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Official Title:	A Phase III, randomized, double-blind, controlled, multicenter study of intravenous PI3K inhibitor copanlisib in combination with standard immunochemotherapy versus standard immunochemotherapy in patients with relapsed indolent non-Hodgkin's lymphoma (iNHL) - CHRONOS-4
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Cover page of integrated protocol

A Phase III, randomized, double-blind, controlled, multicenter study of intravenous PI3K inhibitor copanlisib in combination with standard immunochemotherapy versus standard immunochemotherapy in patients with relapsed indolent non-Hodgkin's lymphoma (iNHL) - CHRONOS-4

This protocol version is an integration of the following documents / sections:

- **Original protocol,** Version 1.0, dated 23 JUN 2015
- **Amendment 01** (global amendment described in Section 15.1) forming integrated protocol Version 2.0, dated 01 SEP 2015
- **Amendment 02** (global amendment described in Section 15.2) forming integrated protocol Version 3.0, dated 18 JUL 2016
- **Amendment 03** (global amendment described in Section 15.3) forming integrated protocol Version 4.0, dated 30 MAR 2017
- **Amendment 05** (global amendment described in Section 15.4) forming integrated protocol Version 5.0, dated 14 AUG 2017
- **Amendment 06** (global amendment described in Section 15.5) forming integrated protocol Version 6.0, dated 25 SEP 2018
- **Amendment 08** (global amendment described in Section 15.6) forming integrated protocol Version 7.0, dated 14 AUG 2019
- **Amendment 09** (global amendment described in Section 15.7) forming integrated protocol Version 8.0, dated 21 MAR 2023

Amendments not included in the consecutive numbering of amendments are local amendments described in Section 15.8 (Country-specific requirements) of this integrated global protocol. These are:

- **Amendment 04**, dated 11 MAY 2017 (local amendment valid for Japan only)
- **Amendment 07**, dated 12 MAR 2019 (local amendment valid for Germany only)

1. Title page

A Phase III, randomized, double-blind, controlled, multicenter study of intravenous PI3K inhibitor copanlisib in combination with standard immunochemotherapy versus standard immunochemotherapy in patients with relapsed indolent non-Hodgkin's lymphoma (iNHL) - CHRONOS-4

Short title	Phase III study of copanlisib with standard immunochemotherapy in relapsed iNHL		
Acronym	**CHRONOS-4**		
Test drug:	BAY 80-6946 / copanlisib		
Study purpose:	Dose-finding, efficacy and safety of copanlisib		
Clinical study phase:	III	Date:	21 MAR 2023
EudraCT no.:	2015-001088-38	Version no.:	8.0
EU CT no.:	2023-504155-27-00		
Sponsor's study no.:	BAY 80-6946 / 17833		
Sponsor:	Non-US: Bayer AG, D-51368 Leverkusen, Germany US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany, NJ 07981-0915, USA		
Sponsor's medical expert:	PPD PPD 100 Bayer Boulevard P.O. Box 915 Whippany, NJ 07981-0915 USA Phone: PPD		

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

This is an electronically generated document that does not bear any sponsor signatures. The signature of the sponsor's medically responsible person is filed in the Trial Master File (TMF) and available on request.

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date: _____ Signature: _____

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

2. Synopsis

Title	A Phase III, randomized, double-blind, controlled, multicenter study of intravenous PI3K inhibitor copanlisib in combination with standard immunochemotherapy versus standard immunochemotherapy in patients with relapsed indolent non-Hodgkin's lymphoma (iNHL) - CHRONOS-4
Short title	Phase III study of copanlisib with standard immunochemotherapy in relapsed iNHL
Acronym	CHRONOS-4
Clinical study phase	III
Rationale	The usual front-line treatment for iNHL consists of the anti-CD20-MAb rituximab given together with an alkylating agent (bendamustine, R-B), or a chemotherapy combination containing an alkylating agent (CHOP). While the R-B combination is preferred in the US, R-CHOP remains the first option in the EU. In second line, patients with R-sensitive disease (the large majority) would usually receive R-B following R-CHOP, and R-CHOP following R-B. Copanlisib has activity as monotherapy in patients with relapsed or refractory iNHL (shown in the results of studies 12781 and 16349 Part A). In addition, based on the current metabolism knowledge of each compound there is low potential for drug-drug interactions between copanlisib and the combination partners. It can therefore be expected that copanlisib would increase the activity of standard 1st and 2nd line immunochemotherapy (R-CHOP/R-B) in patients with relapsed, R-sensitive iNHL warranting re-treatment with a rituximab based regimen. The clinical benefit should be expressed in a prolonged progression-free survival (PFS), and an improved quality of life in comparison to the standard immunochemotherapy.
Study objective(s)	**<u>Safety run-in part</u>** **Primary objective is to determine:** • The recommended phase III dose (RP3D) of copanlisib in combination with standard immunochemotherapy (rituximab and bendamustine [R-B] or rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone [R-CHOP]) to be used in the subsequent phase III part of the study **The secondary objectives are to evaluate (for patients that stay on treatment after Cycle 1):** • Radiological and clinical indicators of treatment efficacy • Safety and tolerability of copanlisib in combination with R-B/R-CHOP **Further objectives are to evaluate:** • Pharmacokinetics (PK) of copanlisib • Biomarkers of efficacy, mode-of-action-related effect, safety, and / or the pathomechanism of the disease

	Phase III part (randomized, controlled trial) **Primary objective is:** • To evaluate whether copanlisib in combination with standard immunochemotherapy, is superior to standard immunochemotherapy in prolonging PFS, in patients with relapsed indolent non-Hodgkin's lymphoma, who have received at least one, but at most three lines of treatment, including rituximab, and/or rituximab biosimilars, and/or anti-CD20 monoclonal antibody -based immunochemotherapy and alkylating agents, and for whom the combination of rituximab with either bendamustine or CHOP represents a valid therapeutic option **Secondary objectives are to evaluate:** • Other radiological and clinical indicators of treatment efficacy (objective response rate (ORR), duration of response (DOR), complete response rate (CRR), time to progression (TTP), time to next anti-lymphoma treatment (TTNT), disease control rate (DCR), overall survival (OS, 5 year survival rate), time to improvement and the time to deterioration in disease-related symptoms - physical) • Safety and tolerability of copanlisib in combination with R-B/R-CHOP **Further objectives are to evaluate:** • PK of copanlisib • Biomarkers of efficacy, mode-of-action-related effect, safety, and / or the pathomechanism of the disease
Test drug(s) **Name of active ingredient** **Dose(s)**	Copanlisib Copanlisib / BAY 80-6946 **Safety run-in part**: Dosing of copanlisib: • in combination with R-B: Starting dose of 45 mg and, if well tolerated, 60 mg, on Days 1, 8 and 15 of each 28-day cycle or • in combination with R-CHOP: Starting dose of 45 mg and, if well tolerated, 60 mg, on Days 1 and 8 of each 21-day cycle. After Cycle 1, dose reductions to 45 mg (if starting dose is 60 mg) and further to 30 mg are possible, should toxicities occur **Phase III part**: Dosing of copanlisib: • in combination with R-B: Starting dose of 60 mg (the determined recommended phase III dose [RP3D] of copanlisib) or • in combination with R-CHOP: Starting dose of 60 mg or 45 mg, depending on the dose level determined in the safety run-in part (RP3D of copanlisib). Dose reductions to 45 mg (if RP3D is 60 mg) and further to 30 mg are possible, should toxicities occur.

Copanlisib/Placebo (C/P) dosing	Cycle length (d)	D1	D8	D15
Cycles 1-6				
C/P in combination with R-B	**28**	**X**	**X**	**X**
C/P in combination with R-CHOP	**21**	**X**	**X**	
Cycle 7 onwards				
C/P monotherapy	**28**	**X**	**X**	**X**

Dosing of immunochemotherapy (Cycles 1-6):

R-B will be administered every 4 weeks (q4w) as follows:

- Rituximab intravenous (IV) 375 mg/m^2 body surface on Day 1 (D1)
- Bendamustine IV 90 mg/m^2 body surface on D1 and D2

R-CHOP will be administered q3w as follows:

- Rituximab IV 375 mg/m^2 body surface on D2
- Cyclophosphamide IV 750 mg/m^2 body surface on D2
- Doxorubicin IV 50 mg/m^2 body surface on D2
- Vincristine IV 1.4 mg/m^2 body surface (maximum dose 2.0 mg) on D2
- Prednisone/prednisolone 100 mg daily orally (PO) from D2 to D6

Route of administration

IV infusion

Duration of treatment

Combination therapy (copanlisib/placebo with R-B or R-CHOP) will be administered for a maximum of 6 cycles (C1-C6). Copanlisib/placebo (study drug) monotherapy will be administered from C7 onwards.

Combination therapy (copanlisib/placebo with R-B or R-CHOP) will be continued until the occurrence of progressive disease (PD) (per central independent blinded radiology review) as defined in Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Owen Criteria for patients with Waldenström macroglobulinemia [WM]), or clinical progression (e.g. Eastern Cooperative Oncology Group [ECOG] performance status of ≥ 3), unacceptable toxicity occurs, or until another criterion is met for withdrawal from study or up to 6 cycles whichever comes first.

Copanlisib/placebo monotherapy (C7 onwards) will be continued until the occurrence of PD (per central independent blinded radiology review) as defined in The Lugano Classification (Owen Criteria for patients with WM), or clinical progression (e.g. ECOG performance status of ≥ 3), unacceptable toxicity occurs, or another criterion is met for withdrawal from study or until completion of monotherapy, whichever comes first.

The maximum duration of treatment with copanlisib/placebo is 12 months (including combination therapy and monotherapy). The duration of treatment in the safety run-in part will be the same as in the phase III part.

Reference drug(s)	Placebo
Name of active ingredient	Not applicable
Dose(s)	**Safety run-in part**: Not applicable **Phase III part**: • In combination with R-B: Dummy 60 mg. • In combination with R-CHOP: Dummy 60 mg or 45 mg, depending on the copanlisib dose level determined in the safety run-in part (RP3D of copanlisib). Dummy dose reductions to 45 mg (if starting dose is 60 mg) and further to 30 mg are possible, should toxicities occur. The dosing of placebo during the combination therapy and monotherapy is the same as for copanlisib, please see above. **Dosing of immunochemotherapy:** Same as in combination with copanlisib, please see above.
Route of administration	IV infusion
Duration of treatment	Same as for copanlisib, please see above.
Background treatment	Immunochemotherapy: rituximab plus B (R-B) or rituximab plus CHOP (R-CHOP) for Cycles 1-6. For administration, see above.
Indication	Relapsed indolent non-Hodgkin’s lymphoma

Diagnosis and main criteria for inclusion /exclusion	**Main criteria for inclusion:** • Histologically confirmed diagnosis of CD20 positive iNHL with histological subtype limited to: o Follicular lymphoma (FL) G1, G2, or G3a o Small lymphocytic lymphoma (SLL) with absolute lymphocyte count <5x10^9/L at study entry o Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM) o Marginal zone lymphoma (MZL) (splenic, nodal, or extra-nodal) • Patients must have relapsed (recurrence after complete response or presented progression after partial response) or progressed after at least one but at most three prior lines of therapy, including rituximab, and/or rituximab biosimilars, and/or anti-CD20 monoclonal antibody (e.g. obinutuzumab) -based immunochemotherapy and alkylating agents (if given concomitantly is considered one line of therapy). A previous regimen is defined as one of the following: at least 2 months of single-agent therapy (less than 2 months of therapy with single agent rituximab, or rituximab biosimilars, or anti-CD20 monoclonal antibody can be considered a previous regimen in the case the patient responded to it); at least 2 consecutive cycles of polychemotherapy; autologous transplant; radioimmunotherapy. Previous exposure to other PI3K inhibitors (except copanlisib) is acceptable provided there is no resistance (resistance defined as no response (response defined as partial response [PR] or complete response [CR]) at any time during therapy, or PD after any response (PR/CR) or after stable disease within 6 months from the end of the therapy with a PI3K inhibitor . • Non-WM patients must have at least one bi-dimensionally measurable lesion (that has not been previously irradiated) according to the Lugano Classification. For patients with splenic MZL this requirement may be restricted to splenomegaly alone since that is usually the only manifestation of measurable disease. • Patients affected by WM who do not have at least one bi-dimensionally measurable lesion in the baseline radiologic assessment must have measurable disease defined as presence of immunoglobulin M (IgM) paraprotein with a minimum IgM level ≥ 2 × upper limit of normal and positive immunofixation test. • Male or female patients ≥ 18 years of age. • Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2. • Life expectancy of at least 3 months. • Availability of fresh tumor tissue and/or archival tumor tissue at Screening. • Adequate baseline laboratory values as assessed within 7 days before starting study treatment. • Left ventricular ejection fraction ≥ 50%. **Main criteria for exclusion:** • Histologically confirmed diagnosis of follicular lymphoma (FL) grade 3b or transformed disease, or chronic lymphocytic leukemia. In patients with clinical suspicion of transformed disease, a fresh biopsy is recommended. • Rituximab, or rituximab biosimilars, or anti-CD20 monoclonal

	antibody (e.g. obinutuzumab) resistance at any line of therapy (resistance defined as lack of response, or progression within 6 months of the last date of rituximab, or rituximab biosimilars, or anti-CD20 monoclonal antibody administration, including maintenance with these drugs). • HbA1c > 8.5% at Screening. • History or concurrent condition of interstitial lung disease and/or severely impaired lung function (as judged by the investigator). • Known lymphomatous involvement of the central nervous system. • Known history of human immunodeficiency virus (HIV) infection. • Hepatitis B (HBV) or C (HCV) infection. Patients positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) will be eligible if they are negative for HBV-DNA, these patients should receive prophylactic antiviral therapy as per rituximab label. Patients positive for anti-HCV antibody will be eligible if they are negative for HCV-RNA. • Cytomegalovirus (CMV) infection. Patients who are CMV PCR positive at baseline will not be eligible. CMV PCR test is considered positive if, the result can be interpreted as a CMV viremia according to local standard of care (SOC). • Congestive heart failure > New York Heart Association (NYHA) class 2. • Uncontrolled hypertension despite optimal medical management (per investigator's assessment).
Study design	The study has two parts: safety run-in / dose finding part and double-blind, controlled, two-arm phase III part. **Safety run-in part:** The study will start with a safety run-in part, where the recommended dose of copanlisib in combination with standard immunochemotherapy to be administered in phase III part (RP3D) will be determined. During the safety run-in part two treatment combinations (copanlisib with R-B and copanlisib with R-CHOP), will be tested at two dose levels of copanlisib (first dose level 45 mg, second dose level, 60 mg) for safety and tolerability. Data Monitoring Committee (DMC) will review all data available from the safety run-in part and evaluate whether protocol specified treatment combinations are safe and tolerable. When the RP3D of copanlisib in combination with R-CHOP or R-B has been defined and confirmed by sponsor, principal investigator, and DMC, enrolment in the phase III part will start. The safety run-in part of this study was completed for copanlisib in combination with R-B and in combination with R-CHOP. The DMC reviewed the safety data and decided that copanlisib dose of 60 mg plus R-B or plus R-CHOP is a recommended and approved dose to be used in the phase III part. Patients recruited into the safety run-in part are treated in an unblinded fashion and will thus not be evaluated as part of the phase III part. **Phase III part:** This is a double-blind, two-arm phase III study in patients with relapsed, rituximab-sensitive iNHL to evaluate efficacy and safety of copanlisib in

	combination with standard immunochemotherapy (R-B or R-CHOP) in comparison to standard immunochemotherapy (R-B or R-CHOP). The patients must have relapsed after at least one but at most three previous lines of therapy; previous treatments must have included rituximab, and/or rituximab biosimilars, and/or anti-CD20 monoclonal antibody -based immunochemotherapy and alkylating agents; and patients must not have a lack of response, or progression within 6 months of the last date of rituximab, or rituximab biosimilars, or anti-CD20 monoclonal antibody administration. Patients will be stratified by: prior to base treatment regimen (R-chemotherapy to R-B, R-B to R-CHOP, and R-B to R-B), NHL histology (FL vs. other iNHL) and duration of progression-free interval on the last rituximab, or rituximab biosimilars, or anti-CD20 monoclonal antibody containing regimen (6-12 months vs. >12 months). Patients who meet the eligibility criteria will be randomly assigned in a 1:1 ratio to one of the double-blinded treatment arms: • **Arm 1**: copanlisib plus R-CHOP or R-B • **Arm 2**: placebo plus R-CHOP or R-B During the phase III part, study DMC will review the unblinded data per DMC charter of all patients treated up to that time point (or as needed) to ensure that patients are not exposed to undue risk. The investigators, patients and the sponsor will remain blinded. The study (applicable to safety run-in part and phase III part) is composed of the following periods: • Screening • Treatment • Safety-follow-up (patients who discontinue study treatment due to progressive disease [PD]) • Active follow-up (patients who complete 12 months' study treatment without PD or discontinue study treatment for any other reason than PD) • Survival follow-up.
Methodology	The primary safety variable in the safety run-in part is occurrence of dose-limiting toxicities in Cycle 1. The primary efficacy variable in the phase III part is PFS (for the definition, see below). Efficacy will be assessed based on radiological tumor evaluations of neck, chest, abdomen and pelvis by using IV [and oral, if indicated, per Imaging Manual] contrast enhanced computed tomography/magnetic resonance imaging (CT/MRI) and positron emission tomography-computed tomography (PET-CT) as a preferred imaging modality. During the treatment phase as well as during the active follow-up period, radiological tumor assessment will be performed every 12 weeks (±7 days) from Cycle 1 Day 1 during Year 1 and 2; every 24 weeks (±7 days) during Year 3, 4 and 5; and every 24 weeks (±14 days) beyond Year 5. Tumor scans will be evaluated locally at the study site and by the blinded independent central review. The response assessment will be based on the Lugano Classification. For patients with WM, response assessment will be done according to the Owen criteria and CT/MRI, if applicable. Bone marrow biopsy will be mandatory at Screening and will be sent to

	central pathology review after local bone marrow assessment. If the baseline biopsy is positive for lymphoma infiltration, it will be mandatory to perform a local bone marrow biopsy assessment again to confirm the first complete response (CR) and also at the investigator's discretion if clinical evaluation leads to suspicion of bone marrow infiltration without further radiological findings. All patients will be followed off study for overall survival at 3-monthly (± 14 days) intervals during the survival follow-up period (up to 10 years after the last patient started study treatment), independent of the patient's reason for study termination, except for patients who object to follow-up data collection. Patients or their healthcare providers will be contacted either in person or by telephone. Safety evaluations will be done at Screening, during treatment, and at the Safety follow-up visit. During the Active follow-up period, adverse events (AEs) and serious adverse events (SAEs) assessed as related to study procedures by the investigator will be reported. Sparse blood samples for pharmacokinetic (PK) analysis will be collected from all patients to characterize the PK of copanlisib and rituximab. Fresh tumor tissue and/or archival tumor tissue must be available at Screening for central pathology review for an exploratory analysis. In addition, pre-treatment tumor tissue samples will be collected when available to investigate or identify biomarkers that may be predictive of copanlisib effects/efficacy in iNHL and to contribute to better understanding the disease. Plasma samples for biomarker analyses will be collected from all patients at baseline and during treatment. In the phase III part, "time to deterioration" and "time to improvement" in disease-related symptoms - physical (DRS-P) will be assessed using the FLymSI-18 questionnaire. Other efficacy variables are FLymSI-18 subscale and total score analyses.
Type of control	Inactive control: placebo (phase III part)
Data Monitoring Committee	Yes
Number of patients	**Safety run-in part**: maximum 2 × 6 patients per combination evaluable for the primary endpoint. **Phase III part**: approximately 520 (including FL and other iNHL). Patients recruited into the safety run-in part will not be evaluated as part of the phase III part.
Primary variable(s)	**Safety run-in part**: The primary safety variable is the occurrence of DLTs in Cycle 1. **Phase III part**: The primary efficacy variable is PFS, defined as the time (in days) from randomization to PD as assessed by blinded independent central review or death from any cause (if no progression is documented).
Time point/frame of measurement for primary variable(s)	**Safety run-in part**: Approximately 6-8 months **Phase III part**: The study duration for primary completion of PFS is at least 52 months with approximately 33 months enrollment period and at least 19 months follow-up.

Plan for statistical analysis	**Safety run-in part**: Safety data will be summarized or listed per dose level. **Phase III part**: The analysis of efficacy will be done in the full analysis set (FAS), which is defined as all patients who are randomized. The primary analysis of PFS will be based on tumor assessments of the central independent blinded review, and will be performed using a log rank test, stratified by the same factors as the stratification factors in randomization. Kaplan-Meier estimates and survival curves will also be presented by treatment group, as well as the hazard ratios with 95% confidence intervals. No formal interim analysis of the primary efficacy endpoint, PFS, is planned. The sample size calculation is based on the number of events required to detect a 50% increase in median PFS time in the FAS, and assumes a median PFS of 24 months under the control treatment, a 1-sided alpha of 0.025, a randomization ratio of 1:1 between the two treatment groups and estimates that approximately 280 PFS events in the iNHL popoulation (progression based on blinded independent central review or death from any cause, whichever occurs first) are required to detect this increase with approximately 92% power. The expectation is that approximately 280 PFS events in the FAS population will also provide sufficient power for an additional PFS analysis in the FL histology population. The “time to event” secondary efficacy variables (overall survival, time to progression, duration of response, time to next anti-lymphoma treatment, time to deterioration and time to improvement in disease-related symptoms - physical (DRS-P) of at least 3 points) will be analyzed in a similar way to PFS. The objective response rate (ORR) and complete response rate (CRR) will be compared between the two treatments using a Cochran-Mantel-Haenszel test with the randomization factors as strata. DCR and CRR will be analyzed in a manner similar to ORR. The analysis of safety will be descriptive only (no statistical test will be applied).

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5PS	5 point score for the visual assessment of PET-CT
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse event of special interest
AITL	angioimmunoblastic T-cell lymphoma
AKT	protein kinase B
ALCL	anaplastic large cell lymphoma
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
B	bendamustine hydrochloride
BCRP	breast cancer resistance protein
bid	twice daily
BL	baseline
BMT	bone marrow transplant
BP	blood pressure
BUN	blood urea nitrogen
C	cycle
CBC	complete blood count
CD	cluster of differentiation
CD20	B lymphocyte antigen CD20
CHOP	cyclophosphamide, hydroxydoxorubicin, vincristine, prednisone
c-KIT	proto-oncogen c-KIT (CD117)
CLL	chronic lymphocytic leukemia
C_{max}	maximum drug concentration
CMR	complete metabolic response
CMV	cytomegalovirus
CR	complete response
CRF	case report form
CRO	contract research organization
CRP	C-reactive protein
CRR	complete response rate
CRu	complete response unconfirmed
CT	computed tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	observed drug concentration measured at the end of the dosing interval
CXR	chest X-ray
CYP3A4	cytochrome P450 isoenzyme 3A4
D	Day
DDI	drug-drug-interaction
dL	deciliter
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid

DOR	duration of response
DPD	dihydropyrimidine dehydrogenase
DPP4	dipeptidyl peptidase-4
DRS-E	disease-related symptoms – emotional (subscale)
DRS-P, DRSP	disease-related symptoms – physical (subscale)
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EOT	end of treatment
ePRO	electronic patient-reported outcome
EU	European Union
EU-CTR	European Union Clinical Trials Regulation
EudraCT	European Union Drug Regulating Authorities Clinical Trial
FAS	full analysis set
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
FL	follicular lymphoma
FLymSI-18	NCCN-FACT Lymphoma Symptom Index-18
FSH	follicle stimulating hormone
FU	follow-up
FWB	functional well-being (subscale)
GCB	germinal center B-cell
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GI	glycemic index
GMP	Good Manufacturing Practice
GPCR	G protein-coupled receptor
GPV	Global Pharmacovigilance
Gr	grade
Hb	hemoglobin
HbA1c	glycated hemoglobin
HBcAb	hepatitis B core antibody
HBe-Ag	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B Virus
HCG	β-human chorionic gonadotropin
HCV	hepatitis C Virus
HCV-Ab	hepatitis C virus-antibody
HDL	high-density lipoprotein
HER	human epidermal growth factor receptor
HIV	human immunodeficiency virus
HIV-Ag/Ab	human immunodeficiency virus-antigen/antibody
IB	Investigator's Brochure
IC	informed consent
IC50	half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMS	isotope dilution mass spectroscopy
IEC	independent ethics committee

IGF-1R	insulin-like growth factor 1 receptor
IgM	immunoglobulin M
IHC	immunohistochemistry
iNHL	indolent non-Hodgkin's lymphoma
INR	international normalized ratio
I.P	improvement in disease-related symptoms – physical
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV, i.v.	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
IxRS	interactive voice response system / interactive web response system
LDH	lactate dehydrogenase
LDi	longest diameter
LDL	low-density lipoprotein
LPL	lymphoplasmacytic lymphoma
LVEF	left ventricular ejection fraction
M-1	metabolite 1
MAb	monoclonal antibody
MALT	mucosa-associated lymphoid tissue
MATE2K	multidrug and toxin extrusion protein 2
MCL	mantle cell lymphoma
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MLBCL	mediastinal large B cell lymphoma
MR	minor response
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
MUGA	multiple gated acquisition
MZL	marginal-zone lymphoma
N	total number of patients
NA, N/A	not available, not applicable
NaOH	sodium hydroxide
NCCN-FACT	National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy
NCI	National Cancer Institute
NE	not evaluable (by investigator / oncologist)
NHL	non-Hodgkin's lymphoma
NIP	non-infectious pneumonitis
NMR	no metabolic response, equivalent with stable disease
NMZL	nodal marginal-zone lymphoma
NOS	no other specification
NYHA	New York Heart Association
OI	opportunistic infection
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PDGFR	platelet-derived growth factor receptor
PDK1	phosphoinositide-dependent kinase 1
PET	positron emission tomography
PET-CT	positron emission tomography-computed tomography
PFS	progression-free survival
P-gp	permeability glycoprotein

pH	negative log of hydrogen ion concentration
PH	pleckstrin homology
PI3K	phosphatidylinositol-3-kinase
PID	patient identification number
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PIP3	phosphatidylinositol-3,4,5-trisphosphate
PK	pharmacokinetic(s)
PKAS	pharmacokinetic analysis set
PMD	progressive metabolic disease, equivalent with progressive disease
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PMR	partial metabolic response
PO	orally
PPD	product of perpendicular diameters
PR	partial response
PRO	patient-reported outcomes
PT	prothrombin time
PTCL	peripheral T-cell lymphoma
PtdIns-4,5-P2	phosphatidylinositol-4,5-bisphosphate
PTEN	phosphatase and tensin homolog
PTT	partial thromboplastin time
q1w	weekly
QoL	quality of life
QTcB	QT interval corrected for heart rate - Bazett
QTcF	QT interval corrected for heart rate - Fridericia
R	rituximab
RAVE	validated electronic data capture system used by Bayer
R-B	rituximab and bendamustine
RBC	red blood cell count
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-CVP	rituximab, cyclophosphamide, vincristine, and prednisone
RNA	ribonucleic acid
RP3D	recommended phase III dose
RTK	receptor tyrosine kinase
SAC	Statistical Analysis Center
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SAS	statistical analysis system
SCR	serum creatinine
SD	stable disease
SDi	shortest diameter
SFU	safety follow-up
SGLT2	sodium/glucose co-transporter 2
SLL	small lymphocytic lymphoma
SmPC	Summary of Product Characteristics
SMZL	splenic marginal-zone lymphoma
SOC	standard of care
SPD	sum of the product of the diameters
StiL	Study Group Indolent Lymphomas
SUSAR	suspected, unexpected, serious adverse reaction
TEAE	treatment-emergent adverse event
TSE	treatment side effects (subscale)
TTNT	time to next anti-lymphoma treatment
TTP	time to progression

UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit normal
UPCR	urine protein to creatinine ratio
US	United States (of America)
VEGF	vascular endothelial growth factor
VGPR	very good partial response
VPN	virtual private network
vs.	versus
WBC	white blood cell count
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary
WM	Waldenström macroglobulinemia
WOCBP	woman of childbearing potential
W.P	worsening of disease-related symptoms – physical

Definitions of terms

The tumor response assessment will be done according to the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (14), henceforth referred to as the Lugano classification.

For patients with WM, response assessment will be done according to the Response Assessment in Waldenström macroglobulinemia: update from the VIth International Workshop (13), henceforth referred to as the Owen criteria.

3. Introduction

3.1 Background

Lymphomas are a heterogeneous group of malignancies originating from lymphoid tissues. Approximately 85% of all lymphomas are non-Hodgkin's lymphomas (NHL), with different subtypes, clinical features and response to therapy (1). The majority of NHLs arises from B-lymphocytes (85-90%) and can be characterized by cell of origin, tumor proliferation rate and histologic pattern of growth.

It is estimated that worldwide there were around 356,000 new cases of NHLs in 2008 (2). The incidence of NHLs is increasing in many regions, but the frequency of specific histologic subtypes of lymphoma varies substantially by geographic region. Over two-thirds of patients are 60 years and older (3).

The non-Hodgkin`s lymphoma have distinct clinical features and can be divided according to their clinical behavior in two prognostic groups: indolent NHL and aggressive NHL. Aggressive NHLs are characterized by high tumor proliferation, symptomatic disease and may evolve into a lethal presentation if not immediately treated. However, with modern immunochemotherapy regimens and stem cell transplantation a definitive cure can be reached in more than 50% of patients (4). Indolent NHLs have a clinical presentation with few symptoms and low tumor proliferation, with a relatively good prognosis and median survival rates longer than 10 years, but they are not curable with current available therapeutic options, especially for those with advanced stages. They respond to standard chemotherapy regimens and to radiotherapy, but their natural history is characterized by remissions and relapses. Although most relapses can be generally treated with success, the quality and duration of remissions decreases over time. Finally, these lymphomas evolve into refractory disease or undergo transformation into an aggressive histologic type with poor prognosis.

The World Health Organization (WHO) lymphoma classification is based on cell of origin and pathophysiology of lymphomas. Indolent NHLs are included in this classification as: follicular lymphoma (FL), small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma (LPL), which is defined as Waldenström's macroglobulinemia (WM) when associated with a monoclonal IgM component and bone marrow involvement, splenic marginal-zone lymphoma (SMZL), nodal marginal-zone lymphoma (NMZL) and marginal-zone lymphoma of mucosa-associated lymphoid tissue (MALT) (5). FL is the second most common subtype of NHL (22% of newly diagnosed cases), followed by MALT lymphoma (7% of all NHL), while other subtypes are rather rare, with SLL, LPL, SMZL and NMZL accounting for 3%, 2%, 2% and 1% of NHL patients, respectively (6, 7).

Despite the indolent nature of indolent lymphomas, treatment is rarely curative. In asymptomatic patients with low-burden disease, a "watch and wait" approach is accepted until disease accelerates. When patients require therapeutic intervention, several options are available, ranging from single agent therapy (rituximab) to immunochemotherapy. Results from a prospective randomized study comparing rituximab + cyclophosphamide, hydroxydoxorubicin, vincristine and prednisone (R-CHOP) and CHOP for patients with follicular lymphoma demonstrated that R-CHOP reduced the relative risk for treatment failure, significantly prolonged the time to treatment failure with significantly higher overall

response rate and a prolonged duration of remission in patients with advanced-stage follicular lymphoma (8). The alkylating agent bendamustine (B) has shown promising results in first-line treatment and in relapsed patients. The study conducted by StiL (Study Group Indolent Lymphomas) comparing R-B with R-CHOP as first-line therapy for iNHL showed significant longer progression-free survival and complete response rate in the R-B group compared to R-CHOP (9).

