to the study drug, enzastaurin/placebo will be held until the event resolves (all CTCAE grades are based on CTCAE v4.03):

- Febrile neutropenia, defined as ANC $< 1.0 \times 10^9$/L with a single temperature of $> 101°F/38.3°C$ or sustained temperature of $\geq 100.4°F/38°C$ for more than one hour
- CTCAE Grade 4 anemia, neutropenia or thrombocytopenia that continues after delaying R-CHOP therapy or Grade 3 thrombocytopenia with clinically significant bleeding that continues after delaying R-CHOP therapy
- CTCAE Grade 3 or 4 transaminase elevations
- CTCAE Grade 3 or 4 nonhematologic toxicity (excluding alopecia) considered clinically relevant. Study drug should be held for Grade 3 or 4 nausea or vomiting that lasts for more than 3 days despite supportive management. (Note: subjects with QTc >500 msec should have ECGs performed in triplicate, approximately five minutes apart. If 2 of the 3 ECGs demonstrate QTc > 500 msec [Grade 3 QTc prolongation], study drug should be held, and a repeat ECG should be performed within 7 days after study drug is held.)

If the event resolves to ≤ Grade 1 or to the subject's baseline value (or if the QTc corrects to ≤ 450 msec [males] or ≤ 470 msec [females]), enzastaurin/placebo should be restarted at a reduced dose of 250 mg (2 tablets) per day. If, after restarting therapy, the subject does not have recurrence of the event after 14 days, the dose of enzastaurin/placebo may be re-escalated to 500 mg (4 tablets) at the discretion of the investigator. If the event has not resolved to Grade 1 or to the subject's baseline (or QTc to ≤ 450 msec [males] or ≤ 470 msec [females]) within 42 days or the same event reoccurs during therapy at the 250 mg/day dose, enzastaurin/placebo will be discontinued.

Except for subjects who had enzastaurin discontinued for QTc prolongation, subjects who had enzastaurin discontinued during the combination phase (in the enzastaurin arm) and experienced a CR or PR at end of combination treatment, may receive single agent enzastaurin during the single-agent phase at the discretion of the investigator.

5.5.1.2 During Single-Agent Therapy

If a subject experiences any of the following events that are considered related to enzastaurin, the drug will be held until the event resolves (all CTCAE grades are based on CTCAE v4.03):

- ANC < 0.5 x 10^9/L for longer than 7 days, or ANC < 1.0 x 10^9/L with a single temperature of > 101°F/38.3°C (or sustained temperature of ≥ 100.4°F/38°C for more than one hour) or platelet count < 25 x 10^9/L
- CTCAE Grade 3 or 4 transaminase elevations
- Other CTCAE Grade 3 or 4 nonhematologic toxicity considered clinically relevant (Note: subjects with QTc > 500 msec should have ECGs performed in triplicate, approximately five minutes apart. If 2 of the 3 ECGs demonstrate QTc > 500 msec [Grade 3 QTc prolongation], study drug should be held, and a repeat ECG should be performed within 7 days after study drug is held.)

If the event resolves to ≤ Grade 1 or to the subject's baseline value (or if the QTc corrects to ≤ 450 msec [males] or ≤ 470 msec [females]), enzastaurin should be restarted at a reduced dose of 250 mg (2 tablets) per day. If, after restarting therapy, the subject does not have recurrence of the event after 14 days, the dose of enzastaurin may be re-escalated to 500 mg (4 tablets) at the discretion of the investigator. If the event has not resolved to Grade 1 or to the subject's baseline (or QTc to ≤ 450 msec [males] or ≤ 470 msec [females]) within 42 days, or the same event reoccurs during therapy at the 250 mg/day dose, the subject will be discontinued from study treatment.

5.5.2 R-CHOP

Dose reductions for R-CHOP chemotherapy will follow standard guidelines according to package insert or local institutional practice. Use of granulocyte-colony stimulating factors (eg, filgrastim or pegfilgrastim) as primary prophylaxis is encouraged. If subjects require delay of therapy due to neutropenia (based on parameters described below), or develop neutropenic fever, cytokines should be administered during subsequent courses. If delay in therapy due to neutropenia, or neutropenic fever occurs even when cytokines are used, the doses of

myelosuppressive agents (cyclophosphamide, doxorubicin) should be decreased to 75% for subsequent courses.

On the day of scheduled treatment:

- ANC ≥ 1.2 x 10^9/L and platelets ≥ 75 x 10^9/L or ANC ≥ 1.0 x 10^9/L and platelets ≥ 50 x 10^9/L if documented bone marrow involvement, full dose.
- ANC < 1.2 x 10^9/L or platelets < 75 x 10^9/L or ANC < 1.0 x 10^9/L and platelets < 50 x 10^9/L if documented bone marrow involvement, delay dose at least 1 week (maximum delay 21 days) until counts are above these levels. Recommend instituting granulocyte-colony stimulating factors if not already done so.

For patients with symptomatic Grade 3 or any Grade 4 non-hematologic toxicity (except alopecia, nausea, and vomiting), treatment should be delayed until toxicity resolves to ≤ Grade 1 or baseline, then continue with 75% doses of offending agents.

Other toxicity delays of any of the individual chemotherapy regimen drugs (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) are allowed. Other toxicity delays for R-CHOP as an unit are allowed to a maximum of two ≥ 14-day delays over all the 6 treatment cycles.

Even if R-CHOP is discontinued early, subjects who would otherwise qualify for single-agent treatment (Section 5.1.3) may move on to the single-agent phase of the study, at the discretion of the investigator.

Rituximab product (Rituxan/MabThera or an FDA-approved rituximab biosimilar) will not be dose reduced, but infusion rates should be changed in accordance with the prescribing information listed in the package insert. Dose reductions for individual component of CHOP are allowed per local institutional practice or package insert.

Dose modifications for changes in weight may be conducted per institutional practice. It is suggested that body weight change of more than 10% from weight used for previous dose calculation should lead to recalculation of BSA and dose adjustment if necessary.

5.6 BLINDING

The combination period follows a double-blind, placebo-controlled design. Subjects will be randomized to receive enzastaurin or placebo tablets identical in appearance to the investigational product. Investigators, subjects and the Sponsor will be blinded to the treatment assignments. Treatment assignment will be unblinded after completion of the post-combination phase tumor assessment.

5.7 CONCOMITANT THERAPY

No other chemotherapy, immunotherapy, surgery for cancer, or experimental medications will be permitted while the patients are on study treatment. Radiation therapy is not permitted during the 6 cycles Combination Phase. Consolidation radiotherapy is permitted after the completion of Combination Phase if it is site SOC, but it must be performed after the tumor assessment is complete. Any disease progression requiring other forms of specific antitumor therapy will be

cause for discontinuation from study treatment. Subjects discontinued from study treatment must continue to be followed for safety and efficacy assessments.

Subjects are allowed to receive full supportive care therapies concomitantly during the study. At each visit, appropriate documentation of all forms of premedication, supportive care, and concomitant medications must be captured on the case report form (CRF).

Concomitant medications and supportive care therapies must also be documented at the time of discontinuation.

Premedication will be given per institutional guidelines.

5.7.1 Effect of Concomitant Medications on Enzastaurin Concentrations

In vitro metabolism studies using human liver microsomes have demonstrated metabolism of enzastaurin is primarily by CYP3A. Concomitant medications that are potent inducers or inhibitors of isozyme CYP3A will therefore affect enzastaurin exposure. Concomitant drugs that are inducers of CYP3A could result in lower exposures of enzastaurin and its metabolites while concomitant drugs that are inhibitors of CYP3A may increase the exposure of enzastaurin and its metabolite(s) in patients. Potent inhibitors of CYP3A, such as ketoconazole, are expected to increase enzastaurin exposure. Based on these considerations, subjects who require therapy with a strong inducer or moderate or strong inhibitor of CYP3A4 should not be enrolled into the study. If medically justified, subjects may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not affect these enzymes can be substituted > 7 days before the first dose of the study drug.

During study participation administration of enzastaurin with a strong inducer or moderate or strong inhibitor of CYP3A4 should be avoided, if possible. However, a subject who develops a condition that may require use of such drugs is not required to permanently discontinue enzastaurin if the subject is experiencing clinical benefit. If medically appropriate, investigators may wish to use a therapeutic alternative that would not be expected to affect these enzymes. For subjects who require temporary use of a strong inducer or moderate or strong inhibitor of CYP3A4, enzastaurin should be interrupted during use of the other medication and then resumed no early than 7 days after its completion. For subjects who require initiation of chronic therapy with a drug that potently affects these enzymes, investigators must consult with the Medical Monitor to consider the best course of action.