For patients with relapsed disease, the same regimen (rituximab in combination with an alternative chemotherapy) can be used. The safety and efficacy of R-CHOP and R-B in this setting were evaluated, showing satisfactory rates of complete response and overall survival. (10, 11). However, it is known that patients will invariably relapse and further active and well-tolerated agents are needed to be used in combination with current therapy.

The high frequency of phosphoinositide 3-kinase (PI3K) pathway alterations in cancer led PI3K to be recognized as an attractive molecular target for novel anti-cancer molecules (12). In this setting, PI3K inhibitors could improve outcome by prolonging progression-free survival and symptom control, thus delaying the need for subsequent treatment.

3.1.1 Copanlisib (BAY 80-6946)

Phosphatidylinositol-3 kinases (PI3Ks) are downstream of most cancer associated tyrosine kinase growth factor receptors (RTKs, such as EGFR/HER, IGF-1R, PDGFR, VEGF, c-KIT or Met), cell adhesion molecules (such as integrins), G protein-coupled receptors (GPCRs), and oncogenes (such as Ras). Once PI3K is activated, it catalyzes the phosphorylation of phosphoinositides to generate PIP3 which binds and activates AKT as well as other Pleckstrin homology domain (PH-domain) containing proteins such as PDK1, GEF, etc. Activating mutations and/or amplification of PI3K alpha isoform, and the deletion of PI3K antagonizing tumor suppressor genes PTEN are frequently found in many tumors, which results in the constitutive activation of PI3K/AKT and therefore promoting cell survival, proliferation, stress adaptation and metastasis. In addition, activation of PI3K/AKT pathway after radio- and/or chemotherapies is also one of the major mechanisms by which tumors escape and become resistant to chemo- and radio-therapies.

Four of these PI3K isoforms (PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ) are categorized as class I enzymes because they can use phosphatidylinositol-4,5-bisphosphate (PtdIns-4,5-P2) as a substrate to generate phosphatidylinositol-3,4,5-trisphosphate (PIP3). Elevated PIP3 in cellular membranes drives several hallmarks of the cancer phenotype: cell proliferation, survival, metabolic reprogramming, and migration. PI3Kα and β are ubiquitous, PI3Kγ and δ are expressed mostly in the hematopoietic tissue.

Copanlisib (BAY 80-6946) is a potent pan-class I inhibitor of PI3K with predominant activity against the α and δ isoforms, with *in vitro* IC_{50}s of 0.5 nM and 0.7 nM, respectively. This novel PI3K inhibitor is being developed for the treatment of advanced and refractory malignancies. Copanlisib is the active ingredient (free base) of BAY 84-1236, the dihydrochloride salt, which for clinical use is formulated as an intravenous (IV) drug product solution.

Copanlisib is primarily metabolized by the cytochrome P450 (CYP) 3A4 with minor contribution of CYP1A1. There is a low risk for clinical drug-drug interactions of

concomitant drug products through inhibition or induction of CYP enzymes, inhibition of uridine diphosphate glucuronosyltransferase (UGT) enzymes and inhibition of dihydropyrimidine dehydrogenase (DPD) by copanlisib as a perpetrator. Copanlisib is a weak substrate of permeability glycoprotein (P-gp) and of breast cancer resistance protein (BCRP). Copanlisib inhibited P-gp- and BCRP-mediated transport in *in vitro* studies. Furthermore, copanlisib is a strong inhibitor of the drug transporter multidrug and toxin extrusion protein 2 (MATE2K).

3.1.2 Clinical experience

As of 01 FEB 2016, approximately 627 patients with advanced cancer have been treated with copanlisib (BAY 80-6946) in Phase 1, Phase 2 and Phase 3 studies. More information on clinical experience can be found in the investigator's brochure (IB) for copanlisib.

Pharmacokinetics

Pharmacokinetic (PK) results of copanlisib indicate dose proportional increases in maximum concentration (C_{max}) and area under the curve (AUC) from time zero to 25 hours (AUC(0-25)) in the dose range 0.1 to 1.2 mg/kg with a terminal phase half-life (t1/2) of 38.2 hours at 0.8 mg/kg (n=28). These data indicate that copanlisib is widely distributed in tissues and support a once weekly dosing regimen. No accumulation was observed after once weekly dosing when comparing PK on Cycle 1 Days 1 and 15 and Cycle 3 Day 15. No evidence of time-dependency in the PK of copanlisib was observed.

Preliminary results of the human ADME (absorption, distribution, metabolism, and excretion) study in healthy volunteers indicate that following a single intravenous dose of 12 mg [^{14}C]-BAY 80-6946, 88.3% of administered dose, with approx. 66.1% of dose excreted in feces, and approximately 22.2% of dose excreted in urine was recovered within 34 days. Copanlisib was found to be the primary circulating moiety in plasma as well as in excreta. The amount of copanlisib excreted unchanged amounts up to 40 to 50%. The morpholinone derivative M-1 was found to be the only relevant metabolite. Oxidative biotransformation of copanlisib was found to be predominantly mediated by cytochrome P450 isoenzyme 3A4 (CYP3A4) and its contribution is about 50% of the metabolic pathway. Therefore, a low drug-drug-interaction (DDI) potential due to several clearance pathways is anticipated.

A preliminary population PK analysis revealed no impact of either body weight, body surface area, or other body size-related factors was found on the clearance of copanlisib which was the basis to switch to a flat-dose regimen of copanlisib.

The recommended (Phase II) dose of monotherapy copanlisib is 60 mg given IV weekly (q1w) in a 3 weeks on/1 week off schedule based on an evaluation of pharmacokinetic and clinical data from ongoing single agent studies.

Study 12871

As of 10 FEB 2014, a total of 57 cancer patients were treated in the Phase I monotherapy study 12871, with 17 patients in the dose escalation cohorts and 34 patients in the maximum tolerated dose expansion cohorts (two cohorts including 9 patients with NHL and 25 patients with solid tumors), as well as 6 patients with Type II diabetes mellitus in the diabetic expansion cohort at 0.4 mg/kg. The maximum tolerated dose of copanlisib, when

administered intravenously (IV) over 1 hour, on Days 1, 8 and 15 of every 28 days given as a single agent, was determined to be 0.8 mg/kg, with a maximum dose of 65 mg in order to control copanlisib exposure in obese patients.

Preliminary efficacy data are available from the NHL expansion cohort of Study 12871. A total of 6 patients with FL and 3 patients with diffuse large B-cell lymphoma (DLBCL) were treated, all initially dosed at 0.8 mg/kg. All 6 patients with FL reached a partial response (PR). In 5 of the 6 patients with FL, the partial response (PR) was confirmed by a second radiological assessment. As of 01 FEB 2015, 2 patients with FL were still on treatment, both having an ongoing PR for 1406 and 935 days.

Out of the 3 patients with DLBCL, 2 dropped out at the end of Cycle 1 and Cycle 2 due to progressive disease. The third patient reached PR as best response but not confirmed by a second radiological assessment (unconfirmed PR). This patient discontinued the study during Cycle 10 due to a perirectal abscess.

None of the NHLs tested had PIK3CA or PTEN mutations but one FL patient had complete PTEN protein loss (as determined by immunohistochemistry [IHC] and 4 had a low PTEN (with 1-5% of tumor cells staining positive for PTEN). Among the 3 DLBCL patients, the 1 patient with sufficient tissue material for gene expression profiling had germinal center B-cell (GCB) DLBCL.

Preliminary analysis of the 57 patients showed that the most common treatment-emergent adverse events (TEAEs), irrespective of relationship to study drug and grade, occurring in ≥ 20% of the patients, were hyperglycemia (64.9%), nausea (52.6%), fatigue (40.4%), diarrhea (33.3%), hypokalemia (31.6%), hemoglobin (decreased) and hypertension (29.8% each), rash / desquamation and vomiting (28.1% each), anorexia (26.3%), constipation (24.6%), cough and dehydration (22.8% each), and dyspnea (21.1%). The most common drug-related TEAEs, regardless of seriousness and severity, occurring in ≥5% of the 57 patients (all cohorts) were hyperglycemia (63.2%), nausea (36.8%), hypertension (21.1%), rash / desquamation and diarrhea (15.8% each), vomiting (12.3%), fatigue (10.5%), hemoglobin (decreased), alopecia, and taste alteration (8.8% each), pruritus, anorexia, and any type of pain (7% each), leukocytes (decreased), neutrophils (decreased), weight loss, rigor / chills, and amylase (increased) (5.3% each).

Three FL patients experienced treatment-emergent pneumonitis, all with a severity of Common Terminology Criteria for Adverse Events (CTCAE) v3.0 Grade 3 and assessed as serious. Of note, no pneumonitis was reported in the 48 patients with solid tumors treated in this study. In 2 asymptomatic cases, diagnosis was based on CT scans performed for restaging of lymphoma. Since remedial drug therapies such as antibiotics and / or corticosteroids were administered, no definitive conclusion can be drawn whether and to what extent study drug interruption or remedial drug therapy contributed to the improvement of pneumonitis. All 3 events of pneumonitis resolved. The 3 patients were non-smokers. Only one of the 3 FL patients with pneumonitis had received prior PI3K inhibitor / mTOR inhibitor treatment more than 1 year before the event and one had had prior radiotherapy. The rapid recovery of pneumonitis observed in one patient favored a viral infection (viral pneumonitis), whereas the 2 other events were considered non-infectious pneumonitis (NIP).

Study 16349

As of 28 FEB 2015, a total of 81 patients with various indolent and aggressive lymphomas were treated at a starting dose of 0.8 mg/kg in the ongoing study 16349 (part A). The objective of the study was to identify activity signals in various histologic NHL subtypes and to further explore the safety profile of copanlisib. In the group of patients with indolent NHL, the following histologies were represented: FL (16 patients), CLL/SLL (14 patients), and MZL (3 patients). Median age was 68 years and 61% of the patients had ≥ 4 previous lines of systemic treatment. As of the cut-off date the median duration of copanlisib treatment was 6 cycles in the indolent group. The objective response rate (ORR) was 40% in FL, 38% in CLL, 100% in SLL, and 67% in MZL.

The most frequent TEAEs, regardless of relationship to study drug, occurring in >20% of the whole study population were hyperglycemia (59.3%), hypertension (56.8%), diarrhea (40.7%), fatigue (35.8%), nausea (32.1%), neutropenia (28.4%) and anemia (27.2%). The two most common study drug-related TEAEs were hyperglycemia (56.8%) and hypertension (53.1%). At the time of the cut-off, a total of 75 patients (92.6%), 30 with indolent, and 45 with aggressive lymphomas, had discontinued the study treatment. Altogether 20 patients (24.7%) stopped treatment because of AEs. No conspicuous cluster of AEs causing treatment discontinuation emerged. Overall 17 out of 81 patients received treatment with short-acting insulin.

Further details can be found in the IB for copanlisib, which contains comprehensive information on the test drug.

3.2 Rationale of the study

The usual front-line treatment for iNHL consists of the anti-CD20-MAb rituximab given together with an alkylating agent (bendamustine, R-B), or a chemotherapy combination containing an alkylating agent (CHOP). While the R-B combination is preferred in the US, R-CHOP remains the first option in the EU. In 2nd line, patients with R-sensitive disease (the large majority) would usually receive R-B following R-CHOP, and R-CHOP following R-B.

Copanlisib has activity as monotherapy in patients with relapsed or refractory iNHL (shown in the results of studies 12781 and 16349 Part A). In addition, based on the current metabolism knowledge of each compound there is low potential for drug-drug interactions between copanlisib and the combination partners. It can therefore be expected that copanlisib would increase the activity of standard 1st and 2nd line immunochemotherapy (R-CHOP/R-B) in patients with relapsed, R-sensitive iNHL warranting re-treatment with a rituximab based regimen. The clinical benefit should be expressed in a prolonged PFS, and an improved quality of life in comparison to the standard immunochemotherapy.

3.3 Benefit-risk assessment

Advanced indolent NHL remains an incurable disease that will invariably relapse after a period of remission. As the efficacy of subsequent lines of therapy decreases over time, prolonging progression-free survival, reducing the symptom burden, and delaying the next round of anti-lymphoma therapy are relevant goals of treatment. To achieve these goals, new

agents with different mechanisms of action and the potential to provide good response with an adequate safety profile are needed. The activity of copanlisib as monotherapy in patients with relapsed and refractory indolent NHL was demonstrated (see Section 3.1.2). The addition of copanlisib to the standard immunochemotherapy is therefore expected to provide a supplementary, clinically meaningful benefit in terms of progression-free survival and symptom control. The most frequent adverse events of copanlisib (hyperglycemia and hypertension) are manageable and not expected to interfere with conducting treatment according to plan. In this study, copanlisib-related and other toxicities will be closely monitored and managed according to a pre-defined program intended to ensure the patients' safety and to avoid undue risk. Combination of copanlisib with standard immunochemotherapy (R-CHOP and R-B) in the safety run-in part is expected to establish a recommended phase III dose (RP3D) and indicate that possible overlapping toxicities are controllable. The safety and feasibility of these combinations will be evaluated at the end of the safety run-in part by a Data Monitoring Committee (DMC). The present study is acceptable after considering the risks and benefits associated with it.

The safety run-in part of this study for copanlisib in combination with R-B and R-CHOP was completed. The DMC reviewed the safety data and decided that a copanlisib dose of 60 mg plus R-B or plus R-CHOP is a recommended and approved dose to be used in the phase III part.

4. Study objectives

4.1 Safety run-in part

The primary objective is to determine:

- The recommended phase III dose (RP3D) of copanlisib in combination with standard immunochemotherapy (R-B or R-CHOP) to be used in the subsequent phase III part of the study.

The secondary objectives are to evaluate (for patients that stay on treatment after Cycle 1):

- Radiological and clinical indicators of treatment efficacy.
- Safety and tolerability of copanlisib in combination with R-B/R-CHOP.

Further objectives are to evaluate:

- Pharmacokinetics (PK) of copanlisib.
- Biomarkers of efficacy, mode-of-action-related effect, safety, and / or the pathomechanism of the disease.

4.2 Phase III part

The primary objective of the phase III part is:

- To evaluate whether copanlisib in combination with standard immunochemotherapy, is superior to standard immunochemotherapy in prolonging progression-free survival

(PFS) in patients with relapsed iNHL, who have received at least one, but at most three lines of treatment, including rituximab, and/or rituximab biosimilars, and/or anti-CD20 monoclonal antibody -based immunochemotherapy and alkylating agents, and for whom the combination of rituximab with either bendamustine or CHOP represents a valid therapeutic option.

The secondary objectives of the phase III part are to evaluate:

- Other radiological and clinical indicators of treatment efficacy (objective response rate (ORR), duration of response (DOR), complete response rate (CRR), time to progression (TTP), time to next anti-lymphoma treatment (TTNT), disease control rate (DCR), overall survival (OS, 5 year survival rate), time to improvement and the time to deterioration in disease-related symptoms - physical).
- Safety and tolerability of copanlisib in combination with R-B/R-CHOP.

The further objectives of the phase III part are to evaluate:

- Pharmacokinetics of copanlisib.
- Biomarkers of efficacy, mode-of-action-related effect, safety, and / or the pathomechanism of the disease.

5. Study design

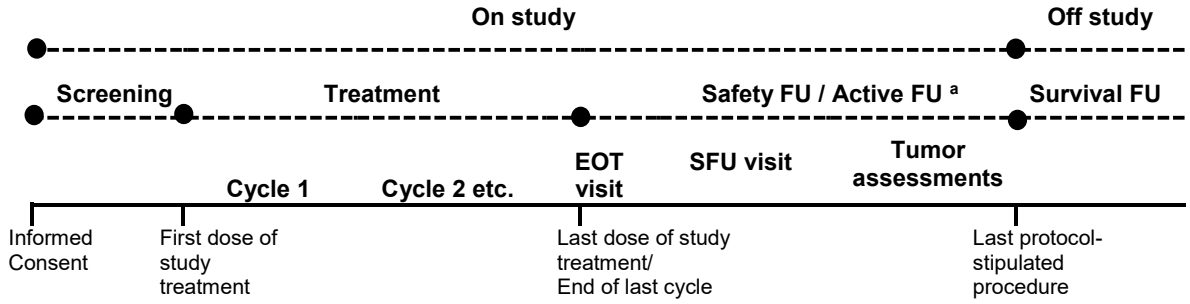
5.1 Design overview

This is a double-blind, two-arm phase III study in patients with relapsed, rituximab-sensitive iNHL to evaluate efficacy and safety of copanlisib in combination with standard immunochemotherapy (R-B or R-CHOP) in comparison to standard immunochemotherapy (R-B or R-CHOP). The patients must have relapsed or progressed after at least one, but at most three previous lines of therapy; previous treatments must have included rituximab and/or rituximab biosimilars, and/or anti-CD20 monoclonal antibody -based immunochemotherapy and alkylating agents (if given concomitantly is considered one line of therapy); and patients must not have a lack of response, or progression within 6 months of the last date of rituximab, or rituximab biosimilars, or anti-CD20 monoclonal antibody administration. For the purpose of this protocol, one month is considered to have 30 days.

The study includes two parts. The safety run-in part will determine the RP3D of copanlisib in combination with standard immunochemotherapy (R-B or R-CHOP) to be used in the subsequent phase III part. The primary objective of the phase III part is to evaluate whether copanlisib in combination with standard immunochemotherapy, is superior to standard immunochemotherapy in prolonging progression-free survival (PFS) in patients with relapsed, rituximab-sensitive iNHL. The study will accrue patients with FL, MZL, SLL, and LPL/WM. In view of the prevalence of various histological types, it is expected that the large majority of study participants will be patients with FL.

The overview of study periods is presented in Figure 5-1.

Figure 5-1 Study periods



EOT = End of treatment; FU = Follow up; SFU = Safety follow-up
a: SFU for patients who discontinue study treatment due to PD; Active FU for patients who complete 12 months' study treatment without PD or discontinue study treatment for any other reason than PD (includes Safety FU).

The following design applies to both safety run-in part and the phase III part unless otherwise specified.

The study is composed of the following periods: Screening, Treatment, Safety follow-up, Active follow-up (if applicable) and Survival follow-up.

The start of the study period is defined by signing the informed consent form (ICF). After an up to 28-day and a minimum of 7-day screening period, patients who meet the entry criteria will be randomized to one of the two arms (only in the phase III part) and start treatment. The start of the treatment period is defined by the first administration of study treatment.

Combination therapy (copanlisib/placebo with R-B or R-CHOP) will be administered for a maximum of 6 cycles (C1-C6). Copanlisib/placebo (study drug) monotherapy will be administered from C7 onwards.

Combination therapy (copanlisib/placebo with R-B or R-CHOP) will be continued until the occurrence of progressive disease (PD) (per central independent blinded radiology review) defined by the Lugano Classification (14) (or Owen criteria for patients with WM [see Appendix 16.5]) or clinical progression (e.g. Eastern Cooperative Oncology Group [ECOG] performance status of ≥ 3), unacceptable toxicity occurs, or until another criterion is met for withdrawal from study (see Section 6.4) or up to 6 cycles whichever comes first.

Copanlisib/placebo monotherapy (C7 onwards) will be continued until the occurrence of PD (per central independent blinded radiology review) as defined in the Lugano Classification (Owen Criteria for patients with WM), or clinical progression (e.g. ECOG performance status of ≥ 3), unacceptable toxicity occurs, or another criterion is met for withdrawal from study or until completion of monotherapy, whichever comes first.

The maximum duration of treatment with copanlisib/placebo is 12 months (including combination therapy and monotherapy).

An end-of -treatment (EOT) visit will be performed no later than 7 days after the decision is made to discontinue study treatment. Following completion of the EOT visit, patients will enter either the Safety follow-up or the Active follow-up period, if applicable. In both cases, the Safety follow-up visit will take place 30 days (a time window of +5 days is allowed) after the last administration of study treatment.

Patients who discontinue study treatment because of PD will enter the Safety-follow up period. Patients who complete 12 months' study treatment without PD or discontinue study treatment for reasons other than PD will enter the Active follow-up period (which also serves as a Safety follow-up), except for patients who object to follow-up data collection. The patients in the Active follow-up will have tumor assessments by central independent blinded review as outlined in this protocol until the end of the Active follow-up period, defined as when either PD is documented or a new anti-tumor treatment is administered, whichever occurs first.

All patients will be followed off-study for overall survival at 3-month (± 14 days) intervals during the Survival follow-up period (up to 10 years after the last patient started study treatment), except for patients who object to follow-up data collection. See Section 9.2.1.5.3.

Efficacy will be evaluated based on radiological tumor evaluations of neck, chest, abdomen and pelvis by using contrast enhanced computed tomography/magnetic resonance imaging (CT/MRI), and positron emission tomography-computed tomography (PET-CT) as an preferred imaging modality (see Section 9.4.2 and Section 9.8). Scans will be performed at Screening, during Treatment as well as during the Active follow-up period (Year 1 and Year 2: every 12 weeks [± 7 days]; Years 3, 4, and 5: every 24 weeks [± 7 days]; beyond Year 5: every 24 weeks [± 14 days]). Response assessment will be based on the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (14) and for patients with WM according to the Owen Criteria (see Appendix 16.5) and CT/MRI, if applicable. As long as the patient has not experienced PD, investigator's assessment is sufficient for case management. In the event of radiological progression, radiological real-time confirmation by central independent blinded evaluation is needed before a final decision is made by the investigator. The evaluation of treatment response (best response: objective response rate and complete response rate) will be also done by central blinded review.

WM patients who do not have radiologically measurable lesion at Screening will not have further radiological assessments as per protocol. Their tumor response will be measured only by laboratory/clinical tests and evaluated by investigators. However, because these patients may on progression develop measurable disease without simultaneous increase in IgM, the imaging material should be submitted for blinded independent central review and PD confirmation. WM patients who have radiologically measurable lesion at Screening will continue having radiological assessments and, in addition, will have laboratory tests performed on the same days.

Bone marrow biopsy will be mandatory at Screening and will be sent to central pathology review after local bone marrow assessment. If the baseline biopsy is positive for lymphoma infiltration, it will be mandatory to perform a local bone marrow biopsy assessment again to confirm the first complete response (CR) and also at the investigator's discretion if clinical evaluation leads to suspicion of bone marrow infiltration without further radiological findings.

Safety evaluations will be done at Screening, during treatment and at the Safety follow-up visit. NCI-CTCAE version 4.03 will be used to grade toxicities/AEs. Doses may be delayed or reduced in cases of clinically significant hematological or other toxicities that are possibly,

probably or definitely related to study treatment. The dose modification levels and the delay of copanlisib/placebo administration will follow pre-defined rules (see Section 7.4.2).

Fresh tumor tissue and/or archival tumor tissue must be available at Screening for central pathology review for an exploratory analysis. In addition, pre-treatment tumor tissue samples will be collected when available to investigate or identify biomarkers that may be predictive of copanlisib effects/efficacy in iNHL and to contribute to better understanding the disease. See Section 9.7.1. In patients with WM, bone marrow biopsy can be used for histological confirmation of the diagnosis and for biomarker analyses.

Sparse blood samples for pharmacokinetic (PK) analysis will be collected in all patients to characterize the PK of copanlisib and rituximab as outlined in Section 9.5. Plasma samples for biomarker analyses will be collected from all patients at baseline and during treatment. Blood samples for exploratory genetic biomarker analysis will be collected on Cycle 1 Day 1 from patients who provide "genetic research" consent (voluntary). See Section 9.7.1.

In the phase III part, "time to deterioration" and "time to improvement" in disease-related symptoms - physical (DRS-P) will be assessed using the FLymSI-18 questionnaire, see Section 9.7.2.

5.2 Safety run-in part

The study will start with a safety run-in part, where the recommended dose of copanlisib in combination with standard immunochemotherapy to be administered in phase III part will be determined, based on an open-label, two dose level, 3+3 design.

During the safety run-in part two treatment combinations (copanlisib with R-B and copanlisib with R-CHOP), will be tested at two dose levels of copanlisib (first dose level of 45 mg and, second dose level of 60 mg) for safety and tolerability. The two dose levels will have a minimum of 3 and maximum of 6 patients evaluable for dose-limiting toxicity (DLT) during Cycle 1.

The dose levels of copanlisib in the safety run-in part will be as follows:

Dose level 1:	45 mg of copanlisib in combination with either R-B or R-CHOP
Dose level 2:	60 mg of copanlisib in combination with either R-B or R-CHOP

For the dosing of R-B and R-CHOP in the safety run-in part, please see Section 7.4. For the treatment assignment in the safety run-in part, please see Section 7.3.1.

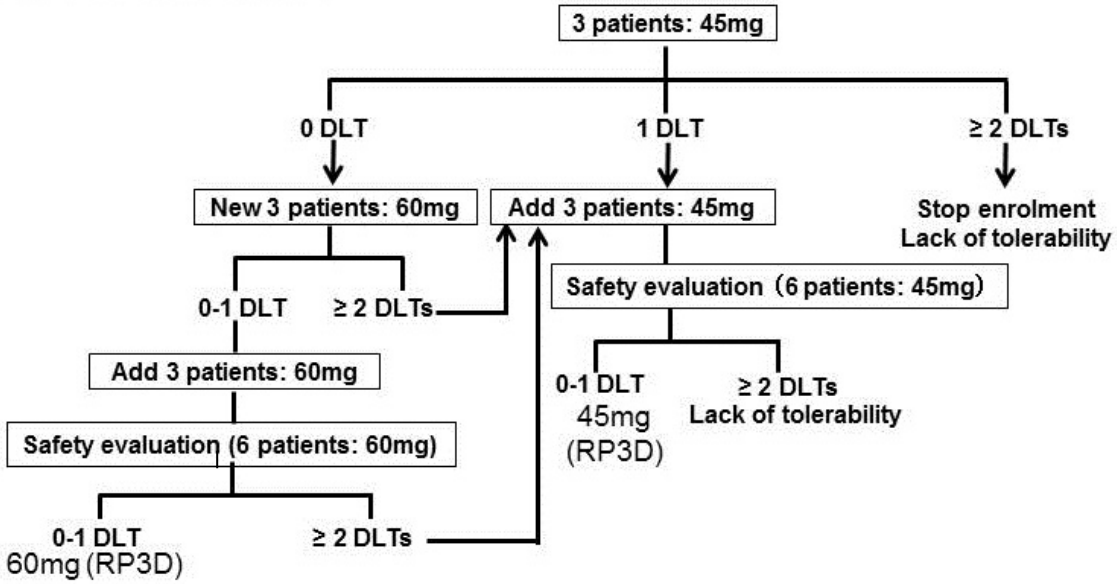
The dose-finding steps are presented in Figure 5-2.

Three patients will initially receive 45 mg of copanlisib. If 2 or more of the first 3 patients experience DLT (see Section 7.4.1 for DLT definitions) at this dose level, the safety run-in would be closed and the combination considered to be not feasible. If 1 out of the first 3 patients experiences a DLT at the 45 mg dose level, 3 additional patients will need to be enrolled at this dose level. If none of the first 3 patients experiences DLT at the 45 mg dose level, 3 new patients will start at 60 mg. If 0-1 patient out of the first 3 experiences DLT at the

60 mg dose level, the cohort will be expanded and 3 additional patients will receive the dose of 60 mg. If 0-1 patient out of 6 experiences DLT, 60 mg will be the recommended dose. If 2 or more out of 6 patients experience DLT at 60 mg, 3 more patients will be assigned to receive the lower dose (45 mg) if there are only 3 patients thus far treated with 45 mg of copanlisib. If 0-1/6 patients display DLT at this dose, then 45 mg will be the recommended dose. If 2 or more of 6 patients experience DLT at 45 mg, then the safety run-in would be closed and the combination considered to be not feasible with the tested schedule.

Patients treated within the safety run-in part and who in the investigator's opinion benefit from treatment can continue combination therapy (copanlisib plus R-B or R-CHOP) for a maximum of 6 cycles followed by copanlisib monotherapy with the same dose of copanlisib administered with immunochemotherapy. The maximum duration of treatment with copanlisib is 12 months (including combination therapy and monotherapy).

Figure 5-2 Overall study design of the safety run-in part



DLT = dose-limiting toxicity; RP3D = recommended phase III dose

All patients enrolled in the safety run-in part need to be evaluated for occurrence of DLTs during the first cycle. Patients not fully evaluable for occurrence of DLTs during the first cycle of therapy will be replaced unless the reason for dropout is a DLT (see Section 6.4.2). Any patient who experiences a DLT during first cycle of therapy should not receive further administration of copanlisib or any other study treatment. The investigator must notify the sponsor immediately of any CTCAE Grade 3 or 4 AEs or clinically relevant laboratory abnormalities.

Transition from safety run-in part to phase III part

DMC will review all data available from the safety run-in part and evaluate whether protocol specified treatment combinations are safe and tolerable. Details of the setup of the DMC and

the DMC meeting will be described in the DMC Charter. When the RP3D of copanlisib in combination with R-CHOP or R-B has been defined and confirmed by sponsor, and DMC, enrolment in the phase III part will start.

The safety run-in part of this study was completed for copanlisib in combination with R-B and in combination with R-CHOP. The DMC reviewed the safety data and decided that a copanlisib dose of 60 mg plus R-B or plus R-CHOP is safe to be used in the phase III part. Patients recruited into the safety run-in part were treated in an unblinded fashion and will thus not be evaluated as part of the phase III part.

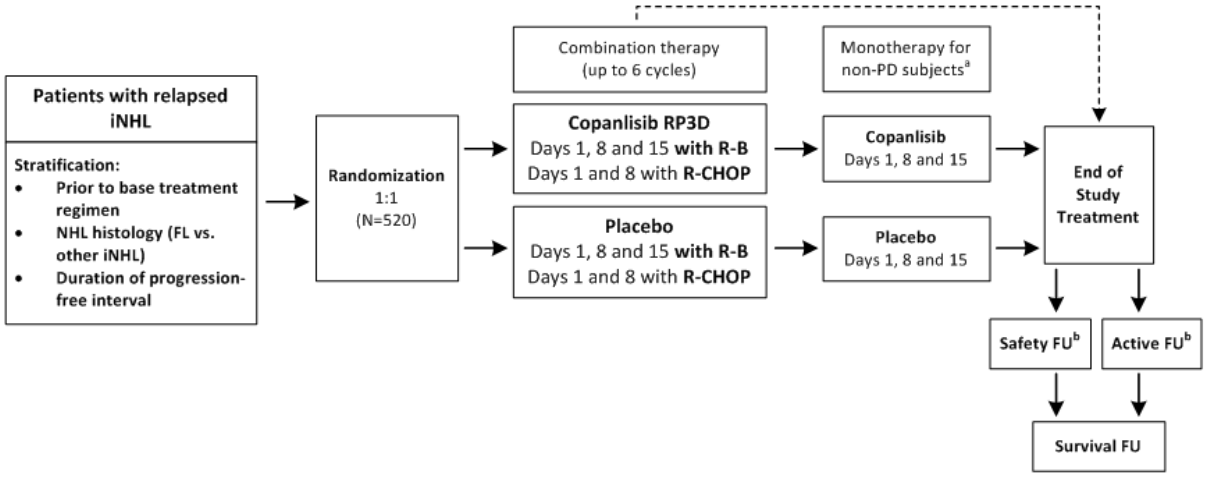
5.3 Phase III

Patients will be stratified by: prior to base treatment regimen (R-chemotherapy to R-B, R-B to R-CHOP, and R-B to R-B), NHL histology (FL vs. other iNHL) and duration of progression-free interval on the last rituximab, or rituximab biosimilars, or anti-CD20 monoclonal antibody containing regimen (6-12 months vs. >12 months). If the copanlisib immunochemotherapy combinations are deemed safe in the safety run-in part of the trial, approximately 520 (including FL and other iNHL) patients who meet the eligibility criteria will be randomly assigned in a 1:1 ratio to one of the double-blinded treatment arms (approx. 260 patients per arm) in the phase III part: **Arm 1**: copanlisib plus R-CHOP or R-B and **Arm 2**: placebo plus R-CHOP or R-B, see Figure 5-3.