A list of moderate and potent CYP3A inhibitors and potent inducers is found in Appendix A.

In order to avoid potential drug-drug interaction it is recommended that subjects enrolled in this study not use traditional Chinese medications while participating in this study.

Subjects on enzyme-inducing anti-epileptic drugs (EIAED) such as phenytoin, carbamazepine, and phenobarbital should be switched to non-EIAEDs such as levetiracetam, gabapentin, topiramate, tiagabine, zonisamide, or clonazepam at least two weeks prior to initiating study drug.

5.7.2 Effect of Enzastaurin on Concomitant Medications

Data indicate that enzastaurin may affect the metabolism of drugs that are metabolized by cytochrome P450 isozymes. A drug interaction study indicates that enzastaurin may increase the effect of warfarin. Subjects who must take warfarin while taking enzastaurin should be monitored carefully and the dose of warfarin adjusted to prevent toxicity.

Pharmacokinetic evaluation in a subset of subjects in the completed Phase 2 study (H6Q-MC-S028) indicated that addition of enzastaurin to R-CHOP did not affect exposure (AUC) to doxorubicin, cyclophosphamide, 4-ketocyclophosphamide or dechloroethyl-cyclophosphamide.

5.7.3 Colony-Stimulating Factors

Use of colony-stimulating factors (eg, filgrastim or pegfilgrastim) as primary prophylaxis is encouraged and may be based on the recommendations of the American Society of Clinical Oncology guidelines, or on the treating institution's own guidelines. However, colony-stimulating factors should not be instituted prior to C1D1 and are prohibited before screening labs are performed.

5.7.4 QT Interval Prolonging Medications

Nonclinical data suggest a potential for QT/QT interval corrected for heart rate (QTc) prolongation for both enzastaurin and its active metabolite. QTc prolongation has also been observed at steady state, following the administration of enzastaurin 500-mg daily doses to cancer patients, and a concentration-QT effect has been observed with higher doses.

Based on these considerations, subjects who require therapy with medications that prolong the QT interval should not be enrolled into the study. If medically justified, subjects may be enrolled if such medications can be discontinued or alternative drugs that do not prolong the QT interval can be substituted > 7 days before the first dose of the study drug.

During study participation administration of enzastaurin with medications that can prolong the QT interval should be avoided. However, a subject who develops a condition that may require use of such drugs is not required to permanently discontinue enzastaurin if the subject is experiencing clinical benefit. If medically appropriate, investigators should use a therapeutic alternative that would not be expected to affect QT interval. For subjects who require temporary use of a medication that can prolong the QT interval, enzastaurin should be interrupted during use of the other medication and then resumed no early than 7 days after its completion. For subjects who require initiation of chronic therapy with a drug that potently affects the QT interval, investigators must consult with the Medical Monitor to consider the best course of action.

A list of drugs that can prolong the QT interval is found in Appendix C.

5.7.5 Central Nervous System (CNS) Prophylaxis

Subjects considered high-risk for CNS relapse (Schmitz et al. JCO 2016) may be administered CNS prophylaxis at the investigator's discretion. However, during combination phase only intrathecal administration of CNS prophylaxis is permitted. During single agent phase, intravenous administration is permitted per investigator's discretion.

5.8 TREATMENT COMPLIANCE

Subject compliance with study drug must be stressed and assessed at each visit. Compliance will be assessed by direct questioning, review of study calendars and counting returned tablets. Each subject should be instructed to return all study drug packaging and unused material to the study site at each visit. The study site will keep a record of all drug dispensed to and returned by subjects throughout the study. Study site personnel will return all unused medication to Denovo or its designee at the end of the study, unless it is the site's policy to destroy or dispose of unused investigational product on site.

Deviations from the prescribed dosage regimen should be recorded in the case report form (CRF).

For subjects who are significantly noncompliant (< 80% or > 120% of expected study drug taken in a visit interval), investigative sites must counsel subjects on the importance of study drug compliance and drug accountability. Subjects who are consistently out of the compliance range may be discontinued.

Treatment compliance information for enzastaurin will be collected through pill counts at each visit. The estimate of percent compliance will be determined by:

$$Percent\ Compliance = \frac{Actual\ number\ of\ tablets\ taken}{Number\ of\ tablets\ expected\ to\ be\ taken}\ X\ 100$$

The number of tablets taken will be determined by counting the number of tablets returned at each visit and subtracting that number from the number of pills dispensed. The number of pills expected to be taken will be determined by the assigned dose and taking into account any prescribed dose holds and reductions.

No minimal level of compliance will be defined for patient inclusion in efficacy analyses. However, exploratory analysis of compliance may be undertaken by regressing percent compliance on selected efficacy endpoints. If significant results are indicated, further analysis may be performed to determine the level of compliance that best delineates each endpoint.

6 EFFICACY, SAFETY EVALUATIONS, AND SAMPLE COLLECTION AND TESTING (STANDARD LABORATORY TESTING AND APPROPRIATENESS OF MEASUREMENTS)

Refer to the Schedule of Events (Section 13) for the timing of study procedures.

6.1 EFFICACY MEASURES

6.1.1 Tumor Assessments and Schedule

Each subject's disease will be assessed by the investigator using standardized criteria: Lugano Classification (Cheson 2014). The scans will be submitted to a central imaging vendor for potential central review as needed.

See Appendix D for detailed guidance on tumor assessments including method of assessment, timing of assessments, and definitions of tumor response and progression.

6.1.2 Primary Efficacy Measure

The primary efficacy endpoint for this trial is OS in subjects who are DGM1 biomarker positive. OS is defined as the elapsed time from the date of randomization to the date of death from any cause. For patients not known to have died as of the data cut-off date, OS will be censored at the last contact date or last date known to be alive, whichever is later.

6.1.3 Secondary Efficacy Measures

- OS in all subjects regardless of DGM1 biomarker status. OS is defined as the time between randomization and death due to any cause.
- EFS including EFS12 and EFS24, for all the subjects, and for the subjects who are DGM1 biomarker positive.
    - EFS is defined as the time from randomization until occurrence of one of the following events, whichever occurs first:
        - Disease progression
        - Relapse from CR
        - Initiation of subsequent systemic anti-lymphoma therapy
        - Death due to any cause
    - EFS 12 is defined as the event-free status at 12 months (%) from randomization.
    - EFS 24 is defined as the event-free status at 24 months (%) from randomization.
- CR as defined in Appendix D in subjects who are DGM1 biomarker positive
- ORR (CR and PR as defined in Appendix D) in subjects who are DGM1 biomarker positive

6.1.4 Exploratory Efficacy Measures

- Chromaturia (orange/red discoloration of urine)
- Germline polymorphisms and tumor gene mutations
- Post-study treatments, lack of post-study treatment
- Subgroup analyses of primary and secondary efficacy measures in China region and US region

6.2 SUBJECT EVALUATIONS

6.2.1 Pretreatment Evaluations

Unless otherwise noted below, all pretreatment evaluations must be performed within 28 days prior to randomization; tests performed as standard of care qualify for eligibility assessment if performed within this timeframe. Eligibility labs may be re-performed to meet eligibility if it is within the specified timeframe prior to randomization. IPI score (including LDH), and imaging scans should be performed before administration of corticosteroids. Subjects must sign an approved informed consent document (ICD) prior to undergoing any study specific evaluations.

- A complete history, physical (including height and weight) and ECOG performance status.
- A unilateral bone marrow biopsy (BMB) should be performed if clinically indicated (eg, to evaluate indeterminant PET-CT findings, cytopenia, or presence of discordant lymphoma).
- **Pretreatment laboratory tests include:** CBC (Hgb, WBC with differential, platelets), chemistry panel (serum creatinine, creatinine clearance, total bilirubin, direct bilirubin, AST/ALT, LDH, alkaline phosphatase (ALP), BUN or Urea, glucose, potassium, sodium, calcium), HIV, hepatitis B and C, and serum pregnancy test (within 7 days prior to randomization for women with reproductive potential). Organ function assessment (hepatic, renal, and bone marrow) as indicated in the eligibility criteria must be performed within 14 days prior to randomization.
- **Biomarker:** Blood test for DGM1. Blood will be stored for immuno-typing (includes potential additional biomarker analysis and lymphoma subtyping). The Sponsor and clinical study site will be blinded to DGM1 results during the study.
- **ECG** with QT corrected by Fridericia's formula ($QTcF = QT/RR^{0.33}$) is recommended.
- **Echocardiogram or nuclear medicine test of ventricular function (MUGA)**
- **Documentation of tumor histology and CD20 expression:** The subject will be enrolled based on confirmation of the histologic diagnosis at the enrolling site. Following enrollment in the study, tumor histology will be confirmed by a central pathology review that will be used for the final study analysis. DLBCL subtype assessment (eg, cell of origin, tumor mutations) may also be performed by central pathology review. Tissue slides/samples must be submitted for review once the subject is enrolled. Instructions for submission of tissue slides/samples will be detailed in a separate manual.
- **Radiology Imaging:** See Appendix D and SOE (Table 6). A PET-CT performed as part of standard of care qualifies for the screening requirement as long as it was performed within 28 days of randomization.

6.2.2 Evaluations on Study

Please see the SOE (Table 6) for the timing of procedures.

- **CBC:** CBC will be performed at all study visits until the subject completes/discontinues study treatment and enters the follow-up phase. The SOE (Table 6) shows the timing of CBCs

- **Chemistries:** Chemistries will be performed at all study visits until the subject completes/discontinues study treatment and enters the follow-up phase. The SOE (Table 6) shows the timing of chemistry testing.
- **Serum Pregnancy:** Performed at all scheduled study visits starting with Cycle 2; must be negative to continue study treatment.
- **Urinalysis:** Urinalysis will be performed using ambient urine sample by the central laboratory. Subjects that do not continue into the single-agent phase will have urinalysis on C1D1 and EOT. Subjects that continue to the single-agent phase will have urinalysis on C1D1 and V9.
- **Urine color assessment:** Urine color assessment using ambient urine sample by the central laboratory will occur on C1D1, C1D8, and C2D1 for all subjects. Subjects that do not continue into the single-agent phase will also have urine color assessment at EOT. Subjects that continue to the single-agent phase will also have urine color assessment at V9. The Sponsor and clinical site will be blinded to the results of the urine color assessment during the study.
- **Urine metabolites:** Frozen urine samples collected will be retained for possible future analysis of enzastaurin metabolites. If such analyses are conducted, the results will be reported separately by the Sponsor.
- **Brief Physical Exam:** vital signs, heart, lungs, abdomen and lymph node exam.
- **Radiology Imaging:** See Appendix D and SOE (Table 6).
- **Bone Marrow Biopsy:** required at end of treatment in those patients who have otherwise achieved a CR and had a positive BMB at screening/baseline.
- **ECG:** ECGs will be performed at C1D2 or C1D3 (to coincide with the first dose of enzastaurin/placebo), C2D1, C4D1, C6D1, V9, V12-17 and EOT. The ECGs on C1D2/C1D3, C2D1, and C4D1 will be performed prior to taking enzastaurin/placebo and approximately 4-6 hours after the subject has taken his/her study medication. ECGs on C6D1, V9, V12-17 and EOT will be performed before study treatment if applicable. If R-CHOP is expected to be delayed greater than 7 days but enzastaurin/placebo is being taken, ECG should be performed as an unscheduled visit at the temporal timepoint and repeated on the appropriate Cycle/Day when cycles are restarted (ie, R-CHOP is administered). The QT interval corrected by Fridericia's formula is recommended and all ECG equipment must have been recently calibrated and well maintained.
- **Population PK:** Two blood samples per subject will be collected on C2D1 and C4D1 for population pharmacokinetic analysis. The sample on C2D1 should be collected prior to administration of enzastaurin (pre-dose); the C4D1 blood sample should be collected between 3-6 hours after the enzastaurin dose. The time of the dose administration and blood sampling will be recorded on a laboratory requisition.

  Approximately 2 mL of blood will be collected with K2EDTA for each sample (See SOE (Table 6).

  Samples will be analyzed for enzastaurin at a laboratory approved by the Sponsor using a validated liquid chromatography tandem mass spectrometry (LC/TS/MS) method. It is intended that the blood samples collected from patients receiving placebo (R-CHOP

alone) will not be analyzed. If a patient discontinues before study completion, an effort should be made to obtain a blood sample at the time of discontinuation.

- **Adverse Events:** Assessment of adverse events will be performed at every visit using CTCAE Version 4.03. A copy of the CTCAE can be downloaded from the CTEP homepage (http://ctep.info.nih.gov).
- **Concomitant Medications:** Concomitant medications with doses and start and stop dates must be recorded.
- **Unblinding:** Unblinding should occur no later than 2 days after the end of combination phase tumor response is determined. The initial single-agent visit, V9, should occur as soon as possible but no later than 3 days after unblinding.
- **Survival:** All subjects will be followed for survival.

6.2.3 Visit Windows

6.2.3.1 During Combination Therapy

During the combination phase of this study each cycle begins with the administration of R-CHOP. CBC, chemistry, urine tests, and pregnancy tests can be performed one to two days prior to the administration of R-CHOP if that is the enrolling site's standard practice. All other assessments to be performed as indicated on the SOE (Table 6). Unless R-CHOP requires delay due to tolerability/AE, every effort should be made to administer R-CHOP to maintain the 21-day cycles (-1/+3 days).

6.2.3.2 During Single-Agent Therapy

During the single-agent phase of the study the visit window is +/- 5 days.

6.2.4 Post-treatment Evaluations/Follow up

- **EOT Testing**: Subjects will have (EOT evaluation as outlined in the SOE (Table 6). EOT date should be the last dosing date of any component of enzastaurin/placebo + R-CHOP, or the date of treatment discontinuation decision is made, whichever comes later**.** All EOT testing/visit in the SOE (Table 6) should be based on this date. The window of +/-7 days is allowed.
- **OS**: All subjects will be followed for survival every 3 months until completion of the study, or 5 years, whichever comes first. If the subject is unable to travel, evaluation of survival can be accomplished by telephone contact, if necessary. At the end of the study all subjects will be contacted one final time to ascertain survival status.
- **Post-treatment Therapy:** Every effort should be made to collect data regarding subsequent DLBCL treatments received, if any, after study treatment is discontinued.

6.2.5 Post-treatment Visit Windows

Following completion of the treatment portion of the study, the visit window will be ± 14 days.

6.3 SAFETY EVALUATIONS

6.3.1 Definitions

6.3.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug whether or not considered to have been caused by the drug. An AE may be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality (21 CFR 312.32a). Examples include: reactions or side effects, a pre-existing condition that worsens in severity or frequency, a concurrent illness, an injury, or a clinically significant laboratory abnormality.

6.3.1.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is an AE that meets at least one of the following criteria:

- Is fatal
- Is life-threatening (A life-threatening AE is an AE that places the subject at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.)
- Requires inpatient hospitalization or prolongs an existing hospitalization, excluding emergency room visits. (See Section 6.3.5 for other excluded events)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the offspring of an exposed subject.(Note: pregnancy in a study subject should be reported promptly to the sponsor on the appropriate form, and depending on the regulations for each region, may also need to be reported promptly to the regulatory authorities.)
- Other important medical events that may not result in death, be life-threatening or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

The onset date of an SAE is defined as the date on which it met the criteria for an SAE; eg, the date of admission to a hospital. The end date is the date on which it no longer met the criteria for an SAE, eg, the date that the subject was discharged from a hospital.

6.3.1.3 Relationship to Investigational Product

In this study, some subjects will be receiving both R-CHOP and enzastaurin; enzastaurin is considered the investigational product and the investigator should assess each AE for its possible relationship to enzastaurin, not the other medications in this treatment regimen. The relationship of an adverse event to the investigational product should be classified by the investigator using the following guidelines:

Definite: Experience follows a reasonable temporal association and could not have been explained by the subjects underlying condition or is confirmed with a positive re-challenge.

Probable: Experience follows a reasonable temporal association, is confirmed by improvement upon discontinuation of investigational product, and is not reasonably explained by the subject's clinical state.

Possible: Experience follows a reasonable temporal association, but may have been produced by the subject's clinical state or other factors.

Unlikely: Experience does not follow a clear temporal association, and is probably produced by the subject's clinical state or other factors.

Unrelated: No relationship between the experience and administration of the investigational product.

For this study, AEs that are considered by the investigator to have a Possible, Probable, or Definite relationship to the investigational product are considered to be "related" to the investigational product.

6.3.1.4 Severity of Adverse Events

The severity of an AE should be defined according to the National Cancer Institute (NCI) Common Toxicity Criteria Adverse Events (CTCAE) Version 4.03. AEs that are **not** listed in the NCI Common Toxicity Criteria should be evaluated using the following guidelines:

1 = Mild AE: Awareness of symptom, but easily tolerated; usually transient requiring no special treatment; does not interfere with usual status or activities

2 = Moderate AE: May be ameliorated by simple therapeutic measures; may interfere with usual activities

3 = Severe AE: Incapacitating, inability to perform usual activities

4 = Life threatening or disabling AE

5 = Fatal AE

6.3.2 Adverse Event Reporting Period

AEs will be recorded from the time of the first administration of study treatment until 7 days after the last administration of study treatment (ie, any components of R-CHOP and enzastaurin/placebo).