- Patients who never received R-B as a previous line of therapy will be randomized to copanlisib/placebo + R-B treatment group
- Patients who received R-B as a previous line of therapy will be randomized to:
    - copanlisib/placebo + R-CHOP treatment group, or
    - copanlisib/placebo + R-B treatment group if ≥ 24 months progression-free interval after the last R-B treatment

During the phase III part DMC will review the unblinded data per DMC charter of all patients treated up to that time point (or as needed) and to ensure that patients are not exposed to undue risk. The investigators, patients and the sponsor will remain blinded.

Figure 5-3 Overall study design of Phase III part



FL = follicular lymphoma; FU = follow-up; iNHL = indolent non-Hodgkin's lymphoma; N = total number of patients; NHL = non-Hodgkin's lymphoma; PD = progressive disease; R-B = rituximab and bendamustine; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; RP3D = recommended phase III dose

a:The maximum duration of treatment with copanlisib/placebo is 12 months (including combination therapy and monotherapy). Study treatment will be continued until occurrence of PD (per central independent blinded radiology review), clinical progression, unacceptable toxicity occurs, or until another criterion is met for withdrawal from study or up to 12 months whichever comes first.

b: Safety follow-up (FU) for patients who discontinue study treatment due to PD; Active FU for patients who complete 12 months' study treatment without PD or discontinue study treatment for any other reason than PD (includes Safety FU).

5.3.1 Primary variable

- The primary variable for the safety run-in part is the occurrence of DLTs in Cycle 1.
- The primary efficacy variable for the phase III part is PFS, defined as the time (in days) from randomization to PD as assessed by blinded independent central review or death from any cause (if no progression is documented). The main analysis of the study will be performed when approximately 280 centrally evaluated PFS events in the FAS have occurred in the study.

5.3.2 Justification of the design

No data are available regarding the dose of copanlisib to be used in combination with standard immunochemotherapy. This study will have a safety run-in part to establish the RP3D of copanlisib to be used in combination with immunochemotherapy. The safety run-in part of this study will investigate the two dose-levels of copanlisib considered to be sufficiently active for a starting dose, 45 mg and 60 mg in combination with the standard dose of R-B or R-CHOP. Therefore patients will only be exposed to treatment that is expected to provide clinical benefit. If the initial dose level of 45 mg is well tolerated, the next dose level will be 60 mg.

The safety run-in part uses the standard design of dose-finding study, with 3-6 patients per dose level, and occurrence of dose-limiting toxicity as primary endpoint. The intensity and frequency of AEs as well as the occurrence of new and unexpected AEs will be carefully monitored. Those patients who have benefit and will stay on treatment after the 1st Cycle will

be also evaluated for treatment efficacy, safety and tolerability of copanlisib in combination with R-CHOP/R-B, pharmacokinetics and biomarkers. All these information will be taken into account when assessing the performance of the study in the phase III part.

The phase III part will start after RP3D of copanlisib is defined. The use of placebo can minimize investigator bias in assessing treatment effects beyond tumor shrinkage. This is particularly important when assessing duration endpoints and patient-reported outcomes. Although treatment with copanlisib is associated with infusion-related increases in blood glucose and increases in blood pressure, the risk of inadvertent unblinding is low. In the majority of the cases, the intensity of both symptoms is low, and both symptoms are not infrequent in the age group to which the majority of patients with indolent NHL belong.

5.3.3 End of study

The end of the study as a whole will be reached as soon as the last visit of the last patient has been reached in all centers in all participating countries (EU and non-EU).

Primary completion

The primary completion event for this study is PFS (progression assessed by blinded independent central review or death from any cause, whichever occurs first). The analysis will be performed when approximately 280 PFS events in the FAS occur.

The primary completion date for this study according to the US Food and Drug Administration (FDA) Amendment Act is specified in a separate document (not part of this study protocol).

6. Study population

Criteria for patients' eligibility, withdrawal and, as well as patients' identification apply to both safety run-in part and phase III part, unless otherwise specified.

6.1 Inclusion criteria

1. Ability to understand and willingness to sign written informed consent. Signed informed consent must be obtained before any study specific procedure.
2. Histologically confirmed diagnosis of CD20 positive iNHL with histological subtype limited to:
    - Follicular lymphoma (FL) grade 1, grade 2, or grade 3a
    - Small lymphocytic lymphoma (SLL) with absolute lymphocyte count $< 5 \times 10^9$/L at study entry
    - Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM)
    - Marginal zone lymphoma (MZL) (splenic, nodal, or extra-nodal)
3. Patients must have relapsed (recurrence after complete response or presented progression after partial response) or progressed after at least one but at most three prior lines of therapy, including rituximab, and/or rituximab biosimilars, and/or anti-CD20

monoclonal antibody (e.g. obinutuzumab) -based immunochemotherapy and alkylating agents (if given concomitantly is considered one line of therapy). A previous regimen is defined as one of the following: at least 2 months of single-agent therapy (less than 2 months of therapy with single agent rituximab, or rituximab biosimilars, or anti-CD20 monoclonal antibody can be considered a previous regimen in the case the patient responded to it); at least 2 consecutive cycles of polychemotherapy; autologous transplant; or radioimmunotherapy. Previous exposure to other PI3K inhibitors (except copanlisib) is acceptable provided there is no resistance (resistance defined as no response (response defined as PR or CR) at any time during therapy, or PD after any response (PR/CR) or after stable disease within 6 months from the end of the therapy with a PI3K inhibitor.

4. Non-WM patients must have at least one bi-dimensionally measurable lesion (that has not been previously irradiated) according to the Lugano Classification (14). For patients with splenic MZL this requirement may be restricted to splenomegaly alone since that is usually the only manifestation of measurable disease.
5. Patients affected by WM who do not have at least one bi-dimensionally measurable lesion in the baseline radiologic assessment must have measurable disease, defined as presence of immunoglobulin M (IgM) paraprotein with a minimum IgM level ≥ 2 × upper limit of normal (ULN) and positive immunofixation test.
6. Male or female patients ≥ 18 years of age.
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
8. Life expectancy of at least 3 months.
9. Availability of fresh tumor tissue and/or archival tumor tissue at Screening.
10. Women of childbearing potential (WOCBP) and men must agree to use effective contraception when sexually active. This applies for the time period between signing of the informed consent form and 12 months (for WOCBP) and 6 months (for men) after the last administration of study treatment. A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include but are not limited to hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for continuous 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy.
    The investigator or a designated associate is requested to advise the patient how to achieve highly effective birth control method (failure rate of less than 1%) e.g. intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, and sexual abstinence. The use of condoms by male patients is required unless the female partner is permanently sterile.
11. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements conducted within 7 days of starting the study treatment:

- Total bilirubin < 1.5 × ULN (< 3 × ULN for patients with Gilbert-Meulengracht syndrome, patients with cholestasis due to compressive adenopathies of the hepatic hilum or documented liver involvement by lymphoma).
- Alanine transaminase (ALT) and aspartate aminotransferase (AST) < 2.5 × ULN (< 5 × ULN for patients with documented liver involvement or with biliary obstruction due to lymphoma).
- Lipase ≤ 1.5 × ULN.
- Glomerular filtration rate (GFR) ≥ 40 mL/min/1.73 m^2 according to the Modification of Diet in Renal Disease (MDRD) abbreviated formula. If not on target, this evaluation may be repeated once after at least 24 hours either according to the MDRD abbreviated formula or by 24 hour sampling. If the latter result is within acceptable range, it may be used to fulfill the inclusion criteria instead.
- International normalized ratio (INR) ≤ 1.5 and partial thromboplastin time (PTT) ≤ 1.5 × ULN. PT can be used instead of INR if PTT ≤ 1.5 × ULN.
- Platelet count ≥ 75,000 /mm^3. For patients with lymphomatous bone marrow infiltration (local assessment), platelet count ≥ 50,000 /mm^3. Platelet transfusion should not be given less than 7 days before the exam collection.
- Hemoglobin (Hb) ≥ 8 g/dL.
- Absolute neutrophil count (ANC) ≥ 1,500/mm^3.

12. Left ventricular ejection fraction (LVEF) ≥ 50%.

6.2 Exclusion criteria

Patients who meet any of the following criteria at the time of screening will be excluded.

1. Previous assignment to treatment during this study. Patients permanently withdrawn from study participation will not be allowed to re-enter the study.
2. Previous (within 28 days or less than 5 half-lives of the drug before start of study treatment) or concomitant participation in another clinical study with investigational medicinal product(s).
3. *Criterion 3 removed in amendment 6*

Excluded medical conditions:

4. Histologically confirmed diagnosis of follicular lymphoma (FL) grade 3b or transformed disease, or chronic lymphocytic leukemia. In patients with clinical suspicion of transformed disease, a fresh biopsy is recommended.
5. Rituximab, or rituximab biosimilars, or anti-CD20 monoclonal antibody (e.g. obinutuzumab) resistance at any line of therapy (resistance defined as lack of response, or progression within 6 months of the last date of rituximab, or rituximab biosimilars, or

anti-CD20 monoclonal antibody administration, including maintenance with these drugs).

6. History or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function (as judged by the investigator).
7. Known lymphomatous involvement of the central nervous system.
8. HbA1c > 8.5% at Screening.
9. Known history of human immunodeficiency virus (HIV) infection. All patients must be screened for HIV up to 28 days prior to study drug start using a blood test for HIV according to local regulations.
10. Hepatitis B (HBV) or C (HCV) infection. All patients must be screened for HBV and HCV up to 28 days prior to study drug start using the routine hepatitis virus laboratorial panel. Patients positive for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb) will be eligible if they are negative for HBV-DNA, these patients should receive prophylactic antiviral therapy as per rituximab label. Patients positive for anti-HCV antibody will be eligible if they are negative for HCV-RNA.
11. Previous or concurrent history of malignancies other than indolent non-Hodgkin's lymphoma within 5 years prior to study treatment **except** for curatively treated:
    - Cervical carcinoma *in situ*
    - Non-melanoma skin cancer
    - Superficial bladder cancer (Ta [non-invasive tumor], Tis [carcinoma in situ] and T1 [tumor invades lamina propria])
    - Localized prostate cancer
12. Congestive heart failure > New York Heart Association (NYHA) class 2.
13. Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 3 months). Myocardial infarction less than 6 months before start of test drug.
14. *Criterion 14 removed in amendment 6*.
15. Uncontrolled hypertension despite optimal medical management (per investigator's assessment).
16. Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 3 months before the start of study medication.
17. Non-healing wound, ulcer, or bone fracture.
18. Active, clinically serious infections (> CTCAE Grade 2).
19. Patients with seizure disorder requiring medication.
20. Patients with evidence or history of bleeding diathesis. Any hemorrhage or bleeding event ≥ CTCAE Grade 3 within 4 weeks of start of study medication.

21. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation.
22. Proteinuria of ≥ CTCAE Grade 3 as assessed by a 24 h total urine protein quantification or estimated by urine protein : creatinine ratio > 3.5 (> 396 mg/mmol) on a random urine sample.
23. Unresolved toxicity higher than NCI-CTCAE grade 1 attributed to any prior therapy/procedure excluding alopecia.
24. Concurrent diagnosis of pheochromocytoma.
25. Pregnant or breast-feeding patients. Women of childbearing potential must have a pregnancy test performed a maximum of 7 days before start of treatment, and a negative result must be documented before start of treatment.
26. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.
27. Any illness or medical conditions that are unstable or could jeopardize the safety of the patients and their compliance in the study.

Excluded previous therapies and medications:

28. Documented evidence of resistance to prior treatment with idelalisib or other PI3K inhibitors defined as:
    - No response (response defined as partial response [PR] or complete response [CR]) at any time during therapy, or
    - Progression (PD) after any response (PR/CR) or after stable disease within 6 months from the end of the therapy with a PI3K inhibitor.
29. Prior treatment with anthracyclines (if patient will be assigned to R-CHOP), if the cumulative dose of anthracyclines will exceed 450 mg/m^2 (or lower local limit) of doxorubicin isotoxic equivalent dose including the predicted 6 cycles of R-CHOP as given in this study.
30. Ongoing immunosuppressive therapy.
31. Radiotherapy or immuno-/chemotherapy less than 4 weeks before start of treatment.
32. Radioimmunotherapy or autologous transplant less than 3 months before start of treatment.
33. Myeloid growth factors within 14 days prior to treatment start.
34. Blood or platelet transfusion within 7 days prior to treatment start.
35. Systemic continuous corticosteroid therapy at a daily dose higher than 15 mg prednisone or equivalent is not allowed. Patients may be using topical or inhaled corticosteroids. Previous corticosteroid therapy must be stopped or reduced to the allowed dose at least 7 days before performing the screening PET-CT and/or CT/MRI, whichever is performed first, and again at least 7 days prior to the first study drug

administration. If a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose after the patient has signed the IC.

36. History of having received an allogeneic bone marrow or organ transplant.
37. Major surgical procedure or significant traumatic injury (as judged by the investigator) within 28 days before start of study medication, open biopsy within 7 days before start of study medication.
38. Anti-arrhythmic therapy (beta blockers or digoxin are permitted).
39. Use of CYP3A4 inhibitors and inducers (see Appendix 16.1). Copanlisib is primarily metabolized by CYP3A4. Therefore, concomitant use of strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir and saquinavir), and strong inducers of CYP3A4 (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) are not permitted from Day -14 of Cycle 1 until the safety follow-up visit.
40. Prior treatment with copanlisib.

Other exclusions:

41. Cytomegalovirus (CMV) infection. Patients who are CMV PCR positive at baseline will not be eligible. CMV PCR test is considered positive if the result can be interpreted as a CMV viremia according to local SOC.
42. Live vaccination, including virus vaccination and yellow fever vaccination, within 6 months before start of study treatment.

For prohibited concomitant therapy please refer to Section 8.1.1.

6.3 Justification of selection criteria

The selection criteria are chosen to ensure that patients with specific risks for administration of the test drug and / or patients with conditions which may have an impact on the aims of the study are excluded, as well as patients with disease considered to be rituximab, and/or rituximab biosimilars, and/or anti-CD20 monoclonal antibody-refractory. Patients with an ECOG score of ≥ 3 will not be enrolled, as well as patients whose comorbidities may compromise safety or the ability to comply with the study procedures.

6.4 Withdrawal of patients from study

6.4.1 Withdrawal

6.4.1.1 Withdrawal criteria

Patients *must* be withdrawn from the study treatment if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result. Patients who withdraw consent from treatment will still participate in the Safety, Active or Survival follow-up

unless they object to follow-up data collection. For this, the patient's oral objection may be documented in the patient's source data.

- If, in the investigator's opinion, continuation of the study would be harmful to the patient's well-being.
- Disease progression as assessed by blinded independent central review and defined in the Lugano Classification and, for patients with WM, according to the Owen Criteria.
- Occurrence of unacceptable toxicity from any study treatment.
- CTCAE Grade 4 arterial hypertension.
- CTCAE Grade 4 dermatologic toxicity.
- Persistent occurrence of post-infusion blood glucose > 500 mg/dL based on laboratory analysis which occurred at the lowest copanlisib/placebo dose level despite optimal glucose lowering therapy (after at least one cycle of treatment).

  Definition of persistent occurrence is based on repeated post-infusion blood glucose laboratory analysis taken at different time during the whole cycle of treatment.
- Non-infectious pneumonitis ≥ CTCAE Grade 3.
- Drug-induced pancreatitis.
- Development of a malignancy other than indolent B-cell NHL. New malignancy will be reported as an SAE.
- Start of a new anti-cancer regimen.
- Phase III part: The patient does not tolerate copanlisib/placebo dose of 30 mg.

  Safety run-in part: The patient does not tolerate copanlisib dose of 30 mg after Cycle 1.
- The patient presents during further testing a positive viral load when initial HBV DNA and/or HCV RNA testing was negative.
- Severe allergic reaction to study treatment (such as CTCAE Grade 3 or 4 hypersensitivity reaction).
- Severe (life-threatening) reaction to rituximab infusion despite optimal supportive treatment.
- Patient lost to follow-up.
- Substantial non-compliance with the requirements of the study.
- Delay in test drug administration due to toxicities for > 28 days (a delay of test drug dosing due to reasons other than toxicity is not included in this definition). Except, in case of delays due to reactivation of CMV where delays could be up to 2 months.

- Development of any intercurrent illness or situation which, in the judgment of the investigator, may affect assessments of clinical status and study endpoints to a relevant degree.
- Detection of illicit drugs or other substances that may, in the opinion of the investigator, have a reasonable chance of contributing to toxicity or otherwise confound results.
- Patients with a positive β-human chorionic gonadotropin (HCG) test or any other sign consistent with pregnancy. Pregnancy will be reported within the same timelines as a SAE via the Pregnancy Monitoring Form.

Patients *must* be withdrawn from the study if any of the following occurs:

- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).

For patients who withdraw consent and object to follow-up data collection, no further study related procedures will be allowed, and no further data, including survival data, will be collected. The patients will not suffer any disadvantage as a result.

Withdrawal from follow-up period

Following completion of the EOT visit, patients who discontinue study treatment due to PD will enter the Safety follow-up period, and patients who complete 12 months' study treatment without PD or discontinue study treatment for reasons other than PD will enter Active follow-up period (which also serves as a Safety follow-up). During the Survival follow-up period all patients will be contacted every 3 months (± 14 days) to determine survival status (up to 10 years after the last patient started study treatment).

Reasons for not performing the Safety follow-up or discontinuation of the Survival follow-up include the following:

- Death
- Objection to follow-up data collection
- Lost to follow-up

Depending on the time point of withdrawal, a withdrawn patient is referred to as either "screening failure" (see Section 6.4.1.2) or "dropout" (see Section 6.4.1.3) as specified below:

6.4.1.2 Screening failure

A patient who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before the time point used for the definition of "dropout" (see below) is regarded a "screening failure".

Re-starting the defined set of screening procedures to enable the "screening failure" patient's participation at a later time point is not allowed – with the following exceptions:

- The patient had successfully passed the screening procedures, but could not start subsequent treatment on schedule.
- Initial screening occurred too early to complete the required washout period after prior therapy.
- The in- / exclusion criteria preventing the patient's initial attempt to participate have been changed (via protocol amendment).
- Screening failed due to positive CMV PCR result.

In any case, the investigator has to ensure that the repeated screening procedures do not expose the patient to an unjustifiable health risk. Also, for re-screening, the patient has to re-sign the informed consent form, even if it was not changed after the patient's previous screening.

Re-screening of patients who have failed screening may only be allowed once after discussion with the sponsor's designated medical representative and after approval by the sponsor. Sponsor approval of re-screening for the patient who has failed screening must be documented. The screening failure will be registered in IVRS/IWRS to close the patient identification number (PID), and rescreening will start again by signing a new ICF and being assigned a new PID.

Laboratory tests at Screening

All initial screening laboratory tests will need to be taken within 7 days prior to planned Day 1 of Cycle 1 (C1D1). If one or more screening laboratory tests do not support eligibility, laboratory re-test is permitted only once without the need of re-consent. Only the laboratory tests with results out of range need to be repeated. Re-testing must be performed within 14 days of the initial test and with approval from the sponsor. However, if this retesting cannot be completed within 7 days of the C1D1, all blood and urinary tests that are required to be within 7 days of C1D1 will need to be repeated. Patients may not begin study drug treatment until the results of re-testing are available and documented to be within protocol-required range. Diagnostic testing performed as part of the original screening or standard of practice (e.g. including fresh tumor tissue, CT scans, bone marrow sample, multiple gated acquisition [MUGA]/echocardiogram and hepatitis testing) will not need to be repeated during the 14 day re-testing period. If re-test laboratory results are still out of eligibility range, this will be considered **a full screening failure**, and only one re-screening will be allowed following the rules as outlined above.

For patients with newly diagnosed diabetes mellitus that cannot meet protocol requirements, a single re-screening (which includes all screening procedures) should be performed when the patient's diabetes is controlled and can meet protocol requirements (see Section 6.1 and 6.2).

6.4.1.3 Dropout

A patient who discontinues study participation prematurely for any reason is defined as a "dropout" if the patient has already been randomized (phase III part) /assigned to treatment (safety run-in part).

6.4.1.4 General procedures

In all cases, the reason for withdrawal must be recorded in the case report form (CRF) and in the patient's medical records.

The patient may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

All patients who discontinue due to AEs or clinical laboratory abnormalities should be followed up until they recover or stabilize, and the subsequent outcome recorded. If any patient dies during the study or within 30 days of the last dose of study drug, the investigator or his/her designated associate(s) will inform the sponsor. The cause of death should be recorded in detail within 24 h of awareness on an SAE form and transmitted to the sponsor.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12 (Premature termination of the study).

6.4.2 Replacement

Safety run-in part

Replacement if:

1. Termination for disease progression in patients with insufficient treatment exposure in Cycle 1 (< 100% of planned dose of the combination)
2. Insufficient treatment exposure due to non-compliance or voluntary withdrawal in Cycle 1 (< 100% of planned dose of the combination)
3. Major protocol violation (affecting the primary efficacy variable). This includes wrong diagnosis at enrollment, prior anti-tumor therapy not according to protocol, and prohibited concomitant anti-tumor therapy during the study.

Phase III part

Patients will not be replaced.

6.5 Patient identification

At Screening upon signing the ICF, each patient will be assigned a unique patient identification number (PID) by Interactive Voice Response System /Interactive Web Response System (IxRS) for unambiguous identification.

The patient number is a 9-digit number consisting of:

Digits 1 to 2 = Country code

Digits 3 to 5 = Center number within the country

(Digits 1 to 5 = Trial unit)

Digits 6 to 9 = Current patient number within the center

7. Treatments

7.1 Treatments to be administered

The study treatment will comprise the following:

1. Test drug copanlisib (BAY 80-6946) administered in combination with standard immunochemotherapy (R-B or R-CHOP)
2. Placebo administered in combination with standard immunochemotherapy (R-B or R-CHOP)
3. Copanlisib administered as monotherapy
4. Placebo administered as monotherapy

Combination therapy (copanlisib/placebo with R-B or R-CHOP) will be administered for a maximum of 6 cycles (C1-C6).

Copanlisib/placebo (study drug) monotherapy will be administered from C7 onwards. There will be no rituximab maintenance therapy administered from C7 onwards.

The maximum duration of treatment with copanlisib/placebo is 12 months (including combination therapy and monotherapy). The duration of treatment in the safety run-in part will be the same as in the phase III part. For the dosage and administration please see Section 7.4.

7.2 Identity of study treatment

Copanlisib (test drug)

Copanlisib is supplied as lyophilized preparation in a 6-mL injection vial. The total amount of BAY 80-6946 per vial is 60 mg. The solution for IV infusion is obtained after reconstitution of the lyophilisate with 0.9% sodium chloride solution.

Please refer to the Pharmacy Manual for detailed instructions for the reconstitution of the lyophilisate and for further dilution of the reconstituted solution.

Please refer to IB for copanlisib for more details regarding drug properties and formulation.

Placebo for copanlisib (only in phase III part)

Placebo is supplied as lyophilized preparation in a 6 mL injection vial. Placebo treatment will follow a dosing scheme to match the active drug product. Accordingly, the developed placebo lyophilisate is equivalent to the 60 mg copanlisib formulation, with regard to the composition of excipients and the instructions for reconstitution and dose preparation.

Reconstitution, dilution and storage of placebo preparation should be performed according to same instructions as for copanlisib.

For the guidance on preserving the blinding during handling of the study treatment, refer to Section 7.5.

Background treatment (Cycles 1-6):

Rituximab

Rituximab will be sourced centrally or locally depending on the local law and requirements. Rituximab biosimilars cannot be prescribed in this study. For full details on rituximab and instructions for dilution, please refer to the current prescribing information / Summary of Product Characteristics (SmPC).

Bendamustine, cyclophosphamide, doxorubicin, vincristine and prednisone/prednisolone

Bendamustine, cyclophosphamide, doxorubicin, vincristine and prednisone will be sourced centrally or locally depending on the local law and requirements. For full details on bendamustine, cyclophosphamide, doxorubicin and vincristine and instructions for dilution, please refer to the current prescribing information / SmPC. In countries where prednisone is not available, prednisolone can be administered instead. Prednisone and prednisolone are not diluted (oral); for full details on prednisone and prednisolone, please refer to the current prescribing information / SmPC.

All centrally supplied study drugs will be labeled according to the requirements of local law and legislation. The label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all centrally supplied study drugs, a system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) will be used, ensuring that each dose of study drug can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies Quality Assurance group.

A complete record of batch numbers and expiry dates of all centrally supplied study treatments as well as the labels will be maintained in the sponsor's study file.

Only patients enrolled in the study may receive study treatment and only authorized site staff may prepare, supply, or administer study treatment.

An approved representative at the site will ensure that all received study drugs are stored in a secured, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator or approved representative at the site is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

7.3 Treatment assignment

7.3.1 Safety run-in part

During the open-label safety run-in part patients who have given written informed consent and who satisfy the entry criteria will be assigned to the combination therapy (copanlisib + R-B or copanlisib + R-CHOP):

- Patients who received R-CHOP or R-CVP as a previous line of therapy will be assigned to copanlisib + R-B treatment group
- Patients who received R-B as a previous line of therapy will be assigned to copanlisib + R-CHOP treatment group

The dose level of copanlisib will be based on the cohort that is open at the time of the patient's enrollment based on 3+3 design.

7.3.2 Phase III part

At the end of the screening period, eligible patients will be randomly assigned in a 1:1 ratio to the two double-blinded treatment arms: copanlisib and R-B/R-CHOP or placebo and R-B/R-CHOP, respectively.

At randomization, IVRS/IWRS will stratify patients according to 3 factors based on baseline characteristics:

- Prior to base treatment regimen: R-chemotherapy to R-B, R-B to R-CHOP, and R-B to R-B
- NHL histology
    - FL histology
    - Other iNHL histology (SLL, MZL, LPL/WM)
- Duration of progression-free interval on the last rituximab, or rituximab biosimilars, or anti-CD20 monoclonal antibody containing regimen: 6-12 months versus >12 months

Resulting from the combination of these 3 stratification factors, patients will be grouped into 12 different strata; within each stratum, patient will be randomized between copanlisib and placebo. The randomization must be performed up to maximum 72 hours before the first dose of study treatment.

- Patients who never received R-B as a previous line of therapy will be randomized to copanlisib/placebo + R-B treatment group

- Patients who received R-B as a previous line of therapy will be randomized to:
  - copanlisib/placebo + R-CHOP treatment group, or
  - copanlisib/placebo + R-B treatment group if ≥ 24 months progression-free interval after the last R-B treatment

Treatment will be assigned based on information obtained from IVRS/IWRS.

The IVRS/IWRS procedure is described in detail in a separate IVRS/IWRS instruction manual.

Due to the potential of bias or unblinding, the size of randomization blocks within the randomization list must not be disclosed to blinded study individuals.

During the course of the study, the randomization list will be provided to the Statistical Analysis Center for the DMC and its meetings, the Bioanalytics group and the Pharmacokinetic Evaluator in order to perform the PK analysis.

7.4 Dosage and administration

Copanlisib and placebo

Copanlisib and placebo for copanlisib (only in phase III part) administration described below applies to all patients in the safety run-in part and patients in the phase III part, for as long as patients are on treatment with copanlisib or placebo.

Copanlisib and placebo for copanlisib formulations are administered in a normal saline solution, intravenously, over 1 hour. No intravenous glucose preparations should be administered on the days of infusion. See Pharmacy Manual for additional details.

See Table 7–1 and Section 5.2 for the dosing of copanlisib/placebo during the study.

Table 7–1 Dosing of copanlisib/placebo during the study

Copanlisib/Placebo (C/P) dosing	Cycle length (d)	D1	D8	D15
Cycles 1-6				
C/P in combination with R-B	28	X	X	X
C/P in combination with R-CHOP	21	X	X	
Cycle 7 onwards				
C/P monotherapy	28	X	X	X

D = day; R-B = rituximab and bendamustine; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

Immunochemotherapy (Cycles 1-6)

R-CHOP will be administered q3w as follows:

- Rituximab IV 375 mg/m^2 body surface on Day 2
- Cyclophosphamide IV 750 mg/m^2 body surface on Day 2
- Doxorubicin IV 50 mg/m^2 body surface on Day 2
- Vincristine IV 1.4 mg/m^2 body surface (max dose 2.0 mg) on Day 2
- Prednisone/prednisolone 100 mg daily PO from Day 2 to Day 6

R-B will be administered q4w as follows:

- Rituximab IV 375 mg/m^2 body surface on Day 1
- Bendamustine IV 90 mg/m^2 body surface on Day 1 and Day 2

Rituximab will be administered taking into account all measures of precaution prescribed by the manufacturer to avoid infusion reactions (rate of infusion, premedication, etc.). Patients will be monitored according to rituximab SmPC/prescribing information.

Cyclophosphamide, vincristine, doxorubicin, prednisone/prednisolone will be utilized according to the respective SmPC/prescribing information.

Bendamustine will be utilized according to SmPC/prescribing information.

Requirements for copanlisib/placebo pre-dose glucose levels

The copanlisib/placebo will be administered only if pre-dose glucose level is <160 mg/dL (fasting) or <200 mg/dL (non-fasting).

Glucose measurements at the site may be done either by laboratory analysis or in capillary blood.

Because of inhibitory effect on PI3K α-isoform, which is implicated in insulin metabolism, copanlisib infusions could be associated with temporarily increase in blood glucose. Addition of meal in close proximity to copanlisib/placebo infusion may exacerbate glucose increase. On infusion days, a low carbohydrate diet is recommended. The timing and content of meal intake and additional glucose testing (if clinically indicated) is managed and monitored by the investigators based on glucose response patterns during prior treatment days. Consultation with diabetologist or endocrinologist is advised.

All glucose measurements done at the site, oral glucose lowering medication and/or insulin administration, if applicable, fasting/non-fasting status and meal intake timing on infusion days will be collected as part of the clinical source documentation.

Dosing criteria

Starting from Cycle 1 Day 8, laboratory tests prior to each infusion may be performed and assessed either the day before or on the planned day of infusion (see Section 9.1), with the exception of blood glucose, which must be performed and assessed on the day of infusion. All

laboratory results must be assessed by the investigator/treating physician/sub-investigator prior to administration of planned dose.

On Day 1 of each subsequent cycle, the dose of copanlisib/placebo with immunochemotherapy (Cycles 2-6) and copanlisib/placebo (Cycle 7 onwards) will be given only if the laboratory test criteria described in Table 7–2 are met. Glucose lowering medication can be used to optimize pre-infusion glucoses (see Section 7.4.3.1 for glucose management).

Table 7–2 Laboratory test criteria for Day 1 dose of subsequent cycles

Laboratory Test [f]	Criteria for Day 1 dose (Cycle 2 and higher)
Glucose	< 160 mg/dL (fasting) or < 200 mg/dL (non-fasting)
Hemoglobin	≥ 8 g/dL [a]
ANC	≥ 1,000/mm^3
Platelets	≥ 75,000/mm^3 [e]
ALT	<2.5 × ULN [b]
AST	<2.5 × ULN [c]
Total bilirubin	< 1.5 × ULN [d]
GFR (MDRD)	≥ 40 mL/min/1.73 m^2

ALT = Alanine aminotransferase; ANC = Absolute neutrophil count; AST = Aspartate aminotransferase; GFR = Glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; ULN = Upper limit of normal.

a: If hemoglobin is < 8 g/dL but ≥ 6 g/dL on the day of planned study drug administration it is permissible to give the study drug dose as scheduled and transfuse within 48 hours after the dose, if the patient is hemodynamically stable and in opinion of investigator benefits outweigh risks. Rationale and treatment should be recorded in source document and eCRF.

b: < 5 × ULN in patients with documented liver involvement by lymphoma or with biliary obstruction due to lymphoma.

c: < 5 × ULN in patients with documented liver involvement by lymphoma or with biliary obstruction due to lymphoma.

d: < 3 × ULN in patients with Gilbert-Meulengracht syndrome, patients with cholestasis due to compressive adenopathies of the hepatic hilum or documented liver involvement by lymphoma.

e: For patients with lymphomatous bone marrow infiltration at study entry (local assessment), platelet count ≥ 50,000/mm^3. This value should be used throughout the study irrespective of bone marrow status changes. Platelet transfusion should not be given less than 7 days before the exam collection.

f: Laboratory tests prior to each infusion may be performed and assessed either the day before or on the planned day of infusion with the exception of blood glucose which must be performed and assessed on the day of infusion.

Note: A blood count will be performed and assessed prior to study drug infusion on Days 8 and 15 of each cycle. On Days 8 and 15, the dose of copanlisib/placebo will be administered only if ANC ≥ 500/mm^3, hemoglobin ≥ 8 g/dL and platelets ≥ 75,000/mm^3.

Doses of copanlisib/placebo scheduled for Days 8 and 15 may be delayed by up to 2 days. A delay of more than 2 days will be considered a missed dose. Missed doses will not be replaced. The minimum interval needed between two infusions of study drug is 5 days.

7.4.1 Definition of dose-limiting toxicities (DLTs)

Dose-limiting toxicity – safety run-in part

Dose-limiting toxicity will be defined as any of the following occurring during Cycle 1 at a given dose level and regarded by the investigator and/or the sponsor to be possibly, probably, or definitely related to copanlisib given in combination with R-B or R-CHOP. NCI-CTCAE

Version 4.03 will be used to assess toxicities/adverse events (AEs). The DMC opinion will decide in case of persisting disagreement between sponsor's and investigator's assessments.

General

- Any grade 5 hematologic or non-hematologic toxicity
- Any delay of >2 weeks of Cycle 2 due to study treatment-related toxicity

Non-hematologic DLT:

- **Any** non-hematologic toxicity grade ≥ 3, **except**:
  - Grade 3 nausea/vomiting/diarrhea of < 3 days duration or responsive to medical therapy within ≤ 3 days of occurrence
  - Increased glucose levels that returned to ≤ 200 mg/dL with or without the use of insulin or oral glucose lowering medications within ≤ 3 days of occurrence
  - Increased blood pressure that returned to <150 mmHg (systolic blood pressure) and <90 mmHg (diastolic blood pressure) with or without the use of anti-hypertensive medication within ≤ 3 days of occurrence

Hematologic DLT:

- Grade 4 absolute neutrophil count decrease lasting >7 days
- Grade 4 febrile neutropenia
- Grade 4 platelet count decreased or Grade 3 platelet count decreased with serious bleeding
- Signs of serious bleeding and/or international normalized ratio (INR) increased or partial thromboplastin time (PTT) prolonged of Grade 3

For certain toxicities such as laboratory assessments without a clear clinical correlate (e.g. lipase increase without signs of a clinical pancreatitis), a discussion between the investigator and the sponsor may take place if that adverse event should be assessed as DLT necessitating dose reduction.

7.4.2 Dose modification

Dose modifications due to toxicities described below apply to copanlisib and placebo for copanlisib ("dummy dose modification"). There will be no dose reductions for rituximab in any cycle. For the safety run-in part, there will be no dose reductions of any components of CHOP or bendamustine in the first cycle. Modifications for CHOP and bendamustine (safety run-in part: Cycle 2 and subsequent cycles, phase III part: all cycles) will be performed according to the measures of precaution and toxicity management per local standards of care, local prescribing information, and according to investigator's experience.

If any of the study treatment (copanlisib/placebo or immunochemotherapy) must be permanently discontinued, all other study treatment must be discontinued as well (excluding the planned discontinuation of R-B or R-CHOP after Cycle 6).

If any drug administration is delayed, all drug combinations (copanlisib/placebo + immunochemotherapy) must be delayed. If severe reactions to R-CHOP or R-B occur despite maximum supportive treatment patients should be withdrawn from the study treatment.

It is recognized that attribution of causality of any AE to the test drug specifically may be difficult. However, in Phase I and II trials, certain toxicities were seen only in relation to copanlisib e.g. transient increases in glucose and blood pressure. Based on this knowledge the investigator may decide on the necessary dose modifications.

Dose modifications and treatment interruptions for copanlisib and placebo must be done according to the guidelines in Section 7.4.2.2 and 7.4.2.3. The investigator may judge a more conservative dose modification more appropriate. If therefore these guidelines are not followed, the rationale for other measures is to be documented in detail in patient's medical record. Deviations from the guidelines must be discussed with the sponsor.

7.4.2.1 Safety run-in part and phase III part

Dose modification levels are outlined in Table 7–3. In the safety run-in part, dose modification rules of copanlisib will apply to patients who stay on treatment beyond 1st cycle and present toxicities that will need dose adjustments. Dose modification of placebo applies only to phase III part.

Table 7–3 Dose levels of copanlisib and placebo

If RP3D dose is **45 mg**:

Dose level 1 (starting dose):	45 mg of copanlisib or placebo
Dose level -1:	30 mg of copanlisib or placebo

If RP3D dose is **60 mg**:

Dose level 1 (starting dose):	60 mg of copanlisib or placebo
Dose level -1:	45 mg of copanlisib or placebo
Dose level -2:	30 mg of copanlisib or placebo

After having fully recovered from toxicity and in the absence of any criteria for further dose reduction or study drug discontinuation, re-escalation from dose level -2 to dose level -1, or from dose level -1 to dose level 1 will be allowed at the investigator's discretion.

Patients who do not tolerate the copanlisib/placebo dose of 30 mg must discontinue study treatment permanently.

7.4.2.2 Hematological toxicity

Neutropenia and febrile neutropenia are listed in the current version of IB as expected adverse events. If the guidelines given in Table 7–4 are not followed, the rationale for other measures is to be documented in detail in the patient's medical record. The use of myeloid growth factors in the prophylactic and therapeutic setting is allowed during study treatment based on local standard of care (SOC) and at investigator's discretion for safety run-in part and phase III part.

Table 7–4 Dose modification of copanlisib/placebo for hematological toxicity

Hematological toxicity (any of the following)	Study treatment action (for any toxicity)
• CTCAE Grade ≥ 3 thrombocytopenia (platelet < 50,000/mm^3) • Febrile neutropenia or ANC<500/mm^3 [a] • INR or PTT CTCAE Grade ≥ 3 with bleeding [b] • CTCAE Grade ≥ 3 anemia (Hb < 8 g/dL)	Delay infusion until criteria displayed in Table 7–2 are met.[d] Patient can be treated at one dose level lower at the investigator's discretion.[c] If more dose reductions are required than allowed per protocol, discontinue copanlisib permanently. The lowest dose level is 30 mg.

ANC = absolute neutrophil count; CTCAE = Common Terminology Criteria of Adverse Events, version 4.03; Hb = hemoglobin; INR = international normalized ratio; PTT = partial thromboplastin time; G-CSF = Granulocyte colony-stimulating factor

a: These patients should recover from neutropenia to ANC≥500/mm^3 without fever. G-CSF should be prescribed when ANC is <1000/mm^3.

b: International normalized ratio (INR) and partial thromboplastin time (PTT) should have returned to ≤ 1.5 and ≤ 1.5 × ULN, respectively, with no signs of bleeding.

c: After having fully recovered from toxicity and in the absence of any criteria for further dose reduction or study drug discontinuation, re-escalation is allowed at the investigator's discretion.

d: Treatment with transfusion is allowed at the investigator's discretion.

7.4.2.3 Non-hematological toxicity

Dose modifications for non-hematologic toxicities attributable to copanlisib/placebo except for glucose increases, dermatologic toxicity, non-infectious pneumonitis and blood pressure increases are outlined in Table 7–5.

Table 7–5 Dose modification of copanlisib/placebo for non-hematological toxicity
(except glucose increases, dermatologic toxicity, non-infectious pneumonitis and blood pressure increases)

		Study Drug Action	
Toxicity [a]	**Occurrence**	**For current course of therapy**	**For next course of therapy**
Grade 1-2	Any appearance	No change	No change
Grade 3 [b]	1st appearance	Interruption until Grade ≤ 2	No change
	2nd appearance	Interruption until Grade ≤ 2	Decrease by one dose level [c]
	3rd appearance	Interruption until Grade ≤ 2	Decrease by one dose level [c]
	4th appearance	Permanent discontinuation	–
Grade 4	Any appearance	Permanent discontinuation	–
Toxicity requiring delay for > 28 days		Permanent discontinuation	–

CTCAE = Common Terminology Criteria for Adverse Events; CMV = cytomegalovirus
a: Toxicities according to CTCAE version 4.03
b: Despite maximum supportive therapy
c: Not applicable for 30 mg dose level
A delay >28 days in study drug administration due to toxicities will cause permanent discontinuation of study treatment. Except, in case of delays due to reactivation of CMV where delays could be up to 2 months.
Copanlisib/placebo must be discontinued if the lowest dose level of 30 mg is not tolerated.
After having fully recovered from toxicity and in the absence of any criteria for further dose reduction or study drug discontinuation, re-escalation to dose level -1 or 1 will be allowed at the investigator's discretion.

Dermatologic toxicity

The guidelines for dose modifications in cases of dermatologic toxicity are outlined in Table 7–6. If these guidelines are not followed, the rationale for other measures will be documented in detail in the patient's medical record.

Table 7–6 Dose modification of copanlisib/placebo for dermatologic toxicity

Toxicity [a] (CTCAE severity grade)	Occurrence	Study drug action	
		For current course of therapy	For next course of therapy
Grade 1 and 2	Any appearance	No change	No change
Grade 3 [a]	1st	Interruption until Grade ≤ 2	Decrease by one dose level
	2nd	Interruption until Grade ≤ 2	Decrease by one dose level
	3rd	Permanent discontinuation	–
Grade 4	1st	Permanent discontinuation	–

CTCAE = Common Terminology Criteria for Adverse Events, version 4.03
a: Despite maximum supportive therapy
The lowest dose level is 30 mg; if a patient is already on the 30 mg dose level study drug and meets criteria for further decrease of dose, study drug will be discontinued permanently.

Non-infectious pneumonitis

In the event of suspected NIP, copanlisib/placebo treatment should be followed as Table 7–7. Pneumonitis is to be reported as such only in the event of NIP.

Table 7–7 Dose adjustment in cases of non-infectious pneumonitis (NIP)

Suspected or confirmed NIP per CTCAE	Action Taken	Re-treatment dose after recovery
Grade 1	No Change	NA
Grade 2	Dose Interruption Until recovery to ≤ grade 1	Decrease dose to the next lowest dose level [a]
Grade 2 second re-occurrence	Permanent Discontinuation	NA
Grade 3	Permanent Discontinuation	NA
Grade 4	Permanent Discontinuation	NA

NA = Not applicable; NIP = Non-infectious pneumonitis; CTCAE = Common Terminology Criteria for Adverse Events.
a: Not applicable for 30 mg dose level. No re-escalation is allowed after the dose reduction.
The lowest dose level is 30 mg; if a patient is already on the 30 mg dose level and cannot tolerate treatment study treatment will be discontinued permanently.

The investigator is requested to differentiate between non-infectious pneumonitis (NIP), and infectious pneumonitis (viral, bacterial, fungal), aspiration pneumonitis, or other pneumonitis clearly not due to a potential hypersensitivity reaction to the copanlisib infusion; and provide the basis for his/her assessment that it is infectious or other, as appropriate. The investigator is requested to report with the most specific clinical terms to describe the condition, not simple "pneumonitis".

Glucose increases and arterial hypertension

a) Glucose increases

Patients who develop transient post-infusion glucose > 250 mg/dL after copanlisib/placebo administration may continue treatment. However, the next infusion must be delayed until the patient's pre-infusion glucose levels return to < 160 mg/dL (fasting) or < 200 mg/dL (non-fasting). Guidelines for the management of glucose increases are given in Section 7.4.3.1.

- Continuing occurrence of post-infusion blood glucose > 500 mg/dL based on repeated laboratory analysis despite optimal glucose lowering therapy after 2 infusions of copanlisib/placebo will require dose reduction by one dose level.
- Further dose reduction is allowed as long as discontinuation criteria were not met.
- Dose re-escalation is allowed when a patient has achieved controlled glucose levels per investigator's judgment.
- Persistent occurrence of post-infusion blood glucose > 500 mg/dL based on laboratory analysis which occurred at the lowest copanlisib/placebo dose level despite optimal glucose lowering therapy (after at least one cycle of treatment) requires permanent discontinuation of the study treatment (see Section 6.4.1.1).

b) Arterial hypertension

No copanlisib/placebo dose should be given if blood pressure is ≥ 150/90 mmHg. Instructions for blood pressure measurement are given in Section 9.6.3.4. Antihypertensive medication may be given to control the increased blood pressure. Dosing can proceed on the scheduled day if there are at least 2 consecutive measurements <150/90 mmHg. Otherwise dosing must be delayed.

If drug-related arterial hypertension (post-dose blood pressure of CTCAE Grade 3 or ≥ 160/100 mmHg) is not manageable with optimal antihypertensive treatment, the dose for the subsequent copanlisib/placebo administrations may be reduced by 1 or 2 dose levels at the investigator's discretion. Guidelines for the treatment of increased blood pressure are given in Section 7.4.3.3. Patients with a post-dose blood pressure that may have life-threatening consequences (e.g. malignant arterial hypertension, transient or permanent neurologic deficit, hypertensive crisis) must permanently discontinue the study drug.

The guidelines for dose modifications of study treatment in case of arterial hypertension are given in Table 7–8.

Table 7–8 Dose modification of study treatment for arterial hypertension

Toxicity (CTCAE severity grade)	Study drug action	Recommendation
Pre-dose measurements BP ≥ 150/90 mmHg	No dose should be given until recovery to < 150/90 mmHg.	Consider administering BP lowering medication. Dosing can proceed on the scheduled day if after at least 2 consecutive measurements BP returns to < 150/90 mmHg. If BP doesn't return to < 150/90 mmHg then delay dosing until next visit.
During infusion: BP ≥ 160/100 mmHg or CTCAE hypertension of Grade 3	Infusion can be interrupted or slowed down and administration of BP lowering therapy should be initiated.	Infusion may be resumed immediately when BP has returned to < 150/90 mmHg or otherwise skipped. Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion[b].
Post-dose: Drug-related BP ≥ 160/100 mmHg[a] or CTCAE hypertension of Grade 3	–	Administration of BP lowering therapy should be initiated according to local standard of care. Additional measurements to be performed as clinically indicated until recovery to < 150/90 mmHg. Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion[b].
CTCAE hypertension of grade 4	Permanent discontinuation	–

BP = Blood pressure; CTCAE severity grade = Common Terminology Criteria for Adverse Events severity grade

a: Not manageable despite optimal antihypertensive treatment.

b: The lowest dose level is 30 mg; if a patient is already on the 30 mg dose level and experiences post-dose hypertension of CTCAE Grade 3 or ≥160/100 mmHg, consider more intensive therapy than previously used.

7.4.3 Treatment of toxicities

Recommendations for the treatment of toxicities described below apply to copanlisib and placebo. For monitoring and management of adverse reactions following R-CHOP and R-B administration please refer to the respective drug's SmPCs/prescribing information.

7.4.3.1 Management of transient post-infusion glucose increases that can occur with copanlisib

Management of transient post-infusion glucose increases on infusion days

Mild to moderate asymptomatic increases of blood glucose may occur with copanlisib infusion, and with larger increases potentially occurring post-prandially.

The guidelines for management of transient post-infusion glucose increases on infusion days are given in Table 7–9.

Table 7–9 Management of transient post-infusion glucose increases

Criteria	Recommendation	Suggested Treatment
On infusion days:		
Asymptomatic glucose increases ≤ 250 mg/dL	• Does not generally require treatment with glucose lowering medication	**None**
Asymptomatic glucose increases > 250 mg/dL	• Should have repeated laboratory glucose determination • If the repeated glucose value is decreasing, the glucose may be followed without glucose lowering medication treatment if hydration status is normal as clinically assessed • Consultation with diabetologist or endocrinologist is recommended	• Hydration if appropriate • When planning next infusion consider prophylaxis with oral glucose lowering medication
Symptomatic or persisting glucose increases > 250 mg/dL	• Hydration status should be clinically assessed • If clinical assessment is consistent with dehydration, fluids should be given as clinically appropriate (orally or IV). • Laboratory test confirming increase should be repeated. If the repeated glucose value is > 250 mg/dL and/or patient is symptomatic and/or the hydration status indicate the need for hydration, glucose lowering medication should be administered • Prompt input from a diabetologist or endocrinologist should be obtained.	• Hydration if appropriate • Rapid/short acting insulin may be given for glucose persisting at > 250 mg/dL, or if the patient is symptomatic during the infusion day. • Rapid/short acting insulin according to the institution sliding scale coverage of glucose persisting at > 250 mg/dL is recommended, with oral or IV hydration as clinically appropriate. • When planning next infusion consider prophylaxis with oral glucose lowering medication

Table 7–9 Management of transient post-infusion glucose increases

Criteria	Recommendation	Suggested Treatment
On subsequent days:		
Max post-infusion glucose > 200 mg/dL noted on subsequent days	• Oral glucose lowering medication recommended on subsequent day • Consultation with diabetologist or endocrinologist is recommended	• The use of sulphonylurea/metaglinides insulin secretagogues medications to manage increased glucose levels post drug infusions is not recommended. • Treatment with glucose lowering medication suggested according the local standards of practice. • Based on mechanisms of action and decreased risk of hypoglycemia, metformin, SGLT-2-inhibitor or DPP4-inhibitor might be useful treatment options

DPP4 = Dipeptidyl peptidase-4; IV = intravenous; SGLT-2 = Sodium/glucose co-transporter 2

The need for glucose monitoring at home should be determined by the investigator based on post-infusion glucose profile and clinical status of the patient.

Monitoring of diabetic patients

If the patient has known diabetes and already monitors his/her blood glucose as part of routine diabetes care, the routine measurements should not be replaced by the study-specific measurements.

7.4.3.2 Management of hyperlipidemia

As lipids are monitored for the duration of this study it is recommended to treat significant deviations from normal range with standard interventions and therapy in standard doses according to local medical practice. Goals of therapy are to keep fasting triglycerides < 300 mg/dL and low-density lipoproteins (LDL) < 190 mg/dL (lower LDL depending on cardiovascular risk) in patients with a life expectancy >1 year. The goals for fasting triglycerides can be raised to < 500 mg/dL for patients with life expectancy <1 year (16). Although there is a paucity of data on the effects of hyperlipidemia and cancer outcomes, these goals have been chosen to decrease risk of established complications of hypertriglyceridemia (pancreatitis) and hypercholesterolemia (cardiovascular events). For evaluation of lipid-panels including triglycerides patients must be fasting prior to sampling according to local standards. For patients who cannot adhere to these fasting requirements the evaluation of lipid-panels including triglycerides and determination of treatment is considered as not feasible.

7.4.3.3 Treatment of blood pressure increases associated with copanlisib

It is important that patients with pre-existing arterial hypertension adhere to their regular medication schedule, and take their usual doses on the days of study drug infusion.

The management of acute blood pressure increases following copanlisib/placebo will need to be individualized for each patient, but experience in Phase I has suggested the benefit of dihydropyridine calcium channel blockers (i.e. amlodipine, felodipine). Nitrates, verapamil and diltiazem can also be considered. In general, it is advisable for sites to be prepared, so that antihypertensive medication is readily available in case of need.

7.4.3.4 Treatment of vomiting and diarrhea

Hydration status of the patient should be clinically assessed, with fluid replacement (oral or IV) as appropriate. Adequate hydration through appropriate fluid maintenance is essential in the treatment of diarrhea or vomiting. Anti-diarrhea medications may be introduced if symptoms occur. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2 to 4 hours until diarrhea-free for 12 hours; a maximum daily dose of 16 mg is not to be exceeded. If clinically indicated, diphenoxylate hydrochloride with or without atropine sulfate can be used. The routine use of standard antiemetics, including 5-HT3 blockers is allowed, see Section 8.1.2 for permitted concomitant therapy. In the event of CTCAE Grade 3 diarrhea with maximal pharmacological support, the administration of the study treatment should be delayed.

7.4.3.5 Treatment of dermatologic toxicity

If dermatologic changes occur, the patient should be treated quickly and aggressively.

Table 7–10 can be used as guidance.

Table 7–10 Guidance on treatment of skin toxicities

	MILD (CTCAE Grade 1)
Dry Skin/Fissures	Emollients, - Eucerin or Aquaphor plus gentle soaps (Dove, Cetaphil, Basis), use fragrance free detergents
Rash	Topical hydrocortisone 2.5% and/or clindamycin 1% gel plus doxycycline 100 mg bid or Minocycline 100 mg bid
Nail Changes	Moisturizers
Pruritus	Pramoxine 1% cream or Sarna Ultra Cream
	MODERATE (CTCAE Grade 2)
Dry Skin/Fissures	Emollients and topical as above plus Ammonium lactate or Urea 20%
Rash	Topical hydrocortisone 2.5% and/or clindamycin 1% gel plus doxycycline 100 mg bid or Minocycline 100 mg bid
Nail Changes	Vinegar soaks (dilute 1:1 white vinegar in water) and soak fingers for 10 minutes a day
Pruritus	H1-anti-histamines
	SEVERE (CTCAE Grade 3 or 4)
Dry Skin/Fissures	As above for Moderate
Rash	As above for Moderate plus Medrol dose pack [a]
Nail Changes	Topical antibacterials/antifungals (ciclopirox) cream or Topical high potency steroids (clobetasol ointment) Consider dermatology consult for nail avulsion
Pruritus	Pregabalin 50-100 mg bid

bid = twice daily; CTCAE = Common Terminology Criteria for Adverse Events, version 4.03
a: Cross check with short-term corticosteroid administration (see Section 6.2 and Section 8.1.2)
Source: (18)

If concomitant corticosteroids are used for dermatologic conditions, the investigator should be alert to potential impact of corticosteroids on increases in blood glucose and in blood pressure. Please refer to excluded previous therapies at Section 6.2. If glucose increases or blood pressure increases during the period of corticosteroid use, please see Section 7.4.3.1 for glucose management, and see Section 7.4.3.3 for blood pressure management.

7.4.3.6 Guidance for monitoring and prophylaxis of opportunistic infection (OI)

7.4.3.6.1 Monitoring guidelines for OI

In addition to the weekly clinical review and laboratory tests outlined in the schedule of assessment, the following should be performed in all patients prior to IV infusion of copanlisib:

- Evaluation of any new onset or worsening of pulmonary symptoms (i.e. cough, dyspnea or fever) that includes a lung examination at each visit prior to infusion.
- Laboratory tests: CD4 (for patients with signs of infection), blood cultures if febrile neutropenia occurs, PCR for CMV (every cycle on Cycle X Day 1 (time window -1

day) during combination therapy and every 3 cycles starting from Cycle 7). CMV can be analyzed retrospectively in case the results are not immediately available.

- Note: If PCR test is positive for CMV, treatment should be delayed until recovery. CMV PCR test is considered positive if, the result can be interpreted as a CMV viremia according to local SOC. Treatment of CMV should be initiated based on local standard of care (SOC). Retreatment with copanlisib will be allowed without dose reduction once PCR test for CMV is negative.

Enhanced monitoring when prior medical history or laboratory parameters could be associated with one of the following risk factors:

- Intensive chemotherapy (≥2 lines of myelosuppressive cytotoxic therapy)
- History of CMV, herpes
- History of lower respiratory tract infection, history of immunodeficiency in the last 12 months (excluding lymphoma)
- Lymphocytes count < 500/mm^3 while on treatment in clinical study.

For patients with identified risk factors and those who developed OI on study treatment, additional assessments can (per institutional recommendation/guideline) include:

- CD4 and CD8 count and ratio, CRP, blood cultures
- Any additional laboratory and diagnostic methods according to local SOC reported as unscheduled laboratory and diagnostic methods of assessment
- Radiological imaging (i.e. chest X-ray [CXR] or CT scans)
    - Note: Treatment of developed OI should be based on local SOC.

7.4.3.6.2 Prophylaxis of OI

Mandatory prophylactic therapy is not recommended in all patients:

- Review of copanlisib data does not support risk benefit ratio favoring prophylaxis in all patients
- Mandatory prophylaxis may cause a higher risk of side effects associated with supportive treatment where no risk factors are present
- Currently implemented schedule of assessments and additional enhancements provide frequent monitoring and flexibility for prophylaxis based on local SOC.

Although not mandated in all patients, OI prophylaxis may be initiated at the discretion of the treating investigator's judgment of the benefit/risk ratio in any patient, irrespective of whether a high-risk feature is present, per local SOC. If so, treatment, dosage and route of administration must be reported on the concomitant medication page of the eCRF.

Prophylactic treatment of OI should be initiated based on SOC in patients when high risk factors are identified (see protocol Section 7.4.3.6.1). Treatment, dosage and route of administration must be reported on the concomitant medication page of the eCRF.

7.5 Blinding

Blinding measures are only applicable for the phase III part which follows double-blind design. The safety run-in part is open-label.

Patients will be randomized to receive copanlisib in combination with R-B/R-CHOP or placebo in combination with R-B/R-CHOP, in a double-blinded fashion, so that neither the investigator, nor the sponsor, nor the patient will know which agent is being administered. The randomization number will be assigned through the IVRS/IWRS based on information entered by the site staff when the patient qualifies for study treatment.

During the phase III part DMC will review the unblinded data per DMC charter of all patients treated up to that time point (or as needed) to ensure that patients are not exposed to undue risk. The investigators, patients and the sponsor will remain blinded.

The appearance of the packaging for copanlisib and placebo will be identical in order to preserve blinding. Both will be packaged in a drug pack labeled with a unique drug pack number which will be pre-printed. The study drug pack number will be assigned to the patient through the IVRS/IWRS.

Because copanlisib solution may have a yellowish color while the placebo solution is colorless, measures will be taken to preserve the blind. This includes an unblinded, study-independent pharmacist (or qualified person) who will handle the preparation of the study drug, and independent monitors, separate from the blinded monitoring team, to conduct the monitoring of the pharmacy and drug supplies. Additional details will be described in the Pharmacy Manual.

In compliance with applicable regulations, in the event of a suspected, unexpected, serious adverse reaction (SUSAR) (see Section 9.6.1.5) related to the blinded treatment, the patient's treatment code will usually be unblinded before reporting to the health authorities, ethic committees and investigators (see Section 9.6.1.4).

Emergency unblinding by the investigator

Unblinding of the patient's treatment assignment may be carried out by the investigator for emergency purposes only. Investigators should note that the occurrence of an SAE should not routinely precipitate the immediate unblinding of the study drug. If unblinding is necessary for the treatment of a patient who has experienced an SAE, the treatment assignment of a patient will be unblinded via instructions provided through the IVRS/IWRS. This system allows the investigator, or other responsible person, to identify the study drug in case of an emergency, without jeopardizing the double-blind integrity of the remainder of the study.

The code can be broken by the investigator, or other responsible person, when knowledge of the patient's treatment is required for the clinical management of the patient. If it becomes necessary to know the individual's treatment during the study and, thus, break the code for that patient, the date and reason are to be entered in the relevant eCRF page. The investigator is required to promptly document and explain to the sponsor's designee any premature unblinding (e.g. unblinding due to an SAE) of the study drug. At the end of the study access to IxRS (which gives access to code break information) for the principal investigator will be revoked.

7.6 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and Good Manufacturing Practice (GMP) requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate/contract research organization [CRO]), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor's study file; the site-relevant elements of this information will be available in the investigator site file.

The responsible site personnel will confirm receipt of all centrally supplied study drugs (sponsor supplied) via IVRS/IWRS. The handling of batch numbers and expiry dates for locally supplied (site supplied) background treatments used in the study will be documented in the sponsor's supporting operational procedures/plans. The personnel will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

Written instructions on medication destruction will be made available to affected parties as applicable.

If performing drug accountability implies a potential risk of contamination, a safety process/ guidance for handling returned drug will be provided.

7.7 Treatment compliance

The administration of intravenous copanlisib/placebo, immunochemotherapy (R-CHOP or R-B) will be performed in the clinic and *must be recorded in the source data and in the eCRF.* Reasons for dose delay, interruption or reduction will also be recorded in the source data and in the eCRF.

Prednisone will be administered PO from Day 2 to Day 6 q3w. In countries where prednisone is not available, prednisolone can be administered instead. Only the dose given on Day 2 *will be administered in the clinic*. From Day 3 to Day 6 prednisone will be self-administered by the patient at home. For prednisone which is self-administered by the patient at home, the patient will return the empty blisters and unused tablets at the visit when the new prednisone is supplied. At this visit, site staff will review the returned amount to verify drug compliance. This review and count will be documented in source data. Any discrepancies between actual and expected amount of returned study medication must be discussed with the patient at the time of the visit, and any explanation must be documented in the source records.

8. Non-study therapy

8.1 Prior and concomitant therapy

For prohibited prior therapy please refer to Section 6.2.