All SAEs will be recorded from the time of randomization until 30 days after the last administration of study treatment. SAEs determined to be related to study drug will be collected beyond 30 days.

Table 5 outlines the AE and SAE reporting.

Table 5. Adverse Events/Serious Adverse Events Reporting Guide

Time	After Informed Consent – Before Study Treatment*	Randomization	First Dose of Study Treatment	7-Days Post Last Dose of Study Treatment	30-Days Post Last Dose of Study Treatment	Long-Term Follow-up
Events to Report	Any clinically significantly medical conditions will be documented as medical history	All SAEs	All AE/SAEs	All new/ongoing AE/SAEs	All new/ongoing SAEs	SAEs related to study drug

Abbreviations: AE, adverse event; SAE, serious adverse event

*Study treatment: any components of R-CHOP and enzastaurin/placebo; Study drug: enzastaurin/placebo.

6.3.3 Recording Adverse Events

AEs should only be recorded by an investigator or by a healthcare provider qualified by training and experience. Subjects should be asked in an open-ended manner about the occurrence of AEs. All AEs, regardless of whether or not ascribed to the investigational product, should be recorded in the CRF.

It is generally not necessary to record both a diagnosis and its associated symptoms and laboratory abnormalities. For example, if "acute renal failure" is recorded as an AE, "creatinine 5 mg/dL" need not be recorded.

If an AE necessitates a procedure, the description of the event (eg, appendicitis) rather than the procedure (appendectomy) should be listed as the AE.

Any ongoing AE should be followed during study visits until resolution (with or without sequelae, or death, or ICF withdrawal, or last evaluation) to be recorded upon the subject discontinuation from the study.

6.3.4 Reporting Serious Adverse Events

The investigator should notify the Sponsor, or Designee, of any event that meets one of the criteria for an SAE within 24 hours of learning of the event. This can be done by completing SAE entry through eCRF in the EDC.

In the event of EDC outage, this SAE notification should be made by email to GlobalSAEInbox@covance.com (FAX numbers are available in case email is not functioning).

Following receipt of this notification, the Sponsor, with input from the investigator, will complete the final SAE Report.

Each SAE should be followed until resolution, or until such time as the investigator determines its cause or determines that it has become stable. This includes all the SAEs that have not resolved upon discontinuation of the subject's participation in the study. Information pertaining to follow-up of SAEs should be reported to the Sponsor within 24 hours of its availability.

It is the investigator's responsibility to report serious adverse events to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) according to the requirements of the IRB/IEC.

6.3.5 Events That Will Not Be Reported Individually

As per 21 CFR 312.32 this section identifies events that the Sponsor does not plan to report individually. Infusion reactions are known adverse reactions with a rituximab product (Rituxan/MabThera or an FDA-approved rituximab biosimilar) and will be documented as an AE only, but will not be reported individually as an SAE.

Hospitalization strictly for administration of R-CHOP will not be reported as SAEs. Hospitalization for elective procedures for treatment of pre-existing conditions (eg, hip replacement for pre-existing osteoarthritis) will not be reported as SAEs unless the condition has worsened since beginning the study drug. Hospitalizations for administrative reasons, such as insurance reimbursement, will not be reported as SAEs.

Disease progression itself is not an SAE. Hospitalization due to signs and/or symptoms meeting serious criteria should be reported as SAEs with the event terms other than progression disease (PD) even though the PD is identified later. Hospitalization strictly for administration of 2nd line treatment should not be reported as a SAE, regardless of PD or not.

6.3.6 Reporting of Study Endpoints

As per 21 CFR 312.32, the Sponsor does not plan to report death from progression of DLBCL, which is a study endpoint, as an SAE.

7 STATISTICAL METHODS

7.1 GENERAL CONSIDERATIONS

Efficacy and safety analyses will be conducted on the full analysis set. For efficacy, analysis will be conducted on an intent-to-treat basis. A per protocol analysis may also be performed. Safety analyses will include data from all patients receiving at least one dose of the investigational product according to the treatment the patients actually received.

Details of the statistical analyses planned can be found in the separate statistical analysis plan. General plans are summarized below.

7.2 DISPOSITION OF SUBJECTS

A detailed description of subject disposition will be provided. It will include:

- Total number of subjects randomized
- Total number of subjects treated
- Summary of reasons for subjects randomized but not treated
- Summary of data on subject discontinuation
- Account of all identified important protocol deviations

7.3 SUBJECT CHARACTERISTICS

Subject characteristics will include a summary of the following:

- Subjects demographics
- Baseline disease characteristics
- Preexisting conditions
- Concomitant drugs
- Subsequent DLBCL therapy(ies)

7.4 SAMPLE SIZE AND EFFICACY ANALYSES

Study sample size was estimated for the primary efficacy objective.

The primary outcome of this study is overall survival (OS), with the primary analysis to be conducted in DGM1 biomarker positive subjects. Study subjects will be randomized 1:1 to R-CHOP plus enzastaurin or R-CHOP plus placebo. The family-wise type-I error rate will be controlled at an α level (1-sided) of 2.5% by applying an alpha allocation plan for the analyses of OS in both the DGM1 biomarker-positive subgroup and the entire ITT population. Since the primary objective of the study is to compare the effect of R-CHOP plus enzastaurin versus R-CHOP on OS in DLBCL subjects who are DGM1 positive, the OS superiority test will be conducted at 1-sided significance level of 2.35% in the DGM1 positive subgroup. The alpha level allocated to the OS analysis in the entire population will be derived based on the actual number of OS events observed in the DGM1 positive subgroup and in the entire population at final analysis using the approach presented by (Spiessens B & Debois M, 2010). At the final

analysis, if the ratio of observed OS events in the DGM1 positive subgroup over the entire population is, as anticipated, 85%, (ie, 66/78 OS events), then statistical significance will be achieved in the OS analysis in the entire population at an alpha level (1-sided) of approximately 1%.

This will be an event driven study. In the trial 66 events are required to provide approximately 90% power to detect a HR of 0.45 for OS in subjects who are positive for the DGM1 biomarker, when using a stratified log-rank statistic having one-sided alpha of 0.0235. Statistical significance will be achieved with an estimated HR $\leq$ 0.613. The target HR of 0.45 is a very strong positive effect on OS, which was supported by the biomarker clinical data in the 'S028' study (HR (95% CI): 0.28 (0.1, 0.81) in the same target population, see Section 1.1).

Assuming control arm patients have one-year survival of approximately 60% to 70% and median survival of approximately 24 to 30 months, the trial will have an approximate sample size of 200 DGM1 biomarker positive subjects. If the enrollment period is 12-18 months, approximately 12 to 24 additional months will be required for 66 events to occur. Recognizing that the number of 66 events is fixed while the sample size is an approximation, the sample size will be re-assessed as the enrollment target of 200 DGM1 biomarker positive subjects is approached.

It is expected that approximately 15% of trial subjects will be DGM1 biomarker negative. Since the trial sponsor and investigators will not have access to data on DGM1 biomarker status, the trial's Data Monitoring Committee will monitor the enrollment required to achieve, in the projected timeframe, the targeted 66 events in the DGM1 biomarker positive subjects. If, for example, the DGM1 biomarker negative rate is approximately 15%, the trial would enroll approximately 235 subjects, with 200 being biomarker positive and 35 being biomarker negative. The final analysis will be performed when

- at least 66 OS events occur from all subjects who are DGM1 biomarker positive (DGM1+), AND
- either 22 OS events (ie, one third of the initially proposed "required" 66 OS events) are reached from US DGM1+ subjects, or 18 months after last subject was randomized, whichever comes first. This requirement is to ensure a meaningful subgroup analysis of OS in each geographic region.

If the addition of enzastaurin provides a statistically significance improvement in OS in the primary analysis in the DGM1™ biomarker positive subjects and the entire population, then this conclusion of benefit would be extended to the DGM1 biomarker negative subjects if, in that subgroup, the estimated HR $\leq$ 0.641, (Rothmann, 2012), which is the estimated effect that would achieve "statistical significance" at alpha level (1-sided) of 2.5% in the entire population with an estimated 78 OS events. The details regarding multiplicity adjustment in all scenarios related to the OS analysis are provided in the statistical analysis plan.

In a supportive analysis of OS data, a Cox proportional hazards model stratified by the factors used to stratify randomization may be used to adjust for major prognostic factors not used to stratify the randomization.