8.1.1 Prohibited concomitant therapy

- CYP3A4 inhibitors and inducers (see Appendix 16.1). Copanlisib is primarily metabolized by CYP3A4. Therefore, concomitant use of strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir and saquinavir), and strong inducers of CYP3A4 (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) are not permitted within two weeks prior to start of study treatment until the SFU visit.
- Grapefruit and grapefruit juice (CYP3A4 inhibitor), Seville oranges and star fruit consumption is not permitted during the study.
- Anti-arrhythmic therapy other than beta blockers or digoxin.
- Concomitant therapy with any anticancer agents, immunosuppressive agents, other investigational anticancer therapies.
- Concomitant radiotherapy (it is assumed that radiation would be indicated only in case of progression, when the patient would come off study treatment anyway). Palliative radiotherapy is allowed (see Permitted concomitant therapy for details).
- Systemic continuous corticosteroid therapy at a daily dose higher than 15 mg prednisone or equivalent is not allowed. Patients may be using topical or inhaled corticosteroids. Previous corticosteroid therapy must be stopped or reduced to the allowed dose at least 7 days before performing the screening PET-CT and/or CT/MRI, whichever is performed first, and again at least 7 days prior to the first study drug administration. If a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose after the patient has signed the IC. The use of corticosteroids as antiemetics prior to copanlisib/placebo administration will not be allowed.
- Since the use of Biotin (vitamin B7) produce high levels of the vitamin, these can interfere with the result of the immunoassay tests including biomarker analysis, HBc-Ab, HBe-Ag, HBs-Ag, HCV-Ab, HIV-Ag/Ab combo, HIV combo, therefore refrain the use of Biotin for at least 72 hours prior to immunoassay test collection.

8.1.2 Permitted concomitant therapy

- Standard therapies for concurrent medical conditions.
- Treatment with non-conventional therapies (for example herbs or acupuncture), and vitamin/mineral supplements is acceptable provided that they do not interfere with the study endpoints, in the opinion of the Investigator. St John's Wort is not permitted.
- Bisphosphonates.
- Patients who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT is stable. Close monitoring is recommended according to standard of care. If either of these values is above the therapeutic range, the doses should be modified and the assessments should be repeated weekly until it is stable.

- Antiemetics: prophylactic anti-emetics may be administered according to standard practice. The routine use of standard antiemetics, including 5-HT3 blockers, such as granisetron, ondansetron, or an equivalent agent, is allowed as needed. The use of corticosteroids as antiemetics prior to study drug administration will be not allowed.
- Palliative and supportive care for the other disease-related symptoms and for toxicity associated with treatment will be offered to all patients in this trial.
- Patients may receive palliative and supportive care for any underlying illness.
- Palliative irradiation shall be permitted provided that:
  - In the opinion of the investigator, the patient does not have PD.
  - The radiation field does not encompass a target lesion
  - The radiation field does not encompass a lung field (to reduce the risk for pneumonitis).
- Low-dose aspirin (maximum 100 mg/day) and low-dose heparin are permitted.
- Patients taking narrow therapeutic index medications should be monitored proactively, if these medications cannot be avoided. These medications may include quinidine and digoxin.
- Substrates of the renal drug transporter MATE2K (e.g. metformin, cimetidine, procainamide and N methylnicotinamide) need to be used with caution. Metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast. Please refer to prescribing information for further information.
- Calcium channel blockers to control pre-existing hypertension.
- Short term (up to 7 days) systemic corticosteroids above 15 mg prednisone or equivalent will be allowed for the management of acute conditions (e.g. treatment of NIP) and as premedication prior to rituximab and bendamustine infusions (if considered standard of care) (see Section 9.6.3.2 for the required glucose measurements). The investigator should be alert to potential impact of corticosteroids on increases in blood glucose and in blood pressure. If glucose increases or blood pressure increases during the period of corticosteroid use as premedication described above, please see Section 7.4.3.1 for glucose management and see Section 7.4.3.3 for blood pressure management.
- G-CSF is mandatory if ANC<1000/mm^3 and should be administered as per label (see also Section 7.4 “Dosing criteria”).

8.2 Post-study therapy

After the end of this study, further therapy is at the discretion of the investigator.

9. Procedures and variables

In the event of a significant study-continuity issue (e.g. caused by a pandemic), alternate strategies for participant visits, assessments, and monitoring may be implemented by the Sponsor or the investigator in consultation with the Sponsor, in line with local health authority/ethics requirements.

9.1 Tabular schedule of evaluations

This section contains three tabular schedule of evaluations which are valid to both safety run-in part and phase III part of the study (unless otherwise specified):

Table 9–1 for copanlisib/placebo + R-B combination therapy,

Table 9–2 for copanlisib/placebo + R-CHOP combination therapy, and

Table 9–3 for copanlisib/placebo monotherapy (from C7 onwards).

The footnotes apply to all tables.

Table 9–1 Study flow chart – Screening and copanlisib + R-B combination therapy

(for procedures during the copanlisib/placebo monotherapy and after treatment, see Table 9–3)

	Screening maximum days before C1D1			Treatment during the combination therapy (C1-C6)									
				Cycle 1					Cycle 2 to Cycle 6				
Days	**-28**	**-14**	**-7**	**D1**	**D2**	**D8**	**D15**	**D22** [ii]	**D1**	**D2**	**D8**	**D15**	**D22** [ii]
Acceptable deviation for study drug administration (unless otherwise specified) (in days) [hh]				-1 to + 2 days [dd]		-1 to + 2 days [dd]			-1 to + 2 days [dd]		1 to + 2 days [dd]		
Screening and enrollment													
Patient informed consent (including genetic) [a]	X												
Check in- and exclusion criteria		X	X	X									
Medical history [b]		X											
IVRS/IWRS transaction [c]	X			X[c]					X				
HBsAg, HBcAb, and anti-HCV antibody (HBV DNA, HCV RNA)[aa,hh]	X								X[aa]				
CMV PCR[gg,hh]	X			X[ee]					X[ee]				
HIV test	X												
Beta-2-microglobulin (for patients with WM/FL)		X											
Serum pregnancy test (if applicable) [d]			X						X[d]				
UPCR/ 24 h total urine protein quantification [cc,hh]			X										
GFR calculation (MDRD abbreviated formula) [e]			X						X				
Safety													
Toxicity / AE assessment [f]		X		X		X	X		X		X	X	
Concomitant medication [f]		X		X		X	X		X		X	X	
Complete physical examination		X		X					X				
Brief physical examination and status check, including lung examination [hh]						X	X				X	X	
12-lead ECG [g]	X			X					X[g]				
MUGA scan or echocardiogram [h]		X							X[h]				
Hemoglobin A1c [i]			X						X[i]				
Complete blood count [hh]			X	X		X	X		X		X	X	
Chemistry panel [k]			X[k]			X	X		X[k]		C2 only	C2 only	
Coagulation panel: PTT,PT and INR			X				X		X				
Urinalysis (dipstick)			X						X				

Table 9–1 Study flow chart – Screening and copanlisib + R-B combination therapy

(for procedures during the copanlisib/placebo monotherapy and after treatment, see Table 9–3)

	Screening maximum days before C1D1			**Treatment during the combination therapy (C1-C6)**									
				Cycle 1					**Cycle 2 to Cycle 6**				
Days	**-28**	**-14**	**-7**	**D1**	**D2**	**D8**	**D15**	**D22** [ii]	**D1**	**D2**	**D8**	**D15**	**D22** [ii]
Acceptable deviation for study drug administration (unless otherwise specified) (in days) [hh]				-1 to + 2 days [dd]		-1 to + 2 days [dd]			-1 to + 2 days [dd]		1 to + 2 days [dd]		
CD4 (for patients with signs of infection) and blood cultures if febrile neutropenia occurs [gg,ff,hh]													
Glucose [l,hh]				X	(X)[bb]	X	X		X	(X)[bb]	X	X	
Blood pressure [n]				X		X	X		X		X	X	
Efficacy													
CT / MRI and tumor evaluations [o]	X			Every 12 weeks									
PET-CT	X			If performed at BL, PET-CT should be repeated after the Cycle 6 if a PD is not detected during the course of treatment and/or to confirm complete response (CR) or disease progression									
Bone marrow biopsy	X			Confirmation of first CR (if positive for lymphoma infiltration at BL)									
Phase III: QoL questionnaire (FLymSI-18) [p]				X					X[p]				
Pharmacokinetic sample [q]				X		X			C6		C3,C6		
Biomarkers													
Fresh and/or or archival tumor tissue (central pathology and biomarkers) [r]	X												
Plasma for tumor genetics [s]				X									
Plasma for non-genetic biomarker analysis [t]	X			X		X	X		C2 only		C2 only	C2 only	
Whole blood for biomarkers [u]				X									
For LPL/WM patients only [v]													
Serum protein electrophoresis [v]		X[v]											(X)[v]
Immunofixation [v]		X[v]											(X)[v]
Serum quantitative IgM test [v]		X[v]											(X)[v]
Serum or plasma viscosity		X[v]							(X)[v]				
Drug administration													
Copanlisib/placebo				X		X	X		X		X	X	
R-B (Cycles 1-6) : rituximab D1, bendamustine D1, D2				X	X				X	X			

For abbreviations and footnotes, see Table 9–3.

Table 9–2 Study flow chart – Screening and copanlisib + R-CHOP combination therapy

(for procedures during the copanlisib/placebo monotherapy and after treatment, see Table 9–3)

	Screening maximum days before C1D1			Treatment during the combination therapy							
				Cycle 1				Cycle 2 to Cycle 6			
Days	**-28**	**-14**	**-7**	**D1**	**D2**	**D8**	**D15 [ii]**	**D1**	**D2**	**D8**	**D15 [ii]**
Acceptable deviation for study drug administration (unless otherwise specified) (in days) [hh]				-1 to + 2 days [dd]		-1 to + 2 days [dd]		-1 to + 2 days [dd]		-1 to + 2 days [dd]	
Screening and enrollment											
Patient informed consent (including genetic) [a]	X										
Check in- and exclusion criteria		X	X	X							
Medical history [b]		X									
IVRS/IWRS transaction [c]	X			X[c]				X			
HBsAg, HBcAb, and anti-HCV antibody (HBV DNA, HCV RNA)[aa,hh]	X							X[aa]			
CMV PCR[gg,hh]	X			X[ee]				X[ee]			
HIV test	X										
Beta-2-microglobulin (for patients with WM/FL)		X									
Serum pregnancy test (if applicable) [d]			X					X[d]			
UPCR/ 24 h total urine protein quantification[cc,hh]			X								
GFR calculation (MDRD abbreviated formula) [e]			X					X			
Safety											
Toxicity / AE assessment [f]		X		X		X		X		X	
Concomitant medication [f]		X		X		X		X		X	
Complete physical examination		X		X				X			
Brief physical examination and status check, including lung examination [hh]						X				X	
12-lead ECG [g]	X			X				X[g]			
MUGA scan or echocardiogram [h]		X						X[h]			
Hemoglobin A1c [i]			X					X[i]			
Complete blood count [hh]			X	X		X		X		X	
Chemistry panel [k]			X[k]			X		X[k]		C2 only	
Coagulation panel: PTT,PT and INR			X					X			
Urinalysis (dipstick)			X					X			

Table 9–2 Study flow chart – Screening and copanlisib + R-CHOP combination therapy

(for procedures during the copanlisib/placebo monotherapy and after treatment, see Table 9–3)

	Screening maximum days before C1D1			Treatment during the combination therapy							
				Cycle 1				Cycle 2 to Cycle 6			
Days	**-28**	**-14**	**-7**	**D1**	**D2**	**D8**	**D15** [ii]	**D1**	**D2**	**D8**	**D15** [ii]
Acceptable deviation for study drug administration (unless otherwise specified) (in days) [hh]				-1 to + 2 days [dd]		-1 to + 2 days [dd]		-1 to + 2 days [dd]		-1 to + 2 days [dd]	
CD4 (for patients with signs of infection) and blood cultures if febrile neutropenia occurs [gg,ff,hh]											
Glucose [l]				X	(X)[bb]	X		X	(X)[bb]	X	
Blood pressure [n]				X		X		X		X	
Efficacy											
CT / MRI and tumor evaluations [o]	X			Every 12 weeks							
PET-CT	X			If performed at BL, PET-CT should be repeated after the Cycle 6 if a PD is not detected during the course of treatment and/or to confirm complete response (CR) or disease progression							
Bone marrow biopsy	X			Confirmation of first CR (if positive for lymphoma infiltration at BL)							
Phase III: QoL questionnaire (FLymSI-18) [p]				X				X[p]			
Pharmacokinetic sample [q]				X	X	X			C6	C3,C6	
Biomarkers											
Fresh and/or or archival tumor tissue (central pathology and biomarkers) [r]	X										
Plasma for tumor genetics [s]				X							
Plasma for non-genetic biomarker analysis [t]	X			X		X	X	C2 only		C2 only	C2 [z] only
Whole blood for biomarkers [u]				X							
For LPL/WM patients only [v]											
Serum protein electrophoresis [v]		X[v]									(X)[v]
Immunofixation [v]		X[v]									(X)[v]
Serum quantitative IgM test [v]		X[v]									(X)[v]
Serum or plasma viscosity [v]		X[v]						(X)[v]			
Drug administration											
Copanlisib/placebo				X		X		X		X	

Table 9–2 Study flow chart – Screening and copanlisib + R-CHOP combination therapy

(for procedures during the copanlisib/placebo monotherapy and after treatment, see Table 9–3)

	Screening maximum days before C1D1			**Treatment during the combination therapy**							
				Cycle 1				**Cycle 2 to Cycle 6**			
Days	**-28**	**-14**	**-7**	**D1**	**D2**	**D8**	**D15** [ii]	**D1**	**D2**	**D8**	**D15** [ii]
Acceptable deviation for study drug administration (unless otherwise specified) (in days) [hh]				-1 to + 2 days [dd]		-1 to + 2 days [dd]		-1 to + 2 days [dd]		-1 to + 2 days [dd]	
R-CHOP (Cycles 1-6): rituximab, cyclophosphamide, doxorubicin and vincristine on D2, prednisone/prednisolone D2-6.					X				X		

For abbreviations and footnotes, see Table 9–3.

Table 9–3 Study flow chart – copanlisib/placebo monotherapy (from C7 onwards)

	Treatment				**EOT**	**Safety FU**	**Active FU** [x]	**Survival FU** [y]
	Cycle 7 and higher				Within (days)			
Days	**D1**	**D8**	**D15**	**D22** [ii]	**7** after decision to stop [hh]	**30** [w] after last dose [hh]		every 3 months
Acceptable deviation for study drug administration (unless otherwise specified) (in days) [hh]	-1 to + 2 days [dd]					+ 5 days [hh]		± 14 days
IVRS/IWRS transaction [c]	X				X			
Serum pregnancy test (if applicable) [d]	X [d]				X [d]	X [d]		
GFR calculation (MDRD abbreviated formula)[e]	X							
CMV PCR [gg,hh]	X[ee]							
HBsAg, HBcAb, and anti-HCV antibody (HBV DNA, HCV RNA)[aa]	X[aa]						X[aa]	
Safety								
Toxicity / AE assessment [f]	X	X	X		X	X	(X)[f]	
Concomitant medication [f]	X	X	X		X	X		
Complete physical examination	X				X			
Brief physical examination and status check, including lung examination [hh]		X	X			(X)		

Table 9–3 Study flow chart – copanlisib/placebo monotherapy (from C7 onwards)

	Treatment				EOT	Safety FU	Active FU [x]	Survival FU [y]
	Cycle 7 and higher				Within (days)			
Days	**D1**	**D8**	**D15**	**D22** [ii]	**7** after decision to stop [hh]	**30** [w] after last dose [hh]		every 3 months
Acceptable deviation for study drug administration (unless otherwise specified) (in days) [hh]	-1 to + 2 days [dd]					+ 5 days [hh]		± 14 days
12-lead ECG [g]	X [g]				(X)[g]			
MUGA scan or echocardiogram [h]	X [h]				(X)[h]			
Hemoglobin A1c [i]	X [i]				X			
Complete blood count [hh]	X	X	X		X	(X)		
Chemistry panel [k]	X [k]				X[k]	(X)		
Coagulation panel: PTT,PT and INR	X				X	(X)		
Urinalysis (dipstick)	X				X			
CD4 (for patients with signs of infection) and blood cultures if febrile neutropenia occurs [gg,ff, hh]								
Glucose [l]	X	X	X					
Blood pressure [n]	X	X	X					
Efficacy								
CT / MRI and tumor evaluations [o]	Every 12 weeks from Cycle 1 Day 1 during Year 1 and 2 and every 24 weeks during Year 3 and beyond [o]				(X)[o]		X[o]	
PET-CT	If performed at BL, PET-CT should be repeated after the Cycle 6 if a PD is not detected during the course of treatment and/or to confirm complete response (CR) or disease progression				(X)[o]		(X)[o]	
Bone marrow biopsy	Confirmation of first CR (if positive for lymphoma infiltration at BL)							
Phase III: QoL questionnaire (FLymSI-18) [p]	X [p]				X	X	X	
For LPL/WM patients only [v]								
Serum protein electrophoresis [v]				(X)[v]	(X)[v]		X[v]	
Immunofixation[v]				(X)[v]	(X)[v]		X[v]	
Serum quantitative IgM test [v]				(X)[v]	(X)[v]		X[v]	
Serum or plasma viscosity [v]	(X)[v]				(X)[v]			
Biomarkers								

Table 9–3 Study flow chart – copanlisib/placebo monotherapy (from C7 onwards)

	Treatment				EOT	Safety FU	Active FU [x]	Survival FU [y]
	Cycle 7 and higher				Within (days)			
Days	**D1**	**D8**	**D15**	**D22** [ii]	**7** after decision to stop [hh]	**30** [w] after last dose [hh]		every 3 months
Acceptable deviation for study drug administration (unless otherwise specified) (in days) [hh]	-1 to + 2 days [dd]					+ 5 days [hh]		± 14 days
Tumor tissue (central pathology and biomarkers) [r]					(X)[r]			
Plasma for tumor genetics [s, hh]					X			
Plasma for non-genetic biomarker analysis [t,hh]					X			
Drug administration								
Copanlisib/placebo	X	X	X					
Survival status, new anticancer therapy								X

AE = adverse event; BL = baseline; C = cycle; CBC = complete blood count; CD = cluster of differentiation; CMV = cytomegalovirus; CT = computed tomography; CR = complete response; CRP = C-reactive protein; CXR = Chest X-ray; D = day; DNA = deoxyribonucleic acid ; ECG = electrocardiogram; EOT = end of treatment; FL = follicular lymphoma; FLymSI-18 = NCCN-FACT Lymphoma Symptom Index-18; FU = follow-up; GFR = glomerular filtration rate; HBV = hepatitis B virus; HbA1C = glycated hemoglobin; HBcAb = Hepatitis B core antibody; HBsAg = Hepatitis B surface antigen; HCV = hepatitis C virus; IgM = immunoglobulin M; INR = international normalized ratio; IV = intravenous; IVRS = interactive voice response system; IWRS = interactive web response system; LDL = low-density lipoprotein; LPL/WM = Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia; LVEF = left ventricular ejection fraction; MDRD = modification of diet in renal disease; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition; OI = opportunistic infection; PCR = polymerase chain reaction; PD = progressive disease; PET-CT = positron emission tomography-computed tomography; PK = pharmacokinetics; PRO = patient-reported outcomes; PT = prothrombin time; PTT = partial thromboplastin time, QoL = quality of life; QTB = QT interval corrected for heart rate – Bazett; QTcF = QT interval corrected for heart rate – Fridericia; RNA = ribonucleic acid; SAE = serious adverse event; SFU = safety follow-up; SmPC = summary of product characteristics; SOC = standard of care; UPCR = urine protein to creatinine ratio; WM = Waldenström macroglobulinemia.

a Written patient informed consent must be obtained prior to any study-specific procedures. Certain results from diagnostic testing prior to the informed consent date and time may be used to fulfill screening criteria (for further details, see Section 13.4).

b Complete medical and surgical history including demographics (see Section 9.3.1), relevant medical history findings, concomitant illnesses, allergy history, prior surgeries, most recent histology of tumor, most recent staging and grading of tumor, history of anti-cancer treatments (including type of treatment, type of response, date and duration of response), and assessment of baseline toxicity.

c IVRS/IWRS transaction to register the patient in the system will be at Screening. IVRS/IWRS randomization transaction will take place maximum 72 hours before the first dose (Cycle 1 Day 1). IVRS/IWRS transactions for medication dispensing at Cycle 2 and above will be on Day 1 of each cycle or as described in the Pharmacy Manual. Please refer to the Pharmacy Manual and the relevant SmPCs for detailed instructions regarding the timing requirements for the

dose preparation. The transaction to register end of treatment will be at the EOT visit.

d After Cycle 1 serum pregnancy test is mandatory on Day 1 of every cycle, at the EOT visit and SFU visit for countries where it is required by local regulations. See Section 9.6.3.1.

e If not on target, this evaluation may be repeated once after at least 24 hours either according to the MDRD abbreviated formula or by 24 hour sampling (see also Appendix 16.7).

f Contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction). During the Active follow-up period, AEs and SAEs assessed as related to study procedures by the investigator will be reported in the usual manner.

g 12-lead ECG (including QTcB and QTcF evaluation) at Screening (within 28 days of Cycle 1 Day 1), on Cycle 1 Day 1 and on Day 1 of every 3rd cycle starting from Cycle 3 (3, 6, 9, etc.), prior to and at the end of copanlisib/placebo infusion (window of up to 2 hours prior to and post- infusion is allowed). At EOT visit, a 12-lead ECG is necessary only if not recorded within the previous 4 weeks.

h MUGA scan/echocardiogram to measure LVEF at Screening (within 14 days before Cycle 1 Day 1), and within 7 days prior to dosing on Day 1 of every 3rd cycle (3, 6, 9, etc.) and at EOT(if not previously done within 4 weeks). Same modality must be used throughout the study. See Section 9.6.3.7.

i Hemoglobin A1c (HbA1c) at Screening, on Day 1 of every three cycles (4, 7, 10, etc.) starting from Cycle 4 and at the EOT visit (if not performed within 4 weeks preceding the EOT visit). Final HbA1C test should be performed approximately 3 months after the EOT visit date whenever possible.

j *Footnote deleted by amendment 2, please see revised visits for CBC*.

k Complete chemistry panel with triglycerides, LDL cholesterol and total cholesterol will be tested only at Screening, on Day 1 of every second cycle (2, 4, 6 etc.) starting from Cycle 2, and at EOT visit. On these days the patients must be fasting prior to sampling according to local standards. If a patient cannot adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible (see Section 9.6.3.1).

l On Cycle 1 Day 1, glucose will be measured at pre-dose, and post-dose 1 h and 2 h after the end of study drug infusion; and at the end of the rituximab infusion (deviation of ± 10 min is allowed); and at the end of bendamustine infusion (±10min) if patient receives corticosteroid premedication prior to bendamustine infusion, according to guidance provided in Section 9.6.3.2. On subsequent infusions, glucose will be measured prior to copanlisib/placebo infusion and 1 h after the end of copanlisib/placebo infusion; and at the end of the rituximab infusion; and at the end of bendamustine infusion (±10min) if patient receives corticosteroid premedication prior to bendamustine infusion.

m *Home glucose monitoring removed by amendment 6*

n Blood pressure will be measured at pre-dose and at specified time points during and after the study drug infusion according to guidance provided in Section 9.6.3.5. In addition, on Day 1, blood pressure will be measured 30 minutes after the start of rituximab infusion and at the end of rituximab infusion from Cycle 1-6 in the R-B treatment group.

o The first IV (and oral, if indicated, per Imaging Manual) contrast enhanced CT/MRI and/or PET-CT scans of neck, chest, abdomen and pelvis must be performed at Screening (including WM patients). During treatment and Active follow-up period including all patients who discontinued treatment due to any other reason than PD, tumor scans will be done with the same modality every 12 weeks (± 7 days) from Cycle 1 Day 1 during Year 1 and 2, every 24 weeks (± 7 days) during Year 3, 4, and 5, and every 24 weeks (±14 days) beyond Year 5. CT/MRI scans are not required at the EOT visit if the patient has been radiologically evaluated within the 4 weeks preceding EOT. Tumor scans will be done until PD is centrally evaluated and documented and will continue up to 2 years beyond study primary completion or until new anti-tumor treatment is administered. PET functional imaging is optional in this study and should be done based on institutional standards. PET-CT can be utilized throughout the study if it is considered standard of care at the institution and according to Section 9.8. See Section 9.2.1.3.

p Phase III: FLymSI-18 questionnaire is to be completed on Day 1 of every cycle, at the EOT visit and Safety FU visit. During the Active FU, patients will complete the FLymSI-18 questionnaire at the same visits as follow-up tumor assessments will be done. The FLymSI-18 should be completed for up to at least

1 year after study primary completion or until the sponsor advises termination of its collection. Questionnaire should be self-administered by the patient at the start of the visit before contact with the investigator or other investigative site personnel. A PRO information sheet will be completed by the study personnel at each visit at which FLymSI-18 questionnaire is to be administered, regardless of whether or not the FLymSI-18 questionnaire is completed by the patient.

q Plasma for PK will be collected as follows: For copanlisib/placebo: Cycle 1 Day 1 and Day 8 of Cycles 1, 3 and 6. For rituximab in R-B treatment group: Cycle 1 Day 1 and Cycle 6 Day 1, for rituximab in R-CHOP treatment group: Cycle 1 Day 2 and Cycle 6 Day 2. PK sampling time points for copanlisib and rituximab are specified in Section 9.5.

r Fresh tumor tissue and/or archival tumor tissue must be available at Screening for central pathology review for an exploratory analysis. In addition, pre-treatment tumor tissue samples will be collected when available to investigate or identify biomarkers that may be predictive of copanlisib effects/efficacy in NHL and to contribute to better understanding the disease (see Section 9.7.1). In patients with WM, bone marrow biopsy can be used for histological confirmation of the diagnosis and for biomarker analyses. A tumor biopsy is encouraged at the time of progression (optional) to allow investigation of copanlisib resistance.

s Plasma for tumor genetics: On Cycle 1 Day 1, blood for plasma preparation should be drawn prior to administration of any study treatment.

t Plasma for non-genetic biomarker analysis will be prepared from whole blood samples. On treatment days, blood for plasma preparation should be drawn prior to administration of any study treatment.

u Whole blood for biomarkers: On Day 1 of Cycle 1 (prior to administration of any study treatment), whole blood will be taken only from patients who have provided genetic consent.

v Only for patients affected by LPL/WM: Serum protein electrophoresis, immunofixation and serum quantitative IgM test to be performed at Screening. Serum or plasma viscosity to be tested at Screening only if hyperviscosity syndrome is suspected.

Only for patients affected by WM: Serum protein electrophoresis, immunofixation and serum quantitative IgM test to be performed on the days of radiological assessment and at EOT only if the last assessment is older than 4 weeks. Serum or plasma viscosity, if abnormal at baseline, then to be repeated every 3rd cycle, starting from Day 1 of Cycle 3, and at EOT. For patients with WM without measurable disease, these procedures will be performed with the same frequency as radiologic assessments.

w The post-treatment follow-up 30 days (window of +5 days allowed) after the last administration of study drug can be conducted via telephone if the patient is no longer being actively seen at the clinic, or patient has started another therapy (see Section 9.2.1.5.1).

x Patients who complete 12 months' study treatment without PD or discontinue study treatment for reasons other than PD will enter the active follow-up period (except for patients who object to follow-up data collection), which also encompasses the safety follow-up period including SFU visit.

y Patients or their health care providers will be contacted either in person or by telephone (except for patients who object to follow-up data collection). The contacts will be made at least every 3 months (± 14 days), until death or until the end of study, whichever occurs first. Duration of survival follow-up period is up to 10 years after the last patient started study treatment. See Section 9.2.1.5.3.

z *Visit added by amendment 1*

aa Blood test for HBV and HCV at Screening (HBsAg, HBcAb and anti-HCV antibody; if HBsAg or HBcAb positive also HBV DNA; if anti-HCV antibody positive also HCV RNA). Patients with positive tests for HBsAg and/or HBcAb will be eligible if they are negative for HBV-DNA. These patients should receive prophylactic antiviral therapy per rituximab label and should perform HBV DNA test with PCR every cycle (±7 days) through treatment and 12 months thereafter. If viral load becomes positive, patient should be withdrawn from the study. Patients with positive test for anti-HCV antibody will be eligible if they are negative for HCV-RNA. These patients should perform HCV RNA test with PCR every cycle (±7 days) through treatment and 6 months thereafter. If viral load becomes positive, patient should be withdrawn from the study.

bb On Day 2 of Cycles 1-6: **R-B group**: glucose test within 30 minutes prior to bendamustine infusion and at the end of the bendamustine infusion (within 30min) for patient receiving corticosteroid premedication prior to the bendamustine infusion; **R-CHOP group**: glucose test within 30 minutes prior to rituximab infusion and at the end of rituximab infusion (within 30 min) for patients receiving corticosteroid premedication prior to the rituximab infusion.

cc Quantification of proteinuria by either a 24 hour total urine protein quantification or by UPCR on a random urine sample preferably taken in mid-morning. This should be reported as the ratio of concentrations of total urine protein (in mg/dL) to urine creatinine (in mg/dL), both done in the same sample (see Section 9.6.3.1). Dipstick analysis is not acceptable to assess proteinuria.

dd Starting from Cycle 1 Day 8, laboratory tests prior to each infusion may be performed and assessed either the day before or on the planned day of infusion with the exception of blood glucose, which must be performed and assessed on the day of infusion.

ee Blood test for CMV should be performed in all patients prior to IV infusion of copanlisib. Every cycle on Cycle X Day 1 (time window -1 day) during combination therapy and every 3 cycles starting from Cycle 7. If PCR test is positive for CMV, treatment should be delayed until recovery. CMV PCR test is considered positive if, the result can be interpreted as a CMV viremia according to local SOC.Treatment of CMV should be initiated based on local SOC. Re-treatment with copanlisib will be allowed without dose reduction once PCR test for CMV is negative. For further details, see Section 7.4.3.6.1.

ff Blood cultures should be performed as per local SOC if the patient develops febrile neutropenia. CD4 count should be performed for patients with signs of infection.

gg For patients with identified risk factors and those who developed OI, additional assessments can include: (1) CD4 and CD8 count and ratio, CRP, blood cultures (2) any additional laboratory and diagnostic methods according to local SOC reported as unscheduled laboratory and diagnostic methods of assessments (3) radiological imaging (i.e. CXR or CT scans) (Note: Treatment of developed OI should be based on local SOC).

hh Modified by amendment 2

ii The safety evaluations to be performed on Day 22 were removed for patients in the copanlisib/placebo + R-B combination therapy group (from C1 to C6) and for all patients during copanlisib/placebo monotherapy (from C7 onwards). The safety evaluations to be performed on Day 15 were removed for patients in the copanlisib/placebo + R-CHOP combination therapy group (from C1 to C6).

9.2 Visit descriptions

9.2.1 Visit descriptions in safety run-in part and phase III part

These apply to both copanlisib/placebo + R-B and copanlisib/placebo + R-CHOP treatment groups unless otherwise specified.

9.2.1.1 Screening period

Screening examinations will be performed after the patient has given written informed consent. The maximum interval allowed between signature of informed consent and start of treatment is 28 days unless written sponsor authorization has been obtained for laboratory re-testing or diagnostic testing (up to additional 14 days permitted). The minimum length of the screening period is 7 days. Certain results from diagnostic testing performed as part of the standard of practice prior to the informed consent date and time may be used to fulfill screening criteria. This includes fresh tissue as noted in the protocol as well as results from tumor scans (CT/MRI and/or PET-CT), bone marrow sample, MUGA/echocardiogram, HIV and hepatitis testing which may also be used provided that they fall into the protocol-specified time window. Archival tissue obtained from the patient at any time during the course of their iNHL may also be used if performed as part of the standard of practice. However, these historical results can only be used after the patient gives informed consent to use them. Tumor scans must also meet the quality standards of the Imaging Manual.