Adjustments will also be made to address the multiplicity of comparisons of R-CHOP plus enzastaurin versus R-CHOP plus placebo with respect to other secondary efficacy measures in

Section 6.1.3. If significance for the OS analysis is achieved in the DGM1 biomarker-positive subgroup and/or in the entire population, then the procedure will proceed to test three secondary measures in a pre-specified hierarchical manner using the specific method described below at the alpha level that is passed through the significance level for testing OS. During the testing, if any endpoint fails at the α level, then the subsequent endpoint(s) will be evaluating in a descriptive manner by presenting point estimates of effect and corresponding confidence intervals but without formal inference including p-values.

1. The analysis of EFS will be performed by using the same statistical methods for the primary endpoint analysis. EFS rate at 12 months and EFS rate at 24 months, will be estimated using survival rate estimated at the timepoint by Kaplan-Meier method. The derivation of standard error, 95% CI of EFS rate and between group comparison will be performed using Greenwood method.
2. The CR in DGM1 biomarker positive subjects, will be analyzed using Cochran-Mantel-Haenszel (CMH) method stratified by randomization factors.
3. ORR (CR+PR) in DGM1 biomarker positive subjects, will be analyzed using CMH method stratified by randomization factors.

With the sample size derived to properly power the testing for the primary efficacy measure (OS), there will be approximately 89% power to detect a treatment difference of 20% in CR rate (secondary measure) at completion of the combination phase in DGM1 biomarker positive subjects, assuming a control arm CR rate at 18%.

Approximately 100 EFS events from DGM1 biomarker-positive patients are expected when the targeted 66 OS events from DGM1 biomarker-positive patients are reached. A total of 100 EFS events would provide 80% and 90% statistical power to detect a treatment effect on EFS when the true HR would be 0.57 and 0.52, respectively, based on a log-rank test at 1-sided alpha level of 0.025.

7.5 SAFETY ANALYSIS

All subjects who receive at least one dose of investigational product will be included in the safety analysis. The analysis will include:

- Summary of extent of exposure
- Summary of the number of blood transfusions required
- Summary of adverse events, serious adverse events and subjects discontinuing for adverse events rates
- Summary of laboratory findings and change from baseline
- Summary of vital signs findings and change from baseline
- Summary of QTc data and change from baseline according to ICH E14
- Summary of other relevant safety observations
- Listings of laboratory and non-laboratory adverse events by maximum CTCAE v4.03 grade and relationship to study treatment

7.5.1 Adverse Events and Serious Adverse Events

AEs and SAEs will be listed and summarized by subject ID number. Additionally, AEs leading to discontinuations will be listed separately. All verbatim terms will be mapped to a System Organ Class and Preferred Term using MedDRA. The number and percentage of subjects experiencing one or more AEs will be summarized by PT, maximum grade reported, and relationship to study treatment. A narrative description will be included for SAEs and AEs leading to discontinuation of the study treatment.

7.5.2 Laboratory Tests

Laboratory tests will be listed by subject ID number and visit number. Laboratory tests will be graded and summarized using CTCAE v4.03. Laboratory data will be summarized using descriptive statistics, by use of shift tables and with listings of clinically significant abnormalities. In these listings, any abnormally high or low values will be flagged according to the laboratory reference range.

7.5.3 QTc

The QT interval will be corrected using Fridericia's formula. QTcF intervals will be summarized categorically by ICH grade and by maximum observed values and change from baseline.

7.6 THE DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be formed having 3 to 5 members of physicians and statistician(s). The mission of the DMC will be to safeguard the interests of study participants and to enhance the integrity and credibility of the trial. The DMC will periodically review safety and efficacy data and data regarding quality of trial conduct. The DMC will provide recommendation to the Sponsor regarding appropriate actions on the conduct of study.

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 PROTOCOL AND REGULATORY COMPLIANCE

The investigator must conduct the study according to this protocol.

In the United States, the study must be conducted by all investigators in compliance with Good Clinical Practices (GCP) as defined in the U.S. FDA Code of Federal Regulations 21 CFR 312 (Investigational New Drug Application), 21 CFR 50 (Protection of Human Subjects), 21 CFR 54 (Financial Disclosure by Clinical Investigators), 21 CFR 56 (Institutional Review Boards) and ICH guidelines (Guideline to Good Clinical Practice). Investigators conducting this study in other countries must comply with the Declaration of Helsinki, ICH-GCP guidelines and all other applicable country-specific regulations.

8.2 PROTOCOL AMENDMENTS

Any changes to this protocol will be initiated by the Sponsor as a protocol amendment. The investigator must submit the amendment to the IRB/IEC, with a revised ICD if applicable. The investigator must receive written approval from the IRB/IEC before the amendment may take effect.

8.3 REGULATORY BINDER

To be in compliance with GCPs, the investigator must maintain accurate, complete, and organized documentation supporting the conduct of the study. This documentation includes, but is not limited to, the following: study personnel qualifications and training, IRB/IEC approvals and communications, communications with the Sponsor, Site Signature & Responsibility Log, laboratory accreditations and reference ranges, Form FDA 1572s, and ICD (copies of IRB/IEC-approved versions, signed/dated originals, or copies for all enrolled subjects).

8.4 INFORMED CONSENT

Prior to the performance of any protocol-specific procedures, informed consent must be obtained and documented by the use of a written ICD approved by the Sponsor and the IRB/IEC. The ICD must be signed and dated by the subject or by the subject's legally authorized representative and by the person conducting the informed consent discussion. The ICD must fulfill the requirements as contained in the U.S. Code of Federal Regulations (21 CFR 50.25), the ICH guidelines (Section 4.8), and the Declaration of Helsinki. In addition to these requirements, the ICD must contain wording whereby the subject permits the review of his/her relevant medical records by representatives of Denovo and by representatives of the U.S. Food and Drug Administration (FDA) or other applicable national or local regulatory or health authorities. The ICD must be written in a language understandable to the subject or to the representative.

A signed and dated copy of the ICD must be given to the person signing the document. The original must be retained by the investigator with the study documentation and be available for inspection by persons conducting an audit of the study (eg, regulatory authorities, Denovo representatives).

The Sponsor will provide the study sites with a template ICD. Modifications to this template may be made by study site personnel to be in compliance with national, regional (eg, state) or local

laws and/or institutional requirements. All versions of the ICD should be reviewed and approved by Denovo prior to the submission of the ICD for IRB/IEC approval.

8.5 INSTITUTIONAL REVIEW BOARDS AND INDEPENDENT ETHICS COMMITTEES

The protocol, ICD, subject recruitment procedures (eg, advertisements), information about payments and compensation available to subjects, and any amendments must be approved by a properly constituted IRB or IEC in compliance with current regulations of the U.S. FDA, ICH guidelines, and any country-specific regulations. Specifically, the study must not be initiated until the investigator has provided Denovo with documentation of IRB/IEC approval of the protocol, the ICD, and all recruiting materials. In addition, prior to their implementation or use, there must be documented IRB/IEC approval for the following: protocol amendments, revised ICDs, subject recruitment materials (eg, advertisements), and study-related supplements that are provided to study subjects.

8.6 IRB/IEC COMMUNICATIONS

The investigator must make timely and accurate reports to the IRB/IEC on the progress of the study, as well as satisfying any other local IRB/IEC regulations regarding reporting, including reporting on safety aspects of the study (eg, SAEs, safety letters). During the conduct of the study, the frequency of IRB/IEC reporting should be based on each institution's review process. Furthermore, at the completion or early termination of the study, a final report must be made to the IRB/IEC by the investigator within the applicable IRB/IEC timeframes.

It is the investigator's obligation to maintain an IRB/IEC correspondence file and to make this available for review by Denovo representatives as part of the study monitoring process. Copies of all correspondence between the investigator and the IRB/IEC (including all attachments to any correspondence) must be provided for the Denovo internal file.

8.7 CURRICULUM VITAE AND MEDICAL LICENSES

The Principal Investigator is responsible for ensuring that the study is being conducted by qualified personnel. Documentation of these qualifications must be maintained within the Regulatory Binder, and includes the following:

Curriculum Vitae (CV): CVs for the Principal Investigator and all sub-investigators listed on the Form FDA 1572 must be signed and dated. These CVs must show affiliation with the institution conducting the study and be current within two years of the personnel initiating their participation in the study.

Medical Licenses: Medical licenses (physicians, physician assistants, nurses) listed on the Form FDA 1572 must be kept current, and copies must be maintained in the Regulatory binder during the entire period of the person's participation in the study.

8.8 SUBJECT CONFIDENTIALITY

The investigator must ensure that the subject's confidentiality is maintained. Subject medical information obtained for the purposes of this study is confidential, and disclosure to third parties, other than those noted below, is prohibited. Subjects should not be identified by name, social security number or medical record number on any documents or materials (samples, slides) sent

to Denovo or its representatives (eg, data management organization) or during verbal communications. Subjects should be identified only by their initials and protocol-assigned subject ID number.

For clinical sites in the US, study personnel should follow the requirements of the Health Insurance Portability and Accountability Act (HIPAA).

All clinical information is confidential, but data generated for this study must be available for inspection on request to representatives of the U.S. FDA, other national or local regulatory or health authorities, Denovo representatives, and the associated IRB/IEC.

All records must be kept in a secured area.

8.9 FINANCIAL DISCLOSURE

Documentation of each investigator's proprietary or financial interest in Denovo Biopharma LLC is required by the U.S. Code of Federal Regulations (21 CFR 54). A financial disclosure form provided by the Sponsor must be completed, signed, and dated by the Principal Investigator and each sub-investigator listed on the Form FDA 1572. This form must be executed prior to the personnel's participation in the study. The original form will be retained by the Sponsor. Each investigator must inform the Sponsor of any change in his/her financial interest in the Sponsor for up to one year after the end of the study.

The U.S. Securities and Exchange Commission (SEC) prohibits any person who has material, non-public information concerning Denovo or a possible transaction involving Denovo from purchasing or selling securities in reliance upon such information or from communicating such information to any other person or entity under circumstances in which it is reasonably foreseeable that such person or entity is likely to purchase or sell such securities in reliance upon such information.

9 QUALITY ASSURANCE

9.1 ROUTINE CLINICAL SITE MONITORING

Denovo CRAs or designees will make a pre-study site visit (if deemed necessary) to determine the qualifications of the investigator, inspect the clinical facilities, and fully inform the investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the course of the study, a Denovo CRA or representative will make routine contacts (eg, telephone communications or site visits) at appropriate intervals to review protocol compliance; to examine CRFs and individual subject's medical records, the Regulatory Binder, the investigational product handling and accountability procedures, and data recording practices; and to ensure that the study is being conducted in compliance with applicable requirements. CRF entries will be verified against source documentation.

The investigator and the site personnel are expected to cooperate with Denovo CRAs or representative and to provide, upon request, all relevant study documentation that is requested at each site visit.

9.2 SITE AUDITS

The investigator must permit inspection of the study files (eg, source documentation such as clinic notes, nurses' notes, radiological and laboratory records, CRFs, Regulatory Binder) by a Sponsor representative and by authorized representatives of the U.S. FDA or other applicable regulatory agencies. If the site is informed of an inspection by any regulatory authority, the investigator should notify Denovo immediately.

10 DATA MANAGEMENT AND RECORD KEEPING

10.1 CASE REPORT FORMS (CRF)

A validated, secure electronic CRF (eCRF) will be used for this study. eCRFs should be completed in a timely manner and must be available for review during routine monitoring visits. All references to specific subjects must be made by subject ID number, not by name. Subject confidentiality should be maintained by obscuring all names, social security numbers or subject record numbers (using a black marker) in any reports or records sent to the Sponsor or its representatives. The Principal Investigator, or designee, is responsible for reviewing each page of the eCRF and for signing the appropriate forms. By signing the eCRF, the investigator attests to the accuracy and completeness of the information contained in the eCRFs.

10.2 RECORD RETENTION

Records that individually or collectively permit the evaluation of the conduct of the study and the quality of the data produced with this study must be maintained for review by the Sponsor's representatives and by U.S. and non-U.S. regulatory authorities. The investigator must retain these records minimally for a period of two years following the date of the last marketing application and until there are no pending or contemplated marketing applications, or for at least two years following the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by applicable regulatory requirements. The Sponsor will inform the investigator in writing when the study-related records are no longer needed. The investigator must notify the Sponsor in writing at least 30 days prior to the intended date of disposal of any study records related to this protocol. If the investigator leaves the institution where the study was conducted, the investigator must inform the Sponsor in writing where the records associated with this protocol are archived and who is responsible for their security.

11 USE OR PUBLICATION OF STUDY-RELATED INFORMATION

All information obtained as a result of this study should be regarded as confidential.

Information regarding use or publication of study-related information will be provided to the investigator in a separate Clinical Trial Agreement.

12 INVESTIGATOR PROTOCOL SIGNATURE PAGE

I understand that all information supplied to me by Denovo Biopharma LLC is confidential.

I understand that this protocol and all amendments must be submitted to the appropriate IRB/IEC.

I have read protocol DB102-02 and its appendices and agree to adhere to all requirements in the conduct of the study.

In signing below, I agree:

- To assume responsibility for the proper conduct of the study at my site
- To conduct the study in compliance with this protocol, any future amendments, and with any other study procedures provided by Denovo Biopharma LLC.
- That I am aware of, and will comply with Good Clinical Practices (GCP) and all applicable regulatory requirements
- To ensure that all persons assisting me with the study are adequately informed about the study and of their study-related duties as delegated by me
- Not to implement any changes to the protocol without written agreement from Denovo Biopharma LLC and prior review and written approval from the Ethics Committee/Institutional Review Board (EC/IRB) except where necessary to eliminate an immediate hazard to study subjects

I acknowledge that failure to adhere to these stipulations may constitute a breach of governmental regulations, may invalidate the data and may result in termination of the study at my site.

_____ _____

Principal Investigator's Signature Date

_____

Principal Investigator's Printed Name

_____

Institution Name

13 SCHEDULE OF EVENTS

Table 6. Schedule of Events

	SCR/ Rand.	Combination Phase (1 Cycle = 21 days, visit -1/+3d)									Single-agent Phase[2] (visit± 5d)		EOT[3]	Follow up[4] (visit ±14d)
Cycle		**C1**			**C2**	**C3**	**C4**	**C5**	**C6**	**V8[1]**	**S1**	**S2**		**Q3 mos until EOS**
Visit		**1**		**2**	**3**	**4**	**5**	**6**	**7**		**9–11**	**12–17**		
Assessments / Days	**-28-0**	**D1**	**D2/3**	**D8**	**D1**	**D1**	**D1**	**D1**	**D1**		**Q6 weeks**	**Q12 weeks**		
Procedures:														
Consent	X													
Medical/Cancer history	X													
IPI	X													
Paraffin/Slides		X[5]												
Physical exam	X	X											X	
Brief physical exam				X	X	X	X	X	X		X	X		
Height/Weight[6]		X			X		X		X		X	X	X	
ECOG PS	X				X		X		X		X	X	X	
Echo or MUGA	X													
ECG[7]	X		X[8]		X		X		X		X[9]	X	X	
AEs		X									X			X[10]
Con meds		X									X			
Randomization[11]	X													
Unblinding										X[12]				
Survival status														X
Subsequent DLBCL therapies														X[13]
Diagnostic/Tumor Assessment Tests:														
PET-CT	X									X[14]	X[15]			X[15]
CT						X[16]					X[15]			X[15]

	SCR/ Rand.	Combination Phase (1 Cycle = 21 days, visit -1/+3d)									Single-agent Phase[2] (visit± 5d)		EOT[3]	Follow up[4] (visit ±14d)
Cycle		**C1**			**C2**	**C3**	**C4**	**C5**	**C6**		**S1**	**S2**		**Q3 mos until EOS**
Visit		**1**		**2**	**3**	**4**	**5**	**6**	**7**	**V8[1]**	**9–11**	**12–17**		
Assessments / Days	**-28-0**	**D1**	**D2/3**	**D8**	**D1**	**D1**	**D1**	**D1**	**D1**		**Q6 weeks**	**Q12 weeks**		
BMB[17]	X									X				
Laboratory Tests:														
CBC[18]	X	X		X	X	X	X	X	X	X	X	X	X	
Chem[18]	X	X		X	X	X	X	X	X	X	X	X	X	
Urinalysis[19]		X									X[9]		X[20]	
Urine color[19]		X		X	X						X[9]		X[20]	
Pregnancy, serum[21]	X				X	X	X	X	X	X	X	X	X	
HIV	X													
Hepatitis B & C	X													
PK[22]					X		X							
Biomarker:														
DGM1 & Immuno-typing[23]		X									X[9]		X[20]	
Study Drugs:														
R-CHOP[24]		X			X	X	X	X	X					
Enzastaurin/placebo[25]			X	X	X	X	X	X	X	X	X	X		

1. Perform on all subjects after completion of last R-CHOP cycle; all assessments except PET-CT, BMB and unblinding to be performed 22 days (-1/+3 days) from last administration of rituximab product. PET-CT, BMB and unblinding occurs as described below (please see footnote #12 and #14).
2. Enzastaurin arm only for those patients with CR (PR at investigator's discretion); Single agent phase begins with first dose of enzastaurin after unblinding. The initial single-agent visit, V9, should occur as soon as possible but no later than 3 days after unblinding. Note: the interval between V11 and V12 is 12 weeks
3. Performed for subjects who discontinue or complete study therapy (-/+ 7 days visit window). If the previous laboratory tests and ECG were performed after last dose of study treatment and this was ≤1 week prior to EOT visit, the laboratory tests and ECG do not need to be repeated. Urinalysis and urine color to be collected if not collected at V9 during the single agent phase.
4. Subjects contacted in person or by telephone.
5. Submit after randomization, preferably before the end of Cycle 1.
6. Height will only be performed at V1.
7. At Visit 1 (C1D2 or C1D3, on whichever day enzastaurin/placebo loading dose is given), C2D1, and C4D1 perform ECG prior to and approximately 4-6 hours after enzastaurin/placebo dose. ECG on C6D1, V9, V12-17 and EOT is performed prior to any study treatment if applicable. During treatment, hold enzastaurin if QTc > 500

msec; perform triplicate ECGs approximately five minutes apart; see Section 5.5.1 for further guidance. If R-CHOP is expected to be delayed greater than 7 days but enzastaurin/placebo is being taken, ECG should be performed as an unscheduled visit at the temporal timepoint and repeated on the appropriate Cycle/Day when cycles are restarted (ie, R-CHOP administered).