Within 28 days before the first study drug administration:

- IVRS/IWRS transaction to register the patient in the system (see Section 6.5).
- Blood test for hepatitis B and C (HBsAg, HBcAb, and anti-HCV antibody; if HBsAg or HBcAb positive also HBV DNA; if anti-HCV antibody positive also HCV RNA).
    - Patients with positive tests for HBsAg and/or HBcAb will be eligible if they are negative for HBV-DNA. These patients should receive prophylactic antiviral therapy per rituximab label and should perform HBV DNA test with PCR every cycle (±7 days) through treatment and 12 months thereafter (27). If viral load becomes positive, patient should be withdrawn from the study.
    - Patients with positive test for anti-HCV antibody will be eligible if they are negative for HCV-RNA. These patients should perform HCV RNA test with PCR every cycle (±7 days) through treatment and 6 months thereafter (27). If viral load becomes positive, patient should be withdrawn from the study.
- Blood test for Cytomegalovirus (CMV) infection. Patients who are CMV PCR positive at baseline will not be eligible. CMV PCR test is considered positive if, the result can be interpreted as a CMV viremia according to local SOC.
- Blood test for HIV according to local regulations.
- 12-lead ECG (including QTcB and QTcF evaluation) (see Section 9.6.3.6).
- IV (and oral, if indicated, per Imaging Manual) contrast-enhanced CT/MRI and/or PET-CT of neck, chest, abdomen and pelvis (including WM patients) after a 7 days

washout of corticosteroids therapy (see Section 6.2). If a PET-CT is performed during initial assessment, the CT portion of the PET-CT has to be of diagnostic quality (with IV contrast agent and with an acceptable radiation dose). See Section 9.4.2.

- Bone marrow biopsy: mandatory at Screening and to confirm the first complete response if positive for lymphoma infiltration at baseline (see Section 9.2.1.3).
- Biomarker sampling (see Section 9.7.1):
    - Fresh tumor tissue and/or archival tumor tissue must be available at Screening for central pathology review for an exploratory analysis. In addition, pre-treatment tumor tissue samples will be collected when available to investigate or identify biomarkers that may be predictive of copanlisib effects/efficacy in NHL and to contribute to better understanding the disease. In patients with WM, bone marrow biopsy can be used for histological confirmation of the diagnosis and for biomarker analyses.
    - Collection of plasma (from whole blood sample) for non-genetic biomarker analysis.

Within 14 days before the first study drug administration:

- Check inclusion and exclusion criteria (see Section 6.1 and Section 6.2)
- Complete medical and surgical history including demographics (see Section 9.3.1), relevant medical history findings, concomitant illnesses, allergy history, prior surgeries, most recent histology of tumor, most recent staging and grading of tumor, history of anti-cancer treatments (including type of treatment, type of response, date and duration of response), and assessment of baseline toxicity.
- Toxicity/AE assessment: any new findings or worsening of any ongoing medical history conditions after the patient has signed the informed consent are to be listed as adverse events (see Section 9.6.1).
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an adverse event related to its administration.
- Complete physical examination (see Section 9.6.3.3.1)
- MUGA scan or echocardiogram to measure LVEF. The method chosen at baseline must be the same throughout the whole study period (see Section 9.6.3.7).
- Only in patients affected by Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM):
    - Serum protein electrophoresis
    - Immunofixation
    - Serum quantitative IgM test
    - Serum or plasma viscosity (if hyperviscosity syndrome is suspected)

- Only in patients affected by WM and FL: Beta-2-microglobulin

Within 7 days before the first study drug administration:

- Check inclusion and exclusion criteria (see Section 6.1 and Section 6.2)
- Laboratory (see Section 9.6.3.1):
  - GFR calculation according to MDRD abbreviated formula. If not on target, this evaluation may be repeated once after at least 24 hours either according to the MDRD abbreviated formula or by 24 hour sampling (see also Appendix 16.7).
  - Serum pregnancy test (if applicable).
  - Urine protein to creatinine ratio (UPCR)/24 h total urine protein quantification measurement
  - Blood tests for complete blood count, complete chemistry and coagulation panels (see Section 9.6.3.1). Patients must be **fasting prior to sampling according to local standards**. If a patient cannot adhere to fasting requirements, the evaluation of lipid panels including triglycerides is considered not feasible
  - Blood test for hemoglobin A1c
  - Urinalysis (dipstick). Microscopy as clinically indicated.

9.2.1.2 Treatment period

After all screening assessments have been completed and the patient's eligibility has been confirmed and documented, the patient will be randomized via IVRS/IWRS.

Note: Placebo infusion applies only to phase III part.

The following assessments should be performed at each visit before receiving study drug (copanlisib/placebo)

- Monitoring for OI (see Section 7.4.3.6.1):

  In addition to the weekly clinical review and laboratory tests outlined in the schedule of assessments, the following should be performed in all patients prior to IV infusion of copanlisib/placebo:

  - Evaluation of any new onset or worsening of pulmonary symptoms (i.e. cough, dyspnea or fever) that includes a lung examination at each visit prior to infusion
  - Laboratory tests: CD4 (for patients with signs of infection), blood cultures if febrile neutropenia occurs, PCR for CMV (every cycle on Cycle X Day 1 (time window -1 day) during combination therapy and every 3 cycles starting from Cycle 7).
    - Note: If PCR test is positive for CMV, treatment should be delayed until recovery. CMV PCR test is considered positive if, the result can be interpreted as a CMV viremia according to local SOC. Treatment of

CMV should be initiated based on local SOC. Re-treatment with copanlisib will be allowed without dose reduction once PCR test for CMV is negative.

9.2.1.2.1 Treatment – Cycle 1

Cycle 1, Day 1

Patients can stay overnight at the site, if needed, based on the investigator's decision

- **Phase III part only:** Quality of life (QoL) questionnaire (FLymSI-18): at the start of a visit, before the patient sees the physician (see Section 9.7.2).
- Check inclusion and exclusion criteria. No patient may receive treatment unless adherence to all selection criteria as given in Section 6.1 and Section 6.2 is established.
- IVRS/IWRS randomization transaction. The randomization must be performed up to maximum 72 hours before the first dose of study treatment (see Section 7.3). Please refer to the Pharmacy Manual and the relevant SmPCs for detailed instructions regarding the timing requirements for the dose preparation. IVRS/IWRS transactions for medication dispensing at Cycle 2 and above will be on Day 1 of each cycle or as described in the Pharmacy Manual (see Section 9.2.1.2.2).
- Toxicity/ AE assessment: any new findings or worsening of any ongoing medical history conditions after the patient signed the informed consent are to be listed as adverse events (see Section 9.6.1).
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).
- Complete physical examination (see Section 9.6.3.3.1).
- 12-lead ECG evaluation (including QTcB and QTcF evaluation) prior to infusion and at the end of infusion (window of up to 2 hours prior to and post-infusion is allowed) (see Section 9.6.3.6).
- Laboratory (see Section 9.6.3.1):
    - Complete blood count
- Monitoring for OI (see Section 7.4.3.6.1)
- Glucose measurements:
    - On Cycle 1 Day 1 glucose will be measured at pre-dose and post-dose 1 h and 2 h after the end of study drug infusion; and at the end of the rituximab infusion (window of ± 10 min is allowed except for the pre-dose measurement); and at the end of the bendamustine infusion (± 10 min) if patient receives corticosteroid premedication prior to bendamustine infusion (see Section 9.6.3.2). Note: If patient needs to take a meal, then glucose test should be taken prior to meal intake.

- Additional glucose measurements to be performed at the clinic as clinically indicated.

- Blood pressure measurement: at pre-dose and at specified time points during and after the study drug infusion according to guidance provided in Section 9.6.3.5. In addition, from Cycles 1 to 6 blood pressure will be measured 30 minutes after the start of rituximab infusion and at the end of rituximab infusion (see Section 9.6.3.5).

- **PK sampling (see Section 9.5)**
  - For copanlisib/placebo : Cycle 1 Day 1: pre-infusion (up to 30 min prior to start infusion, 55 min (within 5 min prior to the end of infusion).
  - For rituximab (**only for the R-B treatment group**): Cycle 1 Day 1: pre-infusion and end of rituximab infusion (within 5 minutes prior to the end of infusion).

- **Biomarker sampling: (see Section 9.7.1)**

  Collection of plasma (from whole blood sample) for biomarker analysis prior to administration of any study treatment.
  - Plasma for tumor genetics
  - Plasma for non-genetic biomarker analysis
  - Whole blood for genetic biomarker analysis (only from patients who provide a separate consent for genetic research)

For patients receiving copanlisib/placebo + R-CHOP treatment:

- Copanlisib/placebo infusion.

For patients receiving copanlisib/placebo + R-B treatment:

- Copanlisib/placebo infusion, before rituximab and bendamustine infusion.
- Rituximab and bendamustine infusion (in this order).

Cycle 1, Day 2

For patients receiving copanlisib/placebo + R-CHOP treatment:

- Rituximab, cyclophosphamide, doxorubicin, and vincristine infusion and from Day 2 to Day 6 prednisone/prednisolone PO.
- On Day 2 of Cycles 1-6: For patients receiving corticosteroid premedication prior to the rituximab infusion:
  - Glucose test within 30 minutes prior to rituximab infusion and at the end of rituximab infusion (within 30 min).
- **PK sampling (see Section 9.5)**
  - For rituximab**:** Cycle 1 Day 2: pre-infusion and end of rituximab infusion (within 5 minutes prior to the end of infusion).

For patients receiving copanlisib/placebo + R-B treatment:

- Bendamustine infusion
- On Day 2 of Cycles 1-6: For patients receiving corticosteroid premedication prior to the bendamustine infusion:
    - Glucose test within 30 minutes prior to bendamustine infusion and at the end of bendamustine infusion (within 30 min).

Cycle 1, Day 8

Starting from Cycle 1 Day 8, laboratory tests prior to each infusion may be performed and assessed either on the day before or on the planned day of infusion, with the exception of blood glucose, which must be performed and assessed on the day of infusion. For dosing criteria, see Section 7.4.

- Toxicity/ AE assessment (Section 9.6.1).
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).
- Brief physical examination and status check, including lung examination, see Section 9.6.3.3.2.
- Laboratory (see Section 9.6.3.1):
    - Blood tests for complete blood count and chemistry panel (excluding triglycerides, LDL cholesterol and total cholesterol).
- Monitoring for OI (see Section 7.4.3.6.1)
- Glucose test prior to copanlisib/placebo infusion and 1 h after the end of copanlisib/placebo IV infusion (window of ± 10 min is allowed except for the pre-dose measurement). Note: If patient needs to take a meal, then glucose test should be taken prior to meal intake. Fasting is not required prior to pre-dose glucose measurement (see Section 7.4).
- Blood pressure measurement: at pre-dose and at specified time points during and after the study drug infusion according to guidance provided in Section 9.6.3.5.
- **PK sampling**
    - Cycle 1 Day 8: Pre- infusion (up to 30 min prior to start infusion), 5 to 15 min, 55 min (or within 5 min prior to end of infusion) and 1.5 to 5 h after start of infusion.
- **Biomarker sampling (see Section 9.7.1):**
    - Collection of plasma for non-genetic biomarker analyses prior to copanlisib/placebo infusion
- Copanlisib/placebo infusion.

Cycle 1, Day 15

All patients:

- **Biomarker sampling (see Section 9.7.1):**
  - Collection of plasma for non-genetic biomarker analyses. In copanlisib/placebo + R-B treatment group, sample is collected prior to copanlisib/placebo infusion.

For patients receiving copanlisib/placebo + R-B treatment:

- Toxicity/ AE assessment (Section 9.6.1).
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).
- Brief physical examination and status check, including lung examination, see Section 9.6.3.3.2.
- Laboratory (see Section 9.6.3.1):
  - Blood tests for complete blood count, chemistry (excluding triglycerides, LDL cholesterol and total cholesterol) and coagulation panels.
- Monitoring for OI (see Section 7.4.3.6.1)
- Blood pressure measurement: at pre-dose and at specified time points during and after the study drug infusion according to guidance provided in Section 9.6.3.5.
- Glucose test prior to copanlisib/placebo infusion and 1 h after the end of copanlisib/placebo IV infusion (window of ± 10 min is allowed except for the pre-dose measurement) (see Section 9.6.3.2). Note: If patient needs to take a meal, then glucose test should be taken prior to meal intake. Patients are not required to be fasting prior to pre-dose glucose measurement (see Section 7.4).
- Copanlisib/placebo infusion

9.2.1.2.2 Treatment – From Cycle 2 to Cycle 6

From Cycle 2 to Cycle 6, Day 1

- **Phase III part only:** Quality of life (QoL) questionnaire (FLymSI-18): at the start of a visit, before the patient sees the physician (see Section 9.7.2).
- IVRS/IWRS transaction for medication dispensing at Cycle 2 and above will be on Day 1 of each cycle or as described in the Pharmacy Manual. Please refer to the Pharmacy Manual and the relevant SmPCs for detailed instructions regarding the timing requirements for the dose preparation.
- Toxicity/ AE assessment (see Section 9.6.1).
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).

- Complete physical examination (see Section 9.6.3.3.1).
- Laboratory (see Section 9.6.3.1):
    - Blood tests for complete blood count, chemistry and coagulation panels. Blood tests for triglycerides, LDL cholesterol and total cholesterol will be done on Day 1 at every second cycle (2, 4, etc.), starting from Cycle 2; on these days patients must be **fasting prior to sampling according to local standards**. If a patient cannot adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.
    - Blood test for hemoglobin A1c will be done on Day 1 of every three cycles (4, 7, 10, etc.) starting from Cycle 4.
    - GFR calculation (see also Appendix 16.7).
    - Urinalysis (dipstick). Microscopy as clinically indicated.
    - Serum pregnancy test: after Cycle 1 serum pregnancy test is mandatory at every cycle for countries where it is required by local regulations.
- **For patients with positive tests for HBsAg and/or HBcAb, and negative for HBV-DNA**: these patients should receive prophylactic antiviral therapy per rituximab label and should perform HBV DNA test with PCR every cycle (±7 days) through treatment and 12 months thereafter (27). If viral load becomes positive, patient should be withdrawn from the study.
- **For patients with positive test for anti-HCV antibody and negative for HCV-RNA**: these patients should perform HCV RNA test with PCR every cycle (±7 days) through treatment and 6 months thereafter (27). If viral load becomes positive, patient should be withdrawn from the study.
- Monitoring for OI (see Section 7.4.3.6.1)
- Glucose test prior to copanlisib/placebo infusion and 1 h after the end of copanlisib/placebo IV infusion; and at the end of the rituximab infusion (window of ± 10 min is allowed); and at the end of the bendamustine infusion (± 10 min) if patient receives corticosteroid premedication prior to bendamustine infusion. Fasting is not required prior to pre-dose glucose measurement, see Section 7.4. Note: If patient needs to take a meal, then glucose test should be taken prior to meal intake.
- Blood pressure measurement: at pre-dose and at specified time points during and after the study drug infusion according to guidance provided in Section 9.6.3.5. In addition, from Cycles 1 to 6 blood pressure will be measured 30 minutes after the start of rituximab infusion and at the end of rituximab infusion (see Section 9.6.3.5).
- 12-lead ECG evaluation (including QTcB and QTcF evaluation) at every 3rd cycle from Cycle 3 Day 1 (i.e. Cycles 3, 6, 9, etc.), prior to dosing and at the end of copanlisib/placebo infusion (window of up to 2 hours prior to and post-infusion is allowed) (see Section 9.6.3.6).

- MUGA scan or echocardiogram to measure LVEF, within 7 days prior to Day 1 of every 3rd cycle (i.e. Cycles 3, 6, 9, etc.) The method to measure LVEF must be the same as at baseline (see Section 9.6.3.7).
- Only in patients affected by WM:
  - Serum or plasma viscosity: if abnormal at Screening, then every 3rd cycle, starting from Day 1 of Cycle 3.
- **Biomarker sampling (see Section 9.7.1)**
  - Only in Cycle 2: collection of plasma for non-genetic biomarker analyses prior to copanlisib/placebo infusion.

For patients receiving copanlisib/placebo + R-CHOP treatment:

- Copanlisib/placebo infusion.

For patients receiving copanlisib/placebo + R-B treatment:

- Copanlisib/placebo infusion before rituximab and bendamustine infusion.
- Rituximab and bendamustine infusion (in this order)
- **PK sampling (see Section 9.5):**
  - Only in Cycle 6 Day 1: pre-infusion and end of rituximab infusion (within 5 minutes prior to the end of infusion).

From Cycle 2 to Cycle 6, Day 2

For patients receiving copanlisib/placebo + R-CHOP treatment:

- Rituximab, cyclophosphamide, doxorubicin, vincristine infusion on Day 2 and from Day 2 to Day 6 prednisone/prednisolone PO.
- On Day 2 of Cycles 1-6: For patients receiving corticosteroid premedication prior to the rituximab infusion:
  - Glucose test within 30 minutes prior to rituximab infusion and at the end of rituximab infusion (within 30 min).
- **PK sampling:** Only in Cycle 6 Day 2: pre-infusion and end of rituximab infusion (within 5 minutes prior to the end of infusion).

For patients receiving copanlisib/placebo + R-B treatment:

- Bendamustine infusion
- On Day 2 of Cycles 1-6: For patients receiving corticosteroid premedication prior to the bendamustine infusion:
  - Glucose test within 30 minutes prior to bendamustine infusion and at the end of bendamustine infusion (within 30 min).

From Cycle 2 to Cycle 6, Day 8

- Toxicity/ AE assessment (see Section 9.6.1)
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).
- Brief physical examination and status check, including lung examination (see Section 9.6.3.3.2).
- Laboratory (see Section 9.6.3.1):
  - Complete blood count
  - Cycle 2 only: blood tests for complete chemistry panel (excluding triglycerides, LDL cholesterol and total cholesterol)
- Monitoring for OI (see Section 7.4.3.6.1)
- Blood pressure measurement: at pre-dose and at specified time points during and after the study drug infusion according to guidance provided in Section 9.6.3.5.
- Glucose test prior to copanlisib/placebo infusion and 1 h after the end of copanlisib/placebo IV infusion (window of ± 10 min is allowed except for the pre-dose measurement). Note: If patient needs to take a meal, then glucose test should be taken prior to meal intake.
- **Biomarker sampling (see Section 9.7.1):**
  - Only in Cycle 2: collection of plasma for non-genetic biomarker analyses prior to copanlisib/placebo infusion.
- **PK sampling (see Section 9.5):**
  - For copanlisib / placebo: Day 8 of Cycles 3 and 6: Pre-infusion (up to 30 min prior to start infusion) and 55 min (within 5 min prior to the end of infusion.
- Copanlisib/placebo infusion

From Cycle 2 to Cycle 6, Day 15

All patients:

- **Biomarker sampling (see Section 9.7.1)**
  - Cycle 2 only: collection of plasma for non-genetic biomarker analyses prior to copanlisib/placebo infusion

For patients receiving copanlisib/placebo + R-B treatment:

- Toxicity/ AE assessment (see Section 9.6.1).
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).
- Laboratory (see Section 9.6.3.1):
  - Complete blood count
  - Cycle 2 only: blood tests for chemistry panel (excluding triglycerides, LDL cholesterol and total cholesterol).
- Brief physical examination and status check, including lung examination (see Section 9.6.3.3.2).
- Monitoring for OI (see Section 7.4.3.6.1)
- Glucose test prior to copanlisib/placebo infusion and 1 h after the end of copanlisib/placebo IV infusion (see Section 9.6.3.2). (window of ± 10 min is allowed except for the pre-dose measurement). Note: If patient needs to take a meal, then glucose test should be taken prior to meal intake
- Blood pressure measurement: at pre-dose and at specified time points during and after the study drug infusion according to guidance provided in Section 9.6.3.5.
- Copanlisib/placebo IV infusion.

For patients receiving copanlisib/placebo + R-CHOP treatment:

- **Only for patients affected by WM**

  The following procedures will be performed on the days of radiological assessments (or with the same frequency as radiologic assessments for patients with WM without measurable disease) (see Section 9.2.1.3):
  - Serum protein electrophoresis
  - Immunofixation
  - Serum quantitative IgM test

From Cycle 2 to Cycle 6, Day 22:

For patients receiving copanlisib/placebo + R-B treatment:

- **Only for patients affected by WM**

  The following procedures will be performed on the days of radiological assessments (or with the same frequency as radiologic assessments for patients with WM without measurable disease) (see Section 9.2.1.3):
  - Serum protein electrophoresis
  - Immunofixation

- Serum quantitative IgM test

9.2.1.2.3 Treatment – From Cycle 7 onwards (during copanlisib/placebo monotherapy)

From Cycle 7 onwards, Day 1

- **Phase III part only:** Quality of life (QoL) questionnaire (FLymSI-18): at the start of a visit, before the patient sees the physician (see Section 9.7.2).
- IVRS/IWRS transaction for medication dispensing at Cycle 2 and above on Day 1 of each cycle or as described in the Pharmacy Manual. Please refer to the Pharmacy Manual and the relevant SmPCs for detailed instructions regarding the timing requirements for the dose preparation.
- Toxicity/AE assessment (see Section 9.6.1)
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).
- Complete physical examination (see Section 9.6.3.3.1)
- Monitoring for OI (See Section 7.4.3.6.1)
- Glucose test prior to copanlisib/placebo infusion and 1 h after the end of copanlisib/placebo IV infusion (window of ± 10 min is allowed except for the pre-dose measurement). Fasting is not required prior to pre-dose glucose measurement, see Section 7.4. Note: If patient needs to take a meal, then glucose test should be taken prior to meal intake.
- 12-lead ECG evaluation (including QTcB and QTcF evaluation) at every 3rd cycle from Cycle 3 Day 1 (i.e. Cycles 3, 6, 9, etc.), prior to dosing and at the end of copanlisib/placebo infusion (window of up to 2 hours prior to and post-infusion is allowed) (see Section 9.6.3.6).
- MUGA scan or echocardiogram to measure LVEF, within 7 days prior to Day 1 of every 3rd cycle (i.e. Cycles 3, 6, 9, etc.) The method to measure LVEF must be the same as at baseline (see Section 9.6.3.7).
- Laboratory (see Section 9.6.3.1):
  - Blood tests for complete blood count, chemistry and coagulation panels. Blood tests for triglycerides, LDL cholesterol and total cholesterol will be done on Day 1 at every second cycle, starting from Cycle 2; on these days patients must be **fasting prior to sampling according to local standards**. If a patient cannot adhere to fasting requirements, the evaluation of lipid-panels including triglycerides is considered not feasible.
  - Blood test for hemoglobin A1c will be done on Day 1 of every three cycles (4, 7, 10 etc.) starting from Cycle 4.

- Urinalysis (dipstick). Microscopy as clinically indicated.
- Serum pregnancy test: after Cycle 1 serum pregnancy test is mandatory at every cycle for countries where it is required by local regulations.
- GFR calculation (see Section 9.6.3.1 and Appendix 16.7)

- **For patients with positive tests for HBsAg and/or HBcAb, and negative for HBV-DNA**: these patients should receive prophylactic antiviral therapy per rituximab label and should perform HBV DNA test with PCR every cycle (±7 days) through treatment and 12 months thereafter (27). If viral load becomes positive, patient should be withdrawn from the study.
- **For patients with positive test for anti-HCV antibody and negative for HCV-RNA**: these patients should perform HCV RNA test with PCR every cycle (±7 days) through treatment and 6 months thereafter (27). If viral load becomes positive, patient should be withdrawn from the study.
- Blood pressure measurement: at pre-dose and at specified time points during and after the study drug infusion according to guidance provided in Section 9.6.3.5.
- Only in patients affected by WM:
  - Serum or plasma viscosity: if abnormal at Screening, then every 3rd cycle, starting from Day 1 of Cycle 3.
- Copanlisib/placebo IV infusion.

Cycle 7 onwards, Day 8

- Toxicity/ AE assessment (see Section 9.6.1).
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).
- Brief physical examination and status check, including lung examination (see Section 9.6.3.3.2).
- Laboratory (see Section 9.6.3.1):
  - Complete blood count
- Monitoring for OI (see Section 7.4.3.6.1)
- Glucose test prior to copanlisib/placebo infusion and 1 h after the end of copanlisib/placebo IV infusion (window of ± 10 min is allowed except for the pre-dose measurement) (see Section 9.6.3.2). Fasting is not required prior to pre-dose glucose measurement, see Section 7.4. Note: If patient needs to take a meal, then glucose test should be taken prior to meal intake.
- Blood pressure measurement: at pre-dose and at specified time points during and after the study drug infusion according to guidance provided in Section 9.6.3.5.

- Copanlisib/placebo IV infusion.

Cycle 7 onwards, Day 15

- Toxicity/ AE assessment (see Section 9.6.1).
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an AE related to its administration (e.g. allergic reaction).
- Brief physical examination and status check, including lung examination (see Section 9.6.3.3.2).
- Laboratory (see Section 9.6.3.1):
  - Complete blood count
- Monitoring for OI (see Section 7.4.3.6.1)
- Glucose test prior to copanlisib/placebo infusion and 1 h after the end of copanlisib/placebo IV infusion (deviation of ± 10 min is allowed except for the pre-dose measurement) (see Section 9.6.3.2). Fasting is not required prior to pre-dose glucose measurement, see Section 7.4. Note: If patient needs to take a meal, then glucose test should be taken prior to meal intake.
- Blood pressure measurement: at pre-dose and at specified time points during and after the study drug infusion according to guidance provided in Section 9.6.3.5.
- Copanlisib/placebo IV infusion.

Cycle 7 onwards, Day 22

- **Only for patients affected by WM**

  The following procedures will be performed on the days of radiological assessments (or with the same frequency as radiologic assessments for patients with WM without measurable disease) (see Section 9.2.1.3):
  - Serum protein electrophoresis
  - Immunofixation
  - Serum quantitative IgM test

9.2.1.3 Tumor assessments

Radiologic tumor evaluations (IV [and oral, if indicated, per Imaging Manual] contrast enhanced CT/MRI scans of neck, chest, abdomen and pelvis) will be performed during the screening, treatment period as well as during the Active follow-up period at the following intervals (see also Section 9.4):

During screening:

- CT/MRI and/or PET-CT scans taken within 28 days of starting study treatment (see Section 9.2.1.1)

During treatment and Active follow-up:

- CT/MRI scans (starting from Cycle 1 Day 1 each year):
  - Year 1: every 12 weeks (±7 days)
  - Year 2: every 12 weeks (± 7 days)
  - Year 3: every 24 weeks (± 7 days)
  - Year 4: every 24 weeks (±7 days)
  - Year 5: every 24 weeks (±7 days)
  - Beyond Year 5: every 24 weeks (±14 days)

At EOT visit, CT/MRI scans are not required, if the patient has been radiologically evaluated within the 4 weeks preceding EOT.

PET functional imaging is the preferred modality and should be done based on institutional standards. If a PET-CT is performed at the baseline (BL) assessment the recommendation is to have it repeated after the Cycle 6 if a PD is not detected during the course of treatment and/or to confirm complete response (CR) or disease progression. It is also recommended to perform a PET-CT, if at a previous imaging visit the tumor response was derived from PET-CT and CT/MRI alone shows any change in the response assessment on subsequent imaging visits (e.g. PR).

Bone marrow biopsy

Bone marrow biopsy will be mandatory at Screening and will be sent to central pathology review after local bone marrow assessment. If the baseline biopsy is positive for lymphoma infiltration, it will be mandatory to perform a local bone marrow biopsy assessment again to confirm the first complete response (CR), and also at the investigator's discretion if clinical evaluation leads to suspicion of bone marrow infiltration without further radiological findings.

Patients affected by WM

Patients affected by WM in whom a lesion is found at Screening, radiologic assessments will continue as defined above. If no lesion is detected at Screening, no further radiologic assessments are necessary as per protocol (for further details see Section 9.4.3). In addition, the following procedures will be performed on the days of tumor assessments (if patients continue radiologic assessments, otherwise these procedures will be performed with the same frequency as radiologic assessments):

- Serum protein electrophoresis
- Immunofixation
- Serum quantitative IgM test

9.2.1.4 End-of-treatment visit

The procedures to be performed at the EOT visit will take place not later than 7 days after the decision is made to discontinue the study treatment or when the patient completes 12 months of treatment (maximum duration of therapy).

They will comprise the following:

- **Phase III part only:** Quality of life (QoL) questionnaire (FLymSI-18): at the start of a visit, before the patient sees the physician (see Section 9.7.2).
- IVRS/IWRS transaction to register end of treatment.
- Toxicity/AE assessment (see Section 9.6.1).
- Concomitant medication review. Please note: contrast media does not need to be recorded as concomitant medication unless there is an adverse event related to its administration (e.g. allergic reaction).
- Complete physical examination (see Section 9.6.3.3.1).
- Review of the capillary blood glucose measurements/ meal timing/oral glucose lowering medication/insulin doses, if applicable (see Section 7.4.3.1).
- Laboratory (see Section 9.6.3.1):
    - Serum pregnancy test (if applicable) in countries where it is required by local regulations.
    - Blood tests for complete blood count, complete chemistry and coagulation panels. Patients must be **fasting prior to sampling according to local standards**. If a patient cannot adhere to fasting requirements, the evaluation of lipid panels including triglycerides is considered not feasible.
    - Blood test for hemoglobin A1c (not required if previous test was performed within 4 weeks preceding the EOT visit).
    - Urinalysis (dipstick). Microscopy as clinically indicated.
- 12-lead ECG including QTcB and QTcF evaluation (if not previously done within four weeks) (see Section 9.6.3.6).
- MUGA scan or echocardiogram to measure LVEF (if not previously done within four weeks) (see Section 9.6.3.7). The method must be the same as used at baseline and throughout the whole study (see Section 9.6.3.7).
- IV (and oral, if indicated, per Imaging Manual) contrast-enhanced CT/MRI of neck, chest, abdomen and pelvis. CT/MRI scans are not required, if the patient has been radiologically evaluated within the 4 weeks preceding EOT (see Section 9.4.2).
- If PET-CT was performed at baseline, the recommendation is to confirm complete response (CR) or disease progression with PET-CT. It is also recommended to perform a PET-CT, if at a previous imaging visit the tumor response was derived from PET-CT and CT/MRI alone shows any change in the response assessment on subsequent imaging visits (e.g. PR). Please refer to Imaging Manual for details.
- Only in patients affected by WM
    - Serum protein electrophoresis, immunofixation and serum quantitative IgM test (to be performed only if the last assessment is older than 4 weeks).

- Serum or plasma viscosity if abnormal at baseline.

- **Biomarker sampling:**
  - A tumor biopsy is highly encouraged at the time of progression (optional) to allow investigation of copanlisib resistance.
  - Collection of plasma for tumor genetics and non-genetic biomarker analyses (see Section 9.7.1)

9.2.1.5 Follow-up periods

An additional contact with the patient may be required before the next scheduled visit or telephone call if the most recent data on survival is needed at a specific time point during Safety follow-up, Active follow-up or Survival follow-up (e.g. for a DMC meeting or data analysis).