8. Perform ECG prior to and approximately 4-6 hours after enzastaurin/placebo first dose on C1D2 or C1D3, whichever day the enzastaurin/placebo loading dose is taken.
9. V9 only.
10. Collect AE/SAEs as described in Section 6.3.2
11. Subjects who meet eligibility criteria should be randomized within 8 weeks of diagnosis or confirmation of diagnosis by the enrolling institution and within the 28-day screening window, Study treatment should be started within 3 days of randomization.
12. Unblinding to treatment arm should occur no later than 2 days after, but not before, the end of combination phase tumor response is determined. Subjects in enzastaurin arm who experience a CR or (PR at the investigator's discretion) will enter Single-agent Phase and continue taking enzastaurin. All other subjects, including those in the placebo arm, will discontinue study treatment and enter Follow up after all applicable EOT assessments are performed.
13. Every effort should be made to collect subsequent DLBCL therapies.
14. Perform at least 4 weeks but preferably 6 to 8 weeks after completion of R-CHOP; weeks calculated from last administration of rituximab product. (See Appendix D)
15. Preform as medically/clinically indicated by standard of care.
16. Perform after R-CHOP administration at the end of Cycle 3 (See Appendix D for further guidance). PET-CT without contrast is acceptable per local SOC.
17. A bone marrow biopsy (BMB) is not required at screening/baseline unless clinically indicated (eg, to evaluate indeterminant PET-CT findings, cytopenia, or presence of discordant lymphoma). BMB is required at end of combination treatment in those patients who have otherwise achieved a CR and had a positive BMB at screening/baseline.
18. For Screening, within 14 days of randomization on study: may be performed 1-2 days prior to R-CHOP administration during combination phase if that is the enrolling site's standard practice and does not compromise patient safety. If in the judgment of the investigator patient safety is not compromised, C1D1 CBC and chemistry not required if Screening CBC and chemistry performed up to 3 days prior to C1D1.
19. Urinalysis and urine color will be performed using ambient urine sample by the central lab; Sponsor and clinical sites will be blinded to the results of urine color.
20. Only for subjects who do not enter into single-agent phase.
21. For Screening, must be negative within 7 days prior to randomization in women with reproductive potential. Subsequent pregnancy tests may be performed 1-2 days prior to R-CHOP administration during combination phase if that is the enrolling site's standard practice.
22. PK samples to be collected: C2D1 pre-dose and C4D1 3-6 hours post enzastaurin/placebo dose.
23. Whole blood sample collected for DGM1 testing and stored for immuno-typing (includes potential additional biomarker analysis and lymphoma subtyping). DGM1 biomarker testing will be performed by the central lab and both the Sponsor and clinical sites will be blinded to the results. Samples will be collected at C1D1 for all subjects and at V9 for those subjects who entered single-agent phase and at EOT for all other subjects.
24. R-CHO administered on Day 1 and prednisone (P) given Days 1-5. At investigator's discretion, rituximab product may be given alone on Day 1 with other components of CHOP given on Day 2. Prednisone would then be given Days 2-6.
25. Loading dose given on C1D2 unless R-CHOP is split over two days, then given on C1D3. Loading dose = 3 tabs TID approximately 30 minutes after a meal. Dose on all following days: 4 tablets QD taken together daily approximately 30 minutes after a meal. If necessary (eg, because of pause in R-CHOP dosing), study drug can be dispensed at an unscheduled visit.

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APPENDIX A. EXAMPLES OF INHIBITORS AND INDUCERS OF CYP 3A4

Strong Inhibitors (Generic Name)	Inducers (Generic name)
Boceprevir	Avasimibe
Clarithromycin	Bosentan
Cobicistat	Carbamazepine
Conivaptan	Efavirenz
Danoprevir (and ritonavir)	Etravirine
Diltiazem	Modafinil
Elvitegravir (and ritonavir)	Nafcillin
Grapefruit and juice	Phenytoin
Idelalisib	Rifampin
Indinavir (and ritonaivir)	St. John's Wort
Itraconazole	
Ketoconazole	
Lopinavir (and ritonavir)	
Mibefradil	
Nefazodone	
Nelfinavir	
Posaconazole	
Ritonavir	
Saquinavir (and ritonaivir)	
Telaprevir	
Telithromycin	
Tipranavir (and ritonavir)	
Troleandomycin	
Voriconazole	
Moderate Inhibitors (Generic Name)	
Aprepitant	
Cimetidine	
Ciprofloxacin	
Clotrimazole	
Crizotinib	
Cyclosprine	
Dronedarone	
Erythromycin	
Fluconazole	
Fluvoxamine	
Imatinib	
Tofisopam	
Verapamil	

Reference: Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (9/26/2016): http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#4 (accessed 27 August 2019).

APPENDIX B. INTERNATIONAL PROGNOSTIC INDEX

This tumor scoring system divides the population into risk groups (Table 8) by assigning one point for the presence of each of 5 variables (Table 7). For this study subjects must have a score of at least 3 in order to participate.

Table 7. Variables

Variable	Criteria	Points
Age	> 60	1
Tumor Stage	III or IV	1
Number extranodal sites	> 1	1
ECOG performance status	> 1	1
Serum LDH	> 1 times normal	1

Table 8. Definition of Risk Groups

Risk Group	Score (number risk factors)
Low	0–1
Low-Intermediate	2
High-Intermediate	3
High	4–5

Source: [Anonymous]. 1993. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 329(14):987-94.

APPENDIX C. DRUGS THAT CAN PROLONG THE QT INTERVAL

Generic Name	Brand Names (Partial List)	Drug Class
Propofol	Diprivan, Propoven	Anesthetic, general
Sevoflurane	Ultane, Sojourn	
Aclarubicin (Only on Non-US Market)	Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin	Anti-cancer
Arsenic trioxide	Trisenox	
Oxaliplatin	Eloxatin	
Vandetanib	Caprelsa	
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic
Disopyramide	Norpace	
Dofetilide	Tikosyn	
Dronedarone	Multaq	
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	
Hydroquinidine,Dihydroquinidine (Only on Non-US Market)	Serecor	
Ibutilide	Corvert	
Procainamide	Pronestyl, Procan	
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	
Sotalol	Betapace, Sotalex, Sotacor	
Azithromycin	Zithromax, Zmax	Antibiotic
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	
Clarithromycin	Biaxin, Prevpac	
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE Dispertab, Stiemycine, Acnasol, Tiloryth	
Levofloxacin	Levaquin, Tavanic	
Moxifloxacin	Avelox, Avalox, Avelon	
Roxithromycin (Only on Non-US Market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	
Citalopram	Celexa, Cipramil	Antidepressant, SSRI
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E (India), Exodus (Brazil), Esto (Israel), Seroplex, Elicea, Lexamil, Lexam, Entact (Greece), Losita (Bangladesh), Reposil (Chile), Animaxen (Colombia), Esitalo (Australia), Lexamil (South Africa)	
Domperidone (Only on Non-US Market)	Motilium, Motillium, Motinorm Costi, Nomit	Antiemetic
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	
Fluconazole	Diflucan, Trican	Antifungal

Generic Name	Brand Names (Partial List)	Drug Class
Pentamidine	Pentam	
Chloroquine	Aralen	Antimalarial
Halofantrine (Only on Non-US Market)	Halfan	
Haloperidol	Haldol (US & UK), Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol (Germany), Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic
Levomepromazine (methotrimeprazine) (Only on Non-US Market)	Nosinan, Nozinan, Levoprome	
Levosulpiride (Only on Non-US Market)	Lesuride, Levazeo, Enliva (with rabeprazole)	
Pimozide	Orap	
Thioridazine	Mellaril, Novoridazine, Thioril	
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	
Sulpiride (Only on Non-US Market)	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical
Sultopride (Only on Non-US Market)	Barnetil, Barnotil, Topral	
Donepezil	Aricept	Cholinesterase inhibitor
Cocaine	Cocaine	Local anesthetic
Terodiline (Only on Non-US Market)	Micturin, Mictrol (not bethanechol)	Muscle relaxant
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opiate
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor
Cilostazol	Pletal	
Ibogaine (Only on Non-US Market)	None	Psychedelic
Terlipressin (Only on Non-US Market)	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss and others	Vasoconstrictor
Papaverine HCl (Intra-coronary)	none	Vasodilator, Coronary

Note: Drugs removed from market not listed.