The final HbA1C test should be performed approximately 3 months after the EOT visit date whenever possible.

9.2.1.5.1 Safety follow-up

If a patient discontinues study treatment at any time during the study for any reason (except death or lost to follow-up) a safety follow-up evaluation should be performed 30 days (window of + 5 days is allowed) after the last dose of study medication. Please note that adverse events should be reported up to 30 days after the last dose of study drug.

- **Phase III part only:** Quality of life (QoL) questionnaire (FLymSI-18): at the start of a visit, before the patient sees the physician (see Section 9.7.2).
- Toxicity/AE assessment (see Section 9.6.1).
- Concomitant medication review.
- Serum pregnancy test (if applicable) in countries where it is required by local regulations.

If clinically indicated:

- Brief physical examination and status check (see Section 9.6.3.3.2).
- Complete blood count (see Section 9.6.3.1)
- Complete chemistry and coagulation panels (see Section 9.6.3.1)

If a patient has begun treatment with another anti-cancer agent or is no longer being seen in the clinic, the post-treatment safety assessment can be conducted via telephone. In this case FLymSI-18 questionnaire does not need to be completed at the safety follow-up visit.

9.2.1.5.2 Active follow-up

Patients who complete 12 months' study treatment without PD or discontinue study drug for reasons other than disease progression will enter the Active follow-up period (which also serves as a Safety follow-up), except for patients who object to follow-up data collection.

The patients in the Active follow-up will have follow-up tumor assessments (also by central independent blinded review), including a local bone marrow analysis to confirm the first complete response in patients with previous bone marrow infiltration during Screening, as outlined in this protocol from the day of randomization until radiological disease progression is centrally evaluated and documented or new anti-tumor treatment is administered (see Section 9.4.2). Active follow-up for tumor assessments will continue for up to 2 years beyond study primary completion. For tumor assessments in patients with WM, see Section 9.4.3.

During the Active FU, patients will complete the FLymSI-18 questionnaire at the same visits as follow-up tumor assessments will be done. The FLymSI-18 should be completed for up to at least 1 year after study primary completion or until the sponsor advises termination of patient-reported outcome (PRO) collection.

During the Active follow-up period, AEs and SAEs assessed as related to study procedures by the investigator will be reported. AE pages of the eCRF and the SAE Form should be completed in the usual manner and forwarded to the applicable sponsor's Global Pharmacovigilance (GPV) department.

For patients with positive tests for HBsAg and/or HBcAb, and negative for HBV-DNA: these patients should receive prophylactic antiviral therapy per rituximab label and should perform HBV DNA test with PCR every cycle (±7 days) through treatment and 12 months thereafter (27). If viral load becomes positive, patient should be withdrawn from the study.

For patients with positive test for anti-HCV antibody and negative for HCV-RNA: these patients should perform HCV RNA test with PCR every cycle (±7 days) through treatment and 6 months thereafter (27). If viral load becomes positive, patient should be withdrawn from the study.

The end of the Active follow-up period is defined as (i) when disease progression is documented, or (ii) when a new anti-tumor treatment is administered, or (iii) up to 2 years beyond primary completion, whichever occurs first.

9.2.1.5.3 Survival follow-up

All patients will be followed off study for overall survival at 3-monthly (±14 days) intervals during the survival follow-up period (up to 10 years after the last patient started study treatment), independent of the reason for study termination, except for patients who object to follow-up data collection. Patients or their healthcare providers will be contacted either in person or by telephone.

Information to be recorded at these contacts:

- Survival status, including date of contact
- Documentation of the first new anti-cancer treatment regimen, including tumor response, if given
- Date and cause of death, if applicable

9.3 Population characteristics

9.3.1 Demographic

Baseline patient data pertaining to demographic information should be documented on the eCRFs including the following:

- Year of birth and age
- Sex
- Race (when allowed by local regulation)
- Ethnicity (when allowed by local regulation)

9.3.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Not pertaining to the study indication
- Start before signing of the informed consent
- Considered relevant for the patient's study eligibility

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 9.6.1.1.

9.3.3 Other baseline characteristics

Disease history of the study indication will be recorded:

- Most recent histology of tumor
- Most recent staging and grading of tumor
- History of anti-cancer treatments (including type of treatment, type of response, date and duration of response)
- Assessment of baseline toxicity: any unresolved toxicity CTCAE Grade 1 attributed to any prior therapy/procedure, not due to the underlying disease, excluding alopecia.
- All medications and significant non-drug therapies taken within 30 days before study entry must be recorded on the eCRF, including:
    - Trade name of medication
    - Reason for medication (indication)
    - Dose of medication
    - Start date and end date or if continuing at patient's last visit

9.4 Efficacy

9.4.1 Primary efficacy variable

The primary efficacy variable of this study is progression free survival (PFS), defined as the time (in days) from randomization to PD as assessed by blinded independent central review or death from any cause (if no progression is documented). Radiological progression will be confirmed in real-time by blinded independent central review. Biochemical progression in patients with WM without lesions evaluable by imaging will be assessed locally.

For secondary and other efficacy variables please refer to Sections 10.3.2.3 and 10.3.2.4.

9.4.2 Radiological tumor assessments

Radiologic (IV contrast-enhanced CT/MRI) tumor assessments will include neck, chest, abdomen and pelvis, and will be evaluated locally at the study site and by the blinded independent central review. PET functional imaging is the preferred modality and should be done based on institutional standards. PET-CT can be utilized throughout the study if it is considered standard of care at the institution and according to Section 9.8.

Tumor assessment schedule

The first radiological (IV [and oral, if indicated, per Imaging Manual] contrast-enhanced CT/MRI) tumor assessment will be performed at Screening (including WM patients). Corticosteroids must be stopped or reduced to the allowed dose (≤ 15 mg of prednisone or equivalent) at least 7 days before performing screening PET-CT and/or CT/MRI (if a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose after the patient has signed the IC). Scans done up to 28 days prior to first dose can be used as baseline studies. The method chosen at baseline in terms of CT or MRI must be the same throughout the study. MRI shall be performed instead of CT when local regulations do not permit the use of CT as requested per protocol schedule.

During the treatment phase as well as during the Active follow-up period, radiological tumor assessment will be performed every 12 weeks (± 7 days) from Cycle 1 Day 1 during Year 1 and 2; every 24 weeks (± 7 days) during Year 3, 4 and 5; and every 24 weeks (±14 days) beyond Year 5. CT/MRI scans are not required at the EOT visit if the patient has been radiologically evaluated within the 4 weeks preceding EOT.

If PET-CT is performed at baseline, it should be repeated after the Cycle 6 if a PD is not detected during the course of treatment and/or to confirm complete response (CR) or disease progression. If a PET-CT is performed, the CT portion of the PET-CT has to be of diagnostic quality (with IV contrast agent and with an acceptable radiation dose). CT/MRI and/or PET-CT scans will be collected by the sponsor from all protocol defined assessments. For details please refer to the Imaging Manual.

Response assessment

The response assessment will be done according to the Lugano Classification (14). For patients with WM, additional criteria apply (see Section 9.4.3). Detailed instructions on tumor assessment are provided in Appendix 16.5.

At each tumor assessment during the course of the study (from baseline to EOT and during active follow up if applicable) radiological measurement of spleen vertical length (from cranial to caudal) must be performed and reported.

As long as the patient has not experienced PD, investigator's assessment is sufficient for case management. In the event of radiological progression, radiological real-time confirmation by central independent blinded evaluation is needed before a final decision on treatment discontinuation is made by the investigator. The evaluation of treatment response (best response: objective response rate and complete response rate) will be also done by central blinded review.

The same technique (e.g. slice thickness, field of view) should be used for all scans during the study treatment period. Preferably all scans should be interpreted by the same investigator/radiologist during the study whenever possible. CT/MRI scans must be performed with contrast agents and must meet the standard of care for imaging of lesions in the respective organ system(s). If at baseline IV (or oral) contrast-enhanced CT is medically contraindicated, sites may acquire MRI (contrast-enhanced) of the neck, abdomen and pelvis, and an unenhanced CT of the chest above lung apices to the bottom of the adrenals. Only if a patient develops contra-indication to both CT and MRI contrast medium during the study, the case examinations should be continued without contrast medium.

A prospective planned central image evaluation by independent radiology experts will be performed independent from the conduct of the clinical part of the study in order to facilitate an independent evaluation of efficacy in this study. All scans obtained for Screening, Treatment, End of Treatment (visit) and Active Follow-up including unscheduled scans should be forwarded to the designated Imaging Core Laboratory for independent radiology evaluation.

PET-CT is preferred modality and recommended for FDG-avid lymphoma types only like FL grade 3a and MZL of nodal type. If obtained, images are to be submitted for independent radiology evaluation. CT scans of PET-CT images used for lesion measurements must be of diagnostic CT quality (CT is required for lesion measurements). If a PET scan is obtained at baseline, all sites of disease selected as target lesions should be preferably PET-positive. PET scans must be performed to confirm CR or disease progression if used from baseline. It is also recommended to perform a PET-CT, if at a previous imaging visit the tumor response was derived from PET-CT and CT/MRI alone shows any change in the response assessment on subsequent imaging visits (e.g. PR). An end-of-treatment PET scan will be performed according to an institutional standards and according to details as described in the Imaging Manual.

The independent reviewers will be experienced radiologists, who will not have been involved in the clinical part of the study and are considered independent from the study. They will be blinded to patient data (excluding those who are specified in the Independent Review Charter,

e.g. for bone marrow biopsy). The primary efficacy variable will be analyzed based on the assessment of the central image evaluation.

9.4.3 Tumor assessments in patients with WM

WM patients who do not have radiologically measurable lesion at Screening will not have further radiological assessments as per protocol. Their tumor response will be measured only by laboratory/clinical tests, and response assessment will be done according to the Owen Criteria. If PD was assessed by an investigator based on laboratory parameters alone, no independent confirmation of PD by independent blinded review is necessary. However, because these patients may during progression develop measurable disease without simultaneous increase in IgM, CT/MRI will be performed according to investigator's criteria and according to details as described in the Imaging Manual. The imaging material should be submitted for blinded independent central review and PD confirmation.

WM patients who have radiologically measurable lesion at Screening will continue having radiological assessments and, in addition, will have laboratory tests performed on the same days. CT/MRI scans will be done and collected according to the schedule specified in the protocol (see Section 9.2.1.3). For patients who have PD assessed based on CT/MRI scans must be submitted for review to confirm disease progression by an independent blinded radiology review.

Sites must notify the sponsor about disease progression and follow procedures outlined in the protocol.

Detailed instructions on tumor assessment are provided in Appendix 16.5.

9.5 Pharmacokinetics / pharmacodynamics

9.5.1 Sampling

Copanlisib/placebo is given in combination with R-B or R-CHOP from Cycle 1 to Cycle 6 and as monotherapy from Cycle 7 onwards. A separate IV line should be used for PK draws. This line must not be used for IV infusion of the drug.

PK sampling will be performed as shown in Table 9–4 (see also Sections 9.1 and 9.2).

Table 9–4 PK assessments in the safety run-in part and phase III part

Treatment: copanlisib/placebo[a] + R-B or copanlisib/placebo + R-CHOP	
PK sampling for copanlisib/placebo	**PK sampling for rituximab**
• Cycle 1 Day 1: pre-infusion (up to 30 min prior to start infusion, 55 min (or within 5 min prior to end of infusion) • Cycle 1 Day 8: pre-infusion (up to 30 min prior to start infusion), 5 to 15 min, 55 min (or within 5 min prior to end of infusion) and 1.5 to 5 h after start of infusion • Day 8 of Cycle 3 and 6: Pre-infusion (up to 30 min prior to start infusion) and 55 min (within 5 min prior to the end of infusion	**R-B** • Cycle 1 Day 1: pre-infusion and end of rituximab infusion (within 5 minutes prior to the end of infusion) • Cycle 6 Day 1: pre-infusion and end of rituximab infusion (within 5 minutes prior to the end of infusion) **R-CHOP** • Cycle 1 Day 2: pre-infusion and end of rituximab infusion (within 5 minutes prior to the end of infusion) • Cycle 6 Day 2: pre-infusion and end of rituximab infusion (within 5 minutes prior to the end of infusion)

PK = pharmacokinetic(s); R-B = rituximab and bendamustine;
R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone
a: applicable to the phase III part only

Details about the collection, processing, storage and shipment of samples will be provided separately (laboratory manual).

9.5.2 Analysis

PK samples will be analyzed for copanlisib, M-1, and other metabolites, as needed, and for rituximab.

Concentration data of copanlisib, its metabolite M-1, and other metabolites, as needed, from this study will be analyzed to estimate the individual maximum drug concentration (C_{max}) and area under the curve (AUC), and to measure the variability of the PK of copanlisib, its metabolite M-1 and other metabolites, as needed, in the safety run-in part and phase III population. A population pharmacokinetic approach will be used for the analysis.

The pharmacokinetic serum exposure (C_{trough} at pre-infusion and C_{max} at the end of infusion) of rituximab will be estimated and compared with historical data from monotherapy.

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient after providing written informed consent for participation in the

study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the patient should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

New lesions or disease progression per se (by itself) should not be regarded as AEs. Instead, the associated signs and symptoms should be recorded as AEs.

In the following differentiation between medical history and AEs, the term "condition" may include abnormal e.g. physical examination findings, symptoms, diseases, laboratory, ECG.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as **medical history** (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as **medical history** (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as **adverse events**. This includes intercurrent illnesses.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

   - The admission results in a hospital stay of less than 12 hours
   - The admission is pre-planned
     (e.g. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)
   - The admission is not associated with an AE
     (e.g. social hospitalization for purposes of respite care).

   However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

   Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect

f. Is another serious or important medical event as judged by the investigator

9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The intensity/severity of an AE will be graded using the NCI-CTCAE, version 4.03. For events not listed in the NCI-CTCAE version 4.03, the following scale will be used:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening
- Grade 5: Fatal

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the CRF.

Causality should be assessed separately for each study treatment as detailed in the CRF. If the investigator feels that the event cannot be firmly attributed to one of the study treatments (e.g. owing to a suspected underlying interaction), the same assessment will be documented for each study treatment.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

Possible answers are "yes" or "no"

An assessment of "no" would include:

1. The existence of a highly likely alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Patient's response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication or treatment:
  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual patient's pharmacodynamics should be considered.
- The assessment is not possible

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no"

9.6.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

The study treatment action should be recorded separately for each study treatment as detailed in the CRF.

- Drug withdrawn
- Drug interrupted
- Dose reduced
- Dose not changed
- Not applicable
- Unknown

9.6.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

9.6.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

9.6.1.3 Assessments and documentation of adverse events

AEs observed, mentioned upon open questioning by a member of the investigator team or spontaneously reported by the patient will be documented in the patient's records and the appropriate eCRF. AEs will be documented in an event-based manner, using NCI-CTCAE v.4.03 guidelines.

The investigator has to record on the respective CRF pages all adverse events occurring in the period that starts with the signing of the informed consent and will end 30 days after the last dose of study drug. The safety follow-up will occur 30 days (window of +5 days is allowed) after the last dose of study drug. During the active follow-up period, AEs and SAEs assessed as related to study procedures by the investigator will be reported. AE pages of the eCRF and

the SAE form should be completed in the usual manner and forwarded to the applicable sponsor's GPV department.

After the end of the follow-up phase there is no requirement to actively collect AEs including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

"Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

For all serious adverse events (SAEs) the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

A laboratory test abnormality considered clinically significant, e.g., causing the patient to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged significant by the investigator, should be reported as an AE. Each event should be described in detail along with start and stop dates, intensity, relationship to investigational product, action taken and outcome.

9.6.1.4 Reporting of serious adverse events

The definition of SAEs is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs occurring during the observation period defined in Section 9.6.1.3 to the recipient detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page in the CRF as well as the complementary pages provided in the Investigator File must be completed for each SAE.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

If disease progression leads to signs and symptoms that meet the criteria for seriousness (see Section 9.6.1.1), the associated signs and symptoms, not the underlying cause, should be reported as SAE, (i.e. progressive disease should not be recorded as SAE). In this case, disease progression should be mentioned on the SAE form as an "alternative explanation".

If a new primary malignancy is noted at any time it must be reported as an SAE, whether or not it is assessed as related to study therapy.

In the event of a fatal or life-threatening reaction, the investigator must seek relevant follow-up information and must complete a follow-up reported to the sponsor as soon as possible but not later than 8 calendar days after the initial report is sent.

For all SAEs, the investigator is required to document in full the course of the SAE and any therapy given, including any relevant findings/records in the report.

For documentation of laboratory findings as SAE, please refer to Section 9.6.3.1.

Notification of the Independent Ethics Committees / Institutional Review Boards (IECs/IRBs)

Notification of the IECs / IRBs about all relevant events (e.g. SAEs, SUSARs) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

9.6.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the investigator's brochure (IB) for copanlisib / summary of product characteristics (SmPC)/ prescribing information for rituximab, bendamustine, cyclophosphamide, doxorubicin, vincristine and prednisone.

Overview listings of frequent events that have occurred so far in the clinical development of copanlisib are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

9.6.1.6 Adverse events of special safety interest

Copanlisib is an investigational drug and current knowledge of the AEs associated with this compound is limited. As with any new chemical entity, there is always potential for AEs that may be class related. Non-infectious pneumonitis (NIP) has been observed with copanlisib, as with other PI3K drugs, and since the sponsor wishes to be aware of any such reports rapidly, NIP has been designated as an AE of special interest (AESI).

Regardless of whether an AE consistent with NIP is assessed as causally related/not related to study drug, or as serious/non-serious, the investigator should notify the sponsor within 24 hours as outlined in Section 9.6.1.4. The AESI should be entered in the SAE form, and if the event is assessed as non-serious, the non-serious assessment should be noted in the form. The AESI will be also entered in the eCRF.

9.6.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a female study patient during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

For a pregnancy in the partner of a male study patient, all efforts will be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE.

9.6.3 Further safety

9.6.3.1 Laboratory

All laboratory analyses will be performed locally. Dipsticks should be available for urinalysis.

- Complete blood count: hemoglobin, hematocrit, red blood cell (RBC), and white blood cell (WBC) (with differential to include absolute neutrophil, lymphocyte, monocyte, basophils and eosinophil counts), and platelet count.
- Complete chemistry panel: calcium, sodium, potassium, chloride, phosphorus, magnesium, bicarbonate (or carbon dioxide if bicarbonate is not routinely measured at the site), total protein, albumin, glucose, blood urea nitrogen (BUN) (or urea if BUN is not routinely measured at the site), creatinine, uric acid, total bilirubin (conjugated and unconjugated bilirubin must be calculated if bilirubin > 1.5 × ULN), creatine kinase, ALT, AST, lactate dehydrogenase (LDH), alkaline phosphatase, lipase, amylase (or pancreatic amylase if amylase is not routinely measured at the site), cholesterol (total and LDL) and triglycerides. For evaluation of lipid-panels including triglycerides the patient **must be fasted prior to sampling according to local standards**. For patients who cannot adhere to these fasting requirements the evaluation of lipid-panels including triglycerides is considered not feasible.
- Coagulation panel: PT, INR, and PTT.
- Urinalysis: blood cells (RBC and leukocytes), glucose, ketones, bilirubin (not mandatory at urinalysis), protein, and pH (dipstick). Additional microscopic examinations will be performed if clinically indicated.
- Serum pregnancy test in women of childbearing potential (WOCBP). Postmenopausal women who have not had periods for more than 1 year or surgically sterilized women will not be required to undergo a pregnancy test (this information should be recorded under medical history on the eCRF). See also Section 6.1.
- Quantification of proteinuria by either a 24 hour total urine protein quantification or by UPCR on a random urine sample preferably taken in mid-morning. This should be reported as the ratio of concentrations of total urine protein to urine creatinine, both done in the same sample. Dipstick analysis is not acceptable to assess proteinuria.
- Measurement of GFR according to the MDRD abbreviated formula (see Appendix 16.7).
- In addition to the weekly clinical review and laboratory tests outlined in the schedule of assessments, the following should be performed in all patients prior to IV infusion of copanlisib/placebo (see Section 7.4.3.6.1):
    - CD4 (for patients with signs of infection), blood cultures if febrile neutropenia occurs, PCR for CMV (every cycle on Cycle X Day 1 (time window -1 day) during combination therapy and every 3 cycles starting from Cycle 7).

- Note: If PCR test is positive for CMV, treatment should be delayed until recovery. CMV PCR test is considered positive if, the result can be interpreted as a CMV viremia according to local SOC. Treatment CMV should be initiated based on local SOC. Re-treatment with copanlisib will be allowed without dose reduction once PCR test for CMV is negative.

For patients with identified risk factors and those who developed OI, additional laboratory assessments can include (see Section 7.4.3.6.1):

- CD4 and CD8 count and ratio, CRP, blood cultures
- Any additional laboratory assessments according to local SOC reported as unscheduled laboratory assessments.

An isolated laboratory abnormality that meets the criteria for a CTCAE Grade 4 classification is not reportable as an SAE, unless the investigator assesses that the event meets standard ICH criteria for an SAE (SAE definition in Section 9.6.1.1). All laboratory abnormalities, including CTCAE Grade 4 abnormalities, will be documented in the laboratory eCRF and will be reviewed on a regular basis.

Baseline laboratory abnormalities that are part of the disease profile should not be reported as an AE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria. If an investigator is in doubt about the applicable reporting obligations, he / she should consult with the study monitor of the sponsor.

9.6.3.2 Glucose measurement on treatment days

For requirements for copanlisib/placebo pre-dose glucose levels, see Section 7.4.

On Cycle 1 Day 1 glucose will be measured at pre-dose, and post-dose 1 h and 2 h after the end of copanlisib/placebo infusion; and at the end of the rituximab infusion (window of ± 10 min is allowed except for the pre-dose measurement); and at the end of the bendamustine infusion (±10 min) if patient receives corticosteroid premedication prior to bendamustine infusion. Additional measurements to be performed at the clinic as clinically indicated.

On subsequent infusions, glucose will be measured prior to copanlisib/placebo infusion and 1 h after the end of copanlisib/placebo; and at the end of the rituximab infusion (window of ± 10 min is allowed except for the pre-dose measurement); and at the end of the bendamustine infusion (±10 min) if patient receives corticosteroid premedicaion prior to bendamustine infusion.

- On Day 2 of Cycles 1-6: For patients receiving corticosteroid premedication prior to the bendamustine infusion:
  - Glucose test within 30 minutes prior to bendamustine infusion and at the end of bendamustine infusion (within 30 min).
- On Day 2 of Cycles 1-6: For patients receiving corticosteroid premedication prior to the rituximab infusion:

- Glucose test within 30 minutes prior to rituximab infusion and at the end of rituximab infusion (within 30 min).

9.6.3.3 Physical examinations

Physical examinations will be performed according to the schedule summarized in the flow chart of Section 9.1.

Abnormal physical examination findings are recorded either as medical history or as adverse events (see Section 9.6.1.1).

9.6.3.3.1 Complete physical examinations

Complete physical examination includes:

- Height (only at Screening)
- Weight
- ECOG performance status assessment,
- NYHA classification (see Appendix 16.4)
- Vital signs (see Section 9.6.3.4)
- Complete review of body systems.

All clinical signs and regions that can be brought in context with the underlying disease, with the anti-cancer treatment to be administered or with relevant accompanying diseases (if present) should be clinically assessed.

At minimum the following aspects/regions need to be assessed as well:

- General appearance
- Skin, hand and feet including clinical assessment of hydration status via hand extensor surface skin turgor
- Eyes
- Ears, nose, throat (including inspection of oral mucosa for hydration status)
- Head and neck
- Lungs
- Heart
- Abdomen
- Lymph nodes
- Musculoskeletal system and spine
- Lower legs
- Neurologic findings

9.6.3.3.2 Brief physical examination and status check

Brief physical examination and status check includes ECOG performance status, vital signs (see Section 9.6.3.4), examination of pertinent organ systems, and brief interim history (change of symptoms).

The examination of pertinent organ systems should investigate at minimum:

- Skin, hand and feet including clinical assessment of hydration status via hand extensor surface skin turgor
- Throat (including inspection of oral mucosa for hydration status)
- Lungs: evaluation of new onset or worsening of pulmonary symptoms, and lung examination.
- Heart examination and NYHA classification (see Appendix 16.4)
- Abdomen
- Neurologic findings

Other clinical signs and regions might be investigated as well, if clinically indicated.

9.6.3.4 Vital signs

Pulse, blood pressure and temperature will be assessed as part of physical examinations according to the schedule summarized in the flow chart of Section 9.1. If clinically indicated, it is at the investigator's discretion to perform these measurements more frequently.

9.6.3.5 Blood pressure measurement on treatment days

- Blood pressure will be measured prior to each copanlisib/placebo dose (no more than 4 measurements) until there are two consecutive results < 150/90 mmHg with at least 15 min interval between the measurements, to be able to start copanlisib/placebo infusion (pre-dose). The investigator can consider a medical intervention to maintain blood pressure values appropriate for infusion. The investigator must delay the infusion until blood pressure values are <150/90 mmHg. The patient should rest for 5-10 minutes before blood pressure is recorded.
- On infusion days: blood pressure will be measured at pre-dose, 30 min (after the start of infusion), right after the end of infusion, and 1 h and 2 hours after the end of infusion

  Note: a time window of ±10 min is allowed for all post-dose BP measurements
- In addition, on Day 1, blood pressure will be measured 30 minutes after the start of rituximab infusion and at the end of rituximab infusion (window of ±10 min is allowed) from Cycle 1 to Cycle 6 in the R-B treatment groups.
- For details on the management of arterial hypertension, see also Sections 7.4.2 (dose modification) and 7.4.3.3 (treatment of blood pressure increases associated with copanlisib).

9.6.3.6 12-lead ECG

12-lead ECGs (including QTcB and QTcF evaluation) will be performed according to the schedule summarized in the flow chart in Section 9.1. The study number, patient number, visit and the date of the ECG will be noted on every ECG.

The patient should rest for 5-10 minutes before the ECG is recorded.

The overall interpretation of the ECG (normal/abnormal, clinical relevance) and the ECG findings will be recorded in the source documentation and in the eCRF.

9.6.3.7 Cardiac function

Cardiac function test: echocardiogram or MUGA scan. The method chosen at baseline (i.e. either echocardiogram or MUGA scan) must be used throughout the whole study period. Additional cardiac function tests are required if any signs or symptoms of cardiac dysfunction occur.

Echocardiogram/MUGA scan should be performed for determination of LVEF.

The study number, patient number, visit and the date of the echocardiogram/MUGA scan are noted on every echocardiogram/MUGA scan.

The overall interpretation of the echocardiogram/MUGA scan and findings will be recorded in the source documentation and in the eCRF.

9.6.3.8 ECOG performance status

Grading definitions are given in Appendix 16.3.

9.6.3.9 Reporting of medical device failures

To countries where applicable: the investigator must report immediately all non-approved medical device failures which could cause health damage, as well as any health damage that may be causally associated with a non-approved medical device failure. For this reporting, the forms provided are to be used and sent to the designated recipient.

9.7 Other procedures and variables

9.7.1 Biomarker investigations

Overview

There following biomarker investigations are included in this study:

1. Tumor-genetic research of fresh (highly preferred) or archival tumor tissue, and possibly of circulating tumor DNA isolated from plasma
2. Non-genetic biomarker testing (may be performed using tumor tissue and/or plasma)
3. Genetic biomarker research

Genetic biomarker research of the whole blood requires a separate 'genetic' research consent (optional testing for research). All other analyses are covered by the main ICF.

Biomarker investigations

The planned biomarker analyses utilize tumor tissue, plasma and blood, and involve the analysis of protein and nucleic acids (i.e., RNA and/or DNA). Details on the collection, processing, storage and shipment of biomarker samples will be provided in separate documents (e.g. sample handling sheets or laboratory manual).

The biomarker results may be reported separately.

Collection and use of biomarker specimens

Tumor Tissue:

Fresh tumor tissue and/or archival tumor tissue must be available at Screening for central pathology review for an exploratory analysis (see Section 6.1). Patients without historical material or fresh tissue biopsy will not be eligible for randomization. In patients with WM, bone marrow biopsy can be used for histological confirmation of the diagnosis and for biomarker analyses.

In addition, one or more of the following pre-treatment tumor tissue samples will be collected during Screening when available with the purpose of investigating or identifying biomarkers that may be predictive of copanlisib effects/efficacy in NHL and to contribute to better understanding the disease.

- Submission of archival tumor tissue from a biopsy performed within 180 days before signing of the informed consent.
- Submission of fresh tissue from a biopsy performed during Screening (between Day -28 and Day -8 prior to the start of study treatment) is highly encouraged when the above is not available.
- In the absence of either of the above, submission of an older archival tumor tissue sample (collected prior to 180 days before signing of the informed consent) is mandatory when available.

A tumor biopsy is also encouraged at the time of progression (optional) to allow investigation of copanlisib resistance.

Archival formalin-fixed paraffin-embedded (FFPE) tissue may be supplied as a block (preferred) or as precut slides. Details on the preparation of slides and number of slides to be prepared as well as detailed guidance on fresh biopsy sample preparation and storage will be described in separate documents (e.g. Sample Handling Sheets or laboratory manual).

All tumor tissues may be used as a source of RNA or protein for the study of gene and protein expression. The tumor tissue may also be used as a source of tumor DNA for the evaluation of tumor-associated alterations in genes of interest (e.g., PIK3CA and genes associated with NHL).

Plasma for tumor genetic biomarker analysis: Blood samples will be obtained and used for plasma preparation at the time points as indicated in the study flow chart (see Section 9.1). Plasma may be used as a source of circulating tumor DNA for the evaluation of mutations in tumor-related genes of interest.

Plasma for non-genetic biomarker analysis: Blood samples will be obtained and used for plasma preparation at the time points as indicated in the study flow chart (see Section 9.1). Plasma may be used to quantify the circulating levels of various proteins.

Whole blood (only applicable for patients who provided 'genetic' research consent): On Cycle 1 Day 1, a whole blood sample will be obtained. The blood sample will be used as a source of DNA and gene products for the evaluation factors that are associated with the drug or the pathomechanisms of the disease. Results will be reported under separate cover.

In addition to the assays listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about the drug (i.e. mode of action or safety of the drug) may be measured, based on newly emerging data from other ongoing trials of these investigational drugs and/or literature data. However, the study sponsors reserve the right not to conduct all or part of the aforementioned biomarker analysis. Data from this biomarker analysis may be correlated with various other data obtained in this study (e.g., clinical efficacy, pharmacokinetics, toxicity).

If a scheduled biomarker sample collection is missed, this should not be regarded as a protocol deviation.

9.7.2 Quality of life questionnaire – Phase III part only

The effect of treatment on the physical symptoms of lymphoma is an important issue for patients; therefore the collection of this information is a routine component in many protocols.

The main purpose of the symptom assessment in this study is to describe any differences between the treatment groups in the time to deterioration and time to improvement in disease-related physical symptoms (DRS-P) of at least 3 points as measured by the DRS-P subscale of the FLymSI-18 questionnaire.