Reference: https://crediblemeds.org (last revision date: June 25, 2019); accessed 20 August 2019

APPENDIX D. TUMOR ASSESSMENT

Tumor Assessment Criteria

The determination of response and progression will be based on standardized criteria: Lugano Classification (Cheson 2014).

Method of Assessment

Imaging-based evaluation will be used in this study as the primary basis of DLBCL response assessment. The recommended and preferred method for radiographic tumor assessment for this study is fluorodeoxyglucose positron emission tomography (FDG-PET)/computed tomography (CT) scan (PET-CT). If PET-CT is unavailable, a contrast-enhanced CT may be substituted; contrast material may be omitted in subjects for whom use of a contrast agent becomes medically contraindicated. MRI scanning is not advised but may be used at the investigator's discretion in subjects for whom this is a necessary alternative to CT scanning.

Hybrid PET-CT scanners may be used to acquire the required CT images only if CT produced by the scanner is of diagnostic quality and includes intravenous contrast (unless medically contraindicated). Non-diagnostic CT images acquired for attenuation purposes during the PET-CT are not acceptable as the only CT scan for the timepoint. Diagnostic CT images with contrast (unless medically contraindicated) with a standalone CT scanner must be acquired if PET-CT is unable to acquire diagnostic CT images.

If the diagnostic CT and PET are acquired on the same day, it is strongly recommended that the PET is performed prior to the CT with IV contrast.

Recommended that PET images be converted to SUV maps to support comparison across timepoints and to standardize viewing conditions.

For radiographic assessments, it is highly recommended that the same method of assessment and the same technique (eg, scan type, scanner, subject position, dose of contrast, injection/scan interval) be used to characterize each identified and reported lesion at baseline and during study treatment and follow-up. Whole-body PET-CT scanning should be extended from the base of the skull to mid-thigh. If CT is used, images of the neck, chest, abdomen, and pelvis should be performed with cuts of ≤ 0.5 mm in slice thickness contiguously.

All relevant radiographic and clinical information required to make each tumor status assessment must be made available for source verification as requested by the study sponsor.

The 5 Point Scale (5-PS) is used for PET interpretation (see table below).

5 Point Scale (5-PS)

Score	Description
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately > liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Adapted from Cheson 2014

Timing of Disease Assessments

During screening, imaging-based tumor assessments should be performed within the specified screening period. On-study tumor assessments should be performed as indicated in the SOE (Table 6) which includes an interim assessment and an end of combination treatment assessment. If PET-CT, rather than CT, performed at the interim assessment timepoint (after Cycle 3 R-CHOP administration), it should be performed as long as possible after the administration of R-CHOP but before the next cycle (eg, C3D20); interim assessment should not result in a change in therapy unless there is biopsy-proven evidence of refractory lymphoma or lymphoma progression.

At the completion of the combination phase, a restaging tumor assessment (PET-CT) will be performed at least 4 weeks but preferably at 6 to 8 weeks after the completion of the last cycle of R-CHOP; weeks calculated from the last administration of rituximab product.

Definitions of Tumor Response and Progression
(Adapted from Cheson 2014)

Complete Response

COMPLETE RESPONSE (CR)	PET-CT Based Response Complete Metabolic Response (CMR)	CT Based Response Complete Response (CR) (all of the following)
Lymph nodes and extralymphatic sites	Score, 1, 2, or 3 with or without residual mass on 5-PS*	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Non-measured lesions	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

*Waldeyer's ring or extranodal sites with high physiologic update or with activation within spleen or marrow (eg with chemotherapy or myeloid colony-stimulating factors) uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
LDi, longest transverse diameter of a lesion

Partial Response

PARTIAL RESPONSE (PR)	PET-CT Based Response Partial Metabolic Response (PMR)	CT Based Response Partial Response (PR) (all of the following)
Lymph nodes and extralymphatic sites	Score, 4 or 5 on 5-PS with reduced uptake compared with baseline and residual mass(es) of any size At interim these findings suggest responding disease At end of treatment these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value; when no longer visible, 0 mm X 0 mm; for a node > 5 mm x 5 mm, but smaller than normal, use actual measurement for calculation
Non-measured lesions	Not applicable	Absent/normal, regressed, no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of nodal response, consideration should be given to further evaluation with MRI or biopsy, or an interval scan	Not applicable

SPD, sum of the product of the perpendicular diameters for multiple lesions

Stable Disease

STABLE DISEASE (SD)	PET-CT Based Response No Metabolic Response (NMR)	CT Based Response Stable Disease (SD)
Target nodes/nodal masses, extranodal lesions	Score, 4 or 5 on 5-PS with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable

Progressive Disease

PROGRESSIVE DISEASE (PD)	PET-CT Based Response Progressive Metabolic Disease (PMD)	CT Based Response Progressive Disease (PD) (at least one of the following)
Individual target nodes/nodal masses, extranodal lesions	Score, 4 or 5 on 5-PS with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	PPD progression An individual node/lesion must be abnormal with: • LDi > 1.5cm and • Increase by ≥ 50% from PPD nadir An increase in LDi or SDi from nadir • 0.5cm for lesions ≤ 2 cm • 1.0cm for lesions > 2cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline; if no prior splenomegaly, must increase by at least 2cm from baseline New or recurrent splenomegaly
Non-measured lesion	None	New or clear progression of preexisting non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5cm in any axis A new extranodal site > 1.0cm in any axis; if < 1.0cm in any axis, its presence must be unequivocal and must be attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

PPD, cross product of the LDi and perpendicular diameter
SDi, shortest axis perpendicular to the LDi

Identification and Follow-up of Tumor Lesions and Organomegaly

PET-CT Based Response Assessment

All involved areas using 5-Point Scale should be assessed.

A bone marrow biopsy (BMB) is not required at screening/baseline unless clinically indicated (eg, to evaluate indeterminant PET-CT findings, cytopenia, or presence of discordant lymphoma). BMB is required at end of treatment in those patients who have otherwise achieved a CR and had a positive BMB at screening/baseline.

CT Based Response Assessment

Target Lesions

Up to 6 of the largest target nodes, nodal masses, or extranodal lesions that are clearly measurable in two diameters (longest diameter [LDi] and shortest diameter) should be selected as target lesions that will be used to quantitate the status of the disease during study treatment. Ideally, the target lesions should be in disparate regions of the body representative of the overall disease burden and include mediastinal, abdominal, and retroperitoneal areas of disease whenever these sites are involved.

Extranodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, and cutaneous lesions.

Target lesions will be measured and recorded at baseline and at the stipulated intervals during treatment.

A measurable node: LDi > 1.5cm

A measurable extranodal lesion: LDi > 1.0cm

Non-Measured Lesions

All other lesions, not selected as measured, dominant disease including nodal, extranodal and assessable disease but are still considered abnormal should be followed as non-measured (non-target) disease (eg, cutaneous, GI, bone, spleen, liver, kidneys, pleural or pericardial effusions, ascites).

Spleen

The spleen should be measured and recorded at baseline and at stipulated intervals during treatment. The spleen will be considered enlarged if > 13 cm in vertical (cranial to caudal) length by CT.

Bone Marrow

Bone marrow assessments will be based on morphologic evaluation of bone marrow biopsies; a 2.5cm unilateral bone marrow biopsy is recommended along with immunohistochemistry and flow cytometry.

APPENDIX E. FONTAINE CLASSIFICATION

Fontaine Classification

Grade	Symptoms
Stage I	Asymptomatic, incomplete blood vessel obstruction
Stage II	Mild claudication, pain in limb
Stage IIA	Claudication at a distance > 200 m
Stage IIB	Claudication at a distance < 200 m
Stage III	Rest pain, mostly in the feet
Stage IV	Necrosis and/or gangrene of the limb

Fontaine R, Kim M, Kieny R. Surgical treatment of peripheral circulation disorders [in German] Helv Chir Acta. 1954;21(5–6):499–533