In the phase III part of this study, physical symptoms of lymphoma will be assessed using the NCCN-FACT Lymphoma Symptom Index-18 (FLymSI-18), version 2 (NCCN-FACT: National Comprehensive Cancer Network - Functional Assessment of Cancer Therapy).

The FLymSI-18 is an instrument that was developed to assess symptoms of lymphoma, symptoms of treatment of lymphoma, and health related QoL of patients with lymphoma. The

instrument was developed in accordance with recent Food and Drug administration (FDA) guidance for the development of instruments for PROs.

The instrument contains 18 items, each of which utilizes a Likert scale with 5 possible responses ranging from 0 “Not at all” to 4 “Very much”. Nine items reflect DRS-P, and the responses to the items are summed to calculate a DRS-P subscale score. Four items represent disease-related emotional symptoms (DRS-E), and the responses to those items may be used to calculate a DRS-E subscale score. Three items represent treatment side effects, and the responses to these items may be summed to calculate a treatment side-effect (TSE) subscale score. Finally, two items represent functional well-being (FWB), and responses to those items may be summed to calculate a FWB subscale score. The questionnaire allows for calculation of total score and four subscales: DRS-P, DRS-E, TSE and FWB (15, 17).

The FLymSI-18 will be administered in the phase III part according to the schedule specified in the study flow chart (see Section 9.1).

The FLymSI-18 should be completed at the start of the visit before the patient sees the physician and before any study-related procedure is conducted, so that any interaction between the patient and physicians or other health care providers does not influence the response to the FLymSI-18 questionnaire.

A PRO information sheet will be provided and completed by the study personnel at each visit at which the FLymSI-18 questionnaire is to be administered, regardless of whether or not the FLymSI-18 questionnaire is completed by the patient. This is to document information such as questionnaire completion, date of completion, and reasons for non-completed questionnaires.

9.8 Appropriateness of procedures / measurements

The efficacy assessments used in this study include those considered standard for the evaluation of objective tumor response in patients with iNHL. The recently published Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (14) support the use of PET-CT for staging and response assessment of routinely FDG-avid histologies, especially in clinical trials. PET-CT is preferred modality and will be allowed for indolent FDG-avid histologies and should be considered for follicular lymphoma grade 3 and marginal zone lymphoma (nodal type). For lymphomas with low FDG avidity, it may be used if there is a suspicion of transformed disease. In all the other cases response assessment according to the Lugano classification will be performed by CT scan. MRI can be used optionally including in the case of contraindication to CT-contrast agents.

See Section 9.7.2 for the use of FLymSI-18 questionnaire in this study.

10. Statistical methods and determination of sample size

10.1 General considerations

Statistical analyses will be conducted by or under the supervision of the sponsor's study statistician, except for the analysis of biomarker data, which will be performed by or under the direction of the sponsor's genomics and biomarker statistical expert.

Statistical analyses will be performed using Statistical Analysis System (SAS); the version used will be specified in the statistical analysis plan (SAP). As a general principle, the safety run-in part and phase III part will be analyzed separately.

Further details on the statistical analyses including handling of missing data will be provided in the SAP.

10.2 Analysis sets

Safety run-in part:

Full analysis set (FAS): All patients in the safety run-in part who receive at least one dose of study drug.

Safety analysis set (SAF): All patients in the safety run-in part who receive at least one dose of study drug.

Pharmacokinetic analysis set (PKAS): All patients in the safety run-in part with a valid PK profile will be included in the analysis of PK data.

Phase III part:

The following statistical analysis sets are defined:

Full analysis set (FAS): All randomized patients in the phase III part. The FAS is the primary population for all efficacy analyses. Patients will be analyzed as randomized.

Safety analysis set (SAF): All randomized patients in the phase III part who received at least one dose of study drug (copanlisib/placebo, R-B or R-CHOP). SAF will be used for the analyses of the safety variables. Patients will be analyzed as treated.

Pharmacokinetic analysis set (PKAS): All patients in the phase III part with a valid PK profile will be included in the analysis of PK data.

10.3 Variables and planned statistical analyses

10.3.1 Safety run-in part

The recommended dose of copanlisib in combination with standard immunochemotherapy will be determined based on a 3+3 design. The primary safety variable is the occurrence of DLTs during Cycle 1. Safety variables will include also treatment-emergent AEs, SAEs, laboratory parameters, and vital signs. The safety data will be listed by dose level. The best overall response will be summarized. For further details on PK and biomarker variables and analysis, see Section 10.3.2.12.

10.3.2 Phase III part

10.3.2.1 Population characteristics

Demographics and baseline characteristics will be summarized by descriptive statistics by treatment group (copanlisib in combination with R-B or R-CHOP versus placebo in combination with R-B or R-CHOP) for the FAS.

10.3.2.2 Primary efficacy variable

The primary efficacy variable is PFS, defined as the time (in days) from randomization to PD or death from any cause (if no progression is documented). The primary data for PFS analysis will be based on blinded independent central review. Radiological progression will be confirmed in real-time by blinded independent central review. Biochemical progression in patients with WM without lesions evaluable by imaging will be assessed locally, and the confirmation of PD by central review is not needed.

10.3.2.3 Secondary efficacy variables

Secondary efficacy variables are objective response rate (ORR), duration of response (DOR), complete response rate (CRR), time to progression (TTP), time to next anti-lymphoma treatment (TTNT), disease control rate (DCR), overall survival (OS, 5 year survival rate), time to improvement and time to deterioration in disease-related symptoms - physical (DRS-P) of at least 3 points of lymphoma as measured by the FLymSI-18 questionnaire (FLymSI = NCCN-FACT Lymphoma Symptom Index). All secondary efficacy variables will be analyzed in the FAS.

Objective response rate (ORR)

ORR is defined as the proportion of patients who have a best overall response

over the whole duration of the study (i.e. up to time of analysis of PFS) of complete

response (CR) or partial response (PR) according to the Lugano Classification and for

patients with WM a best overall response of CR, very good partial response (VGPR), PR, or minor response (MR) according to the Owen Criteria.

Duration of response (DOR)

DOR is defined as the time (in days) from first observed tumor response (CR, VGPR, PR, or MR) until PD or death from any cause, whichever is earlier. Patients without PD or death at the time of analysis will be censored at the date of their last evaluable tumor assessment. DOR will only be analyzed for patients with at least one CR, VGPR, PR, or MR.

Complete response rate (CRR)

CRR is defined as the proportion of patients who have a best overall response of CR during the study (i.e., up to time of analysis of PFS).

Time to progression (TTP)

TTP is defined as the time from randomization to PD or death related to PD, whichever is earlier. Death related to PD is considered to be any death except for:

a) Death due to an AE unrelated to progression
b) Death with a specification of "other" as reason (which excludes PD)

TTP for patients without PD at the time of analysis or death not related to progression will be censored at the date of their last tumor assessment. TTP for patients who have neither tumor assessments post baseline nor death related to PD will be censored at Day 1.

Time to next anti-lymphoma treatment (TTNT)

TTNT is defined as the time from stop of study medication to start of new anti-lymphoma therapy. For patients without new anti-lymphoma treatment at the time of analysis, patients will be censored at last assessment of new anti-lymphoma treatment. For patients stopping the study medication without further assessment of new anti-lymphoma treatment, they will be censored at Day 1. Patients still on study treatment at the time of analysis will not be included in the analysis.

Overall survival (OS)

OS is defined as the time (in days) from randomization until death from any cause. For patients alive at the time of analysis, they will be censored at the last known alive date.

Time to improvement in DRS-P of at least 3 points

Time to improvement in DRS-P of at least 3 points, as measured by the FLymSI-18 questionnaire, is defined as time from randomization to first increase in DRS-P score of at least 3 points from baseline before progression (radiological progression or biochemical progression for WM patients without lesions evaluable by imaging).

If alive patients without progression and without improvement in DRS-P of at least 3 points at the time of analysis, they will be censored at last assessment of DRS-P.

If progression or death occurs before or without improvement in DRS-P of at least 3 points at the time of analysis, i.e., cut-off date, patients will be censored at data cut-off date. For alive patients with no baseline or no post-baseline assessment of DRS-P, and do not have PD, they will be censored at Day 1.

This endpoint will be evaluated for patients with a baseline DRS-P score of 30 points or less (i.e. patients who still have room for improvement in symptoms).

Time to deterioration in DRS-P of at least 3 points

Time to deterioration in DRS-P of at least 3 points is defined as time (in days) from randomization to the occurrence of one of the following, whichever occurs earliest:

- First reduction of DRS-P score from baseline ≥ 3 points
- Radiological progression or biochemical progression for WM patients without lesions evaluable by imaging
- Death from any cause

For patients without event of deterioration in DRS-P of at least 3 points at the time of analysis, i.e., data cut-off, they will be censored at last assessment of DRS-P. For alive

patients with no baseline or no post-baseline assessment of DRS-P, and do not have PD, they will be censored at day 1.

Further sensitivity analyses for the DRS-P analyses may be described in the SAP. Considering at least 3 points decline or increase, respectively, to be an important change with regard to DRS-P is the current assessment. The important change for DRS-P is however under continuing research by the developer of the questionnaire.

Therefore, the value of 3 points might be updated in the SAP, considering forthcoming research findings.

Disease Control Rate (DCR)

DCR is defined as the proportion of patients who have a best response rating of CR, VGPR, PR, MR, or stable disease (SD) (excluding unconfirmed early SD) that is achieved during treatment or within 35 days after termination of study treatment. An unconfirmed early SD is defined as SD on or before Study Day 76, with no additional tumor assessment of SD or better within the following 25 weeks.

10.3.2.4 Other efficacy variables

FLymSI-18 total and subscale scores (DRS-P, DRS-E, TSE, F/WB).

10.3.2.5 Primary efficacy analysis

All randomized patients (FAS) will be included in the primary efficacy analysis.

The analysis will be performed when approximately 280 PFS events (PD by blinded independent central review or death if death is before PD) in the FAS are observed. For patients without documented PD or death at the time of analysis, the PFS time will be censored at the date of the last evaluable tumor assessment or last biochemical assessment for patients with WM without lesions evaluable by imaging. For patients without post-baseline tumor assessments and do not die, PFS time will be censored at day 1. The detailed censoring rules will be documented in statistical analysis plan (SAP).

The date used for the calculation of the PFS is the actual (rather than scheduled) date of assessment (i.e., actual scan date); missing tumor assessments are not considered.

In order to evaluate whether copanlisib in combination with R-B or R-CHOP is superior to placebo in combination with R-B or R-CHOP in prolonging progression free survival, the following null hypothesis will be tested in the FAS:

$H_{0,\,PFS}$: $S_{Copanlisib+R\text{-}B/R\text{-}CHOP}(t) = S_{Placebo+R\text{-}B/R\text{-}CHOP}(t)$ for all time points $t \geq 0$

The alternative hypothesis will be:

$H_{1,PFS}$: $S_{Copanlisib+\ R\text{-}B/R\text{-}CHOP}(t) > S_{Placebo+\ R\text{-}B/R\text{-}CHOP}(t)$ for at least one time point $t \geq 0$, and
$S_{Copanlisib+\ R\text{-}B/R\text{-}CHOP}(t) \geq S_{Placebo+\ R\text{-}B/R\text{-}CHOP}(t)$ for all time points $t \geq 0$,

where $S_{Copanlisib+\ R\text{-}B/R\text{-}CHOP}$ denotes the survival function of the copanlisib + R-B or R-CHOP group and $S_{Placebo+\ R\text{-}B/R\text{-}CHOP}$ denotes the survival function of the placebo + R-B or R-CHOP group in the FAS.

The two treatment groups will be compared using a log-rank test stratified by the same stratification variables as for randomization, with one-sided alpha of 0.025 for the FAS. The test statistic from stratified log rank test is assumed to be asymptotically normal distribution.

Kaplan-Meier estimates and survival curves for PFS will also be presented for each treatment group. A hazard ratio with a 95% confidence interval derived from a stratified Cox proportional hazards model will also be provided.

10.3.2.6 Secondary efficacy analysis

All secondary efficacy endpoints will be analyzed in the FAS at the time as the analysis of the primary efficacy endpoint.

The ORR will be calculated by treatment group, with their 95% confidence interval, as well as the differences of objective response rates between treatment groups and their corresponding 95% confidence intervals in the FAS.

The comparison of ORR, between the two treatment groups, will be made using the "general association Cochran-Mantel-Haenszel statistic" stratified by the same stratification factors used in the PFS analysis.

DCR and CRR will be analyzed in a manner similar to ORR.

The time to deterioration and time to improvement in DRS-P subscale of FLymSI-18, DOR, TTP, and TTNT will be analyzed in a manner similar to PFS.

OS will be analyzed using a stratified log-rank test, in a manner similar to PFS, and the 5-year survival rate will also be provided.

10.3.2.7 Confirmatory statistical test strategy

Details on confirmatory statistical testing strategies will be provided in the SAP.

10.3.2.8 *Section removed by amendment 3.*

10.3.2.9 Other efficacy analysis

An analysis of covariance (ANCOVA) analysis of the physical symptoms of lymphoma (as measured using the FLymSI-18 DRS-P subscale) and other subscales if needed will be performed to assess differences between treatment arms in the FAS based on AUC using the appropriate covariates. Total FLymSI-18 and subscales will be summarized. Further details on PRO data analysis will be provided in the SAP.

10.3.2.10 Subgroup analysis

Descriptive statistics and hazard ratio estimates with 95% confidence interval will be provided for PFS and other secondary endpoints if needed. Subgroups include stratification factors and further important demographics and baseline cancer characteristics, as appropriate.

10.3.2.11 Safety variables and analysis

Safety variables will include treatment-emergent AEs (TEAEs), SAEs, laboratory parameters, ECG and vital signs. The severity of AEs will be graded using the NCI-CTCAE version 4.03

dictionary. A treatment-emergent AE is defined as any event arising or worsening after start of study drug administration until 30 days after the last study drug intake.

Safety variables will be summarized by means of descriptive statistics and/or frequency tables as appropriate. Summaries will be given by treatment group.

All TEAEs, drug related TEAEs, serious TEAEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) classification and worst CTCAE grade. The summaries of vital signs and ECG will also be provided.

10.3.2.12 Further variables and their analysis

Pharmacokinetic (PK)

Individual PK will be estimated by means of individual maximum drug concentration (C_{max}) and the area under the curve (AUC) for copanlisib, its metabolite M-1, and other metabolites, as needed. C_{trough} and C_{max} of rituximab will be estimated. See Section 9.5.

Individual concentration-time data will be provided in a clinical study report appendix.
A population pharmacokinetic approach will be used for the copanlisib PK analysis, and the results will be documented in a separate report.

The data from the safety run-in part and phase III part will be pooled for PK analysis.

Biomarkers

All biomarker analyses that will be performed are considered exploratory; specifics of these analyses will be described in the separate Biomarker Evaluation Plan and may be reported separately.

10.3.3 Missing data / drop-outs

Drop-out patients will not be replaced in phase III part of the study. Every effort will be made to obtain actual tumor assessments date, death date and contact date for alive patients. The further imputation rules for missing data will be documented in SAP. Further information relating to missing data is given in Section 11.4.

10.4 Determination of sample size

Safety run-in part

Maximum 2 × 6 evaluable patients per combination (dependent on visibility of DLT) will be included into two dose levels to identify the RP3D.

Phase III part

EAST 6.4 was used to calculate a sufficient sample size in the FAS, targeting an increase of 50% in median PFS time, under the copanlisib + R-B/R-CHOP combination arms. Assuming a median PFS of 24 months under the control treatment, 1-sided alpha of 0.025, power of 90%, and a randomization ratio of 1:1 between the experimental and control arms, 256 events (progression based on blinded independent central review or death from any cause, whichever occurs first) were required to detect a 50% increase in PFS in the FAS population. The number of required PFS events was increased from 256 to approximately 280 events to adequately power an analysis of the targeted increase in median PFS time in the FL histology population.

The expected study duration to reach approximately 280 PFS events is at least 52 months, and the expected accrual duration was approximately 33 months with a 15 month linear ramp-up (maximum accrual rate being approximately 20 patients per month). The monthly dropout (loss to follow-up and unevaluable for tumor assessment) rate was assumed to be 0.48%. With these assumptions, a total of approximately 520 patients were required to be accrued into the two treatment groups, combined.

10.5 Planned interim analyses

No formal interim analysis is planned for the primary efficacy endpoint (i.e. PFS). OS analysis will also be performed at the time of final analysis of PFS.

A DMC will be instituted for independent review of ongoing data from this trial in accordance with a separate DMC Charter. The DMC will operate independently of the sponsor and investigators.

11. Data handling and quality assurance

11.1 Data recording

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based EDC software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network (VPN).

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE system contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator's site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all patients enrolled in this study.

Source documentation

It is the expectation of the sponsor that key data entered into the CRF has source documentation available at the site.

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

Data recorded from screening failures

Data of 'only screened patients' will be recorded at least as source data, as far as the reason for the premature discontinuation is identifiable. At minimum, the following data should be recorded in the CRF:

- Demographic information (patient number; year of birth / age; sex; if applicable race / ethnicity)
- Date of informed consent
- Reason for premature discontinuation
- Date of last visit.

These data will be transferred to the respective database.

For screening failures with an SAE, the following data should be collected in the CRF in addition to the data specified above:

- All information about the SAE.
- All information related to the SAE such as:
    - Concomitant medication
    - Medical history
    - Other information needed for SAE complementary page

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's

requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of patients are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on CRF as well as for data from other sources (e.g. IVRS, laboratory, ECG, adjudication committees).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

Medical Dictionary for Regulatory Activities (MedDRA) will be used for AEs and medical history, and WHO-Drug Dictionary (WHO-DD) for concomitant medications. The SAS datasets to be used for statistical analysis to be included in the clinical study report will remain unmodified after the data is declared clean and ready for analysis.

After its initial release for biometrical analysis, the clinical database is planned to be re-opened for the inclusion of the following additional data: pharmacokinetic data, biomarker data.

11.4 Missing data

Every effort should be made to document the tumor response even after discontinuation of treatment.

In cases where patients indicate they do not want to "continue", investigators must determine whether this refers to discontinuation of study treatment, unwillingness to attend follow-up visits, unwillingness to either have telephone contact, contact with study personnel, or to allow contact with a third party (e.g., family member, doctor). In all cases, every effort should be made to continue to follow the patients for tumor assessment until patients develop radiological progression by blinded independent central review or biomedical progression in patients with WM without lesions evaluable by imaging. Survival information including

survival status, death date and/or contact date should be determined for all patients during the survival follow up.

11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
    - Safety findings from this study (e.g. SAEs)
    - Results of parallel clinical studies
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing patients, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual patient's withdrawal can be found in Section 6.4.1.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

Study personnel are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center’s investigator site file.

Whenever the term “investigator” is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g. health authority, ethics committee, sponsor) before patient recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor’s study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

External data evaluation bodies

Data Monitoring Committee (DMC)

A DMC will be established that will closely interact with the sponsor’s Global Pharmacovigilance (GPV) department in order to assess all safety-relevant information.

The DMC will review study data and provide an independent recommendation on the advisability of continuing the study as planned. Reviews will take place as outlined in the

DMC charter. The DMC will conduct its reviews based on data summaries and on an individual case basis. The summaries (i.e., tables and listings) will be generated by external Statistical Analysis Center (SAC). Details will be decided based on the sponsor's currently valid operational instruction manual. The format and content of these data summaries will be specified by the sponsor in conjunction with the DMC and may change during the study if indicated. All summaries will be based on data provided by the sponsor from the study database. The sponsor will be blinded to phase III part of the study.

Decisions on trial termination, amendment, or cessation of patient recruitment based on risk/benefit assessment will be made after recommendations from the DMC have been assessed by the sponsor.

Central radiological evaluation

Radiological evaluation of CT/MRI scans and PET-CT scans if performed will be performed centrally.

Central pathology review

The retrospective confirmation of histopathological diagnosis will be performed centrally and analyzed only as an exploratory analysis.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research patients has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g. IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial patients without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Patient information and consent

All relevant information on the study will be summarized in an integrated patient information sheet and informed consent form provided by the sponsor or the study center. There will be two informed consent forms in this study: Patients will be asked to provide a “general” consent for participation to the study and for their specimens to be collected and used in protein analyses and tumor DNA/RNA analyses. In addition, an optional “genetic” consent is for patient specimens to be used in analyses involving nucleic acids. A sample patient information and informed consent form is provided as a document separate to this protocol.

Based on this patient information sheet, the investigator or designee will explain all relevant aspects of the study to each patient / legal representative or proxy consenter (if the patient is under legal protection), prior to his/her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each patient / legal representative or proxy consenter will be informed about the following aspects of premature withdrawal:

- Each patient has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The patient’s consent covers end-of-study examinations as specified in the visit description described in Section 9 to be conducted after withdrawal of consent.
- The patient’s data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Patient-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The patient has the right to object to

the generation and processing of this post-withdrawal data. For this, the patient's oral objection may be documented in the patient's source data.

Each patient / legal representative or proxy consenter will have ample time and opportunity to ask questions.

Only if the patient / legal representative or proxy consenter voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator will personally sign and date the form. The patient / legal representative or proxy consenter will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or patient's clinical record must clearly show that informed consent was obtained prior to these procedures. Certain results from diagnostic testing performed as part of the standard of practice prior to the informed consent date and time may be used to fulfill screening criteria. This includes fresh tissue as noted in the protocol as well as results from tumor scans (CT/MRI and/or PET-CT), bone marrow sample, MUGA/echocardiogram, HIV and hepatitis testing which may also be used provided that they fall into the protocol-specified time window. Archival tissue obtained from the patients at any time during the course of their iNHL may also be used if performed as part of the standard of practice. However, these historical results can only be used after the patient gives informed consent to use them. Tumor scans must also meet the quality standards of the Imaging Manual.

If the patient is not capable of providing a signature, a verbal statement of consent can also be given in the presence of an impartial witness (independent of the sponsor and the investigator). This is to be documented by a signature from the informing physician as well as by a signature from the witness.

For adults under legal protection, consent shall be given by the legal guardian(s). The consent of an adult under legal protection shall also be requested where such a person is able to express his/her own will. His/her refusal or the withdrawal of his/her consent may not be disregarded.

The informed consent form and any other written information provided to patients / legal representatives or proxy consenters will be revised whenever important new information becomes available that may be relevant to the patient's consent, or there is an amendment to the protocol that necessitates a change to the content of the patient information and / or the written informed consent form. The investigator will inform the patient / legal representative or proxy consenter of changes in a timely manner and will ask the patient to confirm his/her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB's approval / favorable opinion in advance of use.

13.5 Publication policy and use of data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Bayer fulfills its commitment to publicly disclose study results through posting the result of the studies on public registries in accordance with applicable law and regulations.

In accordance with the current European Union Clinical Trials Regulation (EU-CTR), result summaries will be submitted within one year from the end of the study in all participating countries. No preliminary data analysis (e.g. on EU data only) will be performed, as this might compromise data integrity and the scientific validity of the study.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

Non-study-related use of data, samples or images

Encoded images may be used to underline the results of the study in scientific publications or for other scientific purposes like training of doctors on the appearance or characteristics of disease on images. See also Section 9.7.1.

13.6 Compensation for health damage of patients / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Patient names will not be supplied to the sponsor. Only the patient number will be recorded in the CRF, and if the patient name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the patients will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient's identity will remain confidential.

The investigator will maintain a list to enable patients to be identified.

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15. Protocol amendments

15.1 Amendment 1

Amendment 1 is a global amendment dated 01 SEP 2015.

15.1.1 Overview of changes to the study

15.1.1.1 Modification 1 – language regarding reconstitution, dilution and storage of copanlisib modified

Detailed information regarding reconstitution and dilution of copanlisib and the storage of copanlisib solution was removed from the protocol; this information can be found in the Pharmacy Manual or in the IB. The rationale for the text deletion was to avoid future protocol amendments due to changes in this language.

Clinical study protocol section affected by this modification:

Section 7.2 Identity of study treatment

15.1.1.2 Modification 2 – language on exclusion criterion clarified

Language related to exclusion criterion regarding previous treatment with bendamustine was clarified to be consistent with the language provided in Section 7.3 Treatment assignment. Patients who had previous treatment with bendamustine are excluded from the study, if bendamustine-based therapy was followed by a treatment-free interval of less than 12 months following that R-B course and patients have also received a cumulative dose of doxorubicin > 250 mg/m^2.

Clinical study protocol section affected by this modification:

Section 6.2 Exclusion criteria

15.1.1.3 Modification 3 –dosing criteria modified

Language was modified to clarify that blood count must be performed and assessed on the day of infusion, and not the day before the infusion. This modification was done to be consistent with the recommendation given in Section 7.4 regarding Table 7-3.

Clinical study protocol sections affected by this modification:

Section 7.4 Dosage and administration

Section 9.2.1.2.1 Treatment – Cycle 1 – Cycle 1, Day 8

15.1.1.4 Modification 4 – adjustment of biomarker sampling time point

One additional plasma collection for non-genetic biomarker analysis was added to Cycle 2 Day 15 (C2D15) for patients in the R-CHOP treatment group. This modification was done to have the same biomarker sampling time points in the R-CHOP treatment group as in the R-B treatment group and to better align the biomarker plasma collection time points in the present study with the time points used in the Phase 2 trial of copanlisib in NHL (Study 16349).

Clinical study protocol sections affected by this modification:

Section 9.1 Tabular schedule of evaluations – Table 9-2 Study flow chart

Section 9.2.1.2.2 Treatment – From Cycle 2 to Cycle 6

15.1.1.5 Modification 5 – administrative change

The sponsor’s medically responsible person was changed.

Clinical study protocol sections affected by this modification:

Signature of the sponsor’s medically responsible person

15.1.2 Changes to the protocol text

Changes to the protocol text done in Amendment 1 are provided in Section 15.1.2 of the Amendment 1.

15.2 Amendment 2

Amendment 2 is a global amendment dated 18 JUL 2016.

15.2.1 Overview of changes

15.2.1.1 Modification 1 – update of clinical experience with copanlisib

Introductory information on the number of patients treated with copanlisib was updated based on most recent data. The results from copanlisib study 16349 part A were also updated.

Section affected by this modification: 3.1.2 Clinical experience.

15.2.1.2 Modification 2 – definition on rituximab-sensitive iNHL removed

Rituximab (R)-sensitive iNHL is defined as patients that do not have R-resistance (rituximab resistance defined as lack of response to a rituximab-containing regimen, or progression within 6 months of treatment with a rituximab-containing regimen). For consistency, text about R-sensitive iNHL was withdrawn from Section 3.2 “Rationale of the study” because it was not according to the definition of resistance.

Section affected by this modification: 3.2 Rationale of the study.

15.2.1.3 Modification 3 – allowed prior immunochemotherapy regimens and treatment assignment clarified

- It was clarified that R-B, R-CVP or R-CHOP are allowed as prior lines of immunochemotherapies. This change was done according to the standard treatment for indolent NHL. Text describing the rules for randomization based on prior immunochemotherapy and exclusion criterion 29 regarding the prior treatment with bendamustine were modified accordingly.
- Language regarding the cumulative dose of anthracyclines was also updated. This study will include patients after least 1 but at most 3 previous lines of treatment. According to the new treatment assignment, if a patient received previous treatment with a scheme containing anthracycline (except CHOP) and can be included in R-CHOP group (also received bendamustine), the equivalent cumulative dose of anthracyclines should be calculated due to the risk of cardiomyopathy. In this case, the remaining dose must be sufficient for 6 cycles of R-CHOP.
- It was also clarified that patients must have relapsed or progressed after at least one but at most three prior lines of therapy. Relapse is a term used for return of the disease in patients that achieved complete remission, but it can be attributed to patients that achieved a sustained remission (not complete). The more appropriate term in this case is progressive disease. Patients with relapsed or progressive disease are allowed in the study if they are not resistant to rituximab.
- The definition of resistance to a prior treatment with other PI3K inhibitors was also modified in the inclusion criterion to be consistent with the definition given in exclusion criterion.
    - Exclusion criteria were clarified; patients with evidence of progression since last treatment will have the same washout period for previous treatments as patients without evidence of progression. This change was made to ensure a minimum washout period for all patients.

Sections affected by this modification: Synopsis, 4.2 Phase III part, 5.1 Design overview, 5.3 Phase III, 6.1 Inclusion criteria, 6.2 Exclusion criteria, 7.3.1 Safety run-in part, 7.3.2 Phase III part.

15.2.1.4 Modification 4 – update to inclusion criteria

- Even though SLL and CLL have the same tissue infiltration morphology and immunophenotype, they mainly differentiate between cytopenias and absolute peripheral B lymphocyte count. Patients previously diagnosed with CLL would be allowed to enter the study if they have at the study entry the diagnosis of SLL with absolute lymphocyte count $< 5 \times 10^9$/L. Requirement for the absolute lymphocyte count at diagnosis was removed from the inclusion criterion.
- Clarification was added that WM patients who do not have radiologically measurable lesion should have a positive immunofixation test result in addition to elevated IgM levels ($\geq 2 \times$ ULN) at Screening to indicate the presence of IgM paraprotein. The modification was done because IgM level alone does not show that the protein is clonal. Immunofixation establishes that the elevated IgM is clonal and therefore a real paraprotein.
- The inclusion criteria referring to platelet count in patients with confirmed lymphomatous bone marrow infiltration was also updated and clarified in order to ensure consistency across all copanlisib studies being done by the sponsor at this time. Dosing criterion in Table 7-3 was modified accordingly.
- The description of effective contraception and the definition of a woman of childbearing potential (WOCBP) and a post-menopausal state were clarified. In addition, it was clarified that the use of condoms by male patients is required unless the female partner is permanently sterile to ensure the effective contraception for males who appear to mainly confer risk to females (WOCBP) via exposure to copanlisib in seminal fluid. These changes were made according to recommendations related to contraception and pregnancy testing in clinical trials by the Clinical Trial Facilitating Group.

Section affected by these modifications: 6.1 Inclusion criteria.

15.2.1.5 Modification 5 – modification of exclusion criterion related to arterial hypertension

Following the investigators' and lymphoma specialists' feedback, the eligibility criteria was revised to eliminate the conservative requirement for blood pressure levels during eligibility evaluation considering the most important safety points are appropriate blood pressure levels prior to study treatment and available prophylactic treatments.

Section affected by this modification: Synopsis, 6.2 Exclusion criteria.

15.2.1.6 Modification 6 – exclusion of patients based on plasma glucose levels removed

- Exclusion of patients with fasting plasma glucose > 160 mg/dL at Screening was removed. The rationale for this change was to eliminate the eligibility evaluation requirement for plasma glucose testing considering the study patient population and to ensure enrollment of patients with diabetes mellitus in a compensation state that will be confirmed by HbA1c testing at Screening. HbA1c testing at Screening provides an

overview of the average blood glucose for the past 2 to 3 months, allowing exclusion of patients with insufficient glucose control. Such information is not provided by fasting plasma glucose. It was also clarified that the HbA1c >8.5% level concerns all patients, not only patients with diabetes mellitus.

Section affected by this modification: Synopsis, 6.2 Exclusion criteria.

15.2.1.7 Modification 7 – inclusion of patients with chronic HCV or HBV infection and prophylaxis for HBV and monitoring of HBV and HCV added

Patients with chronic HCV or HBV infection will be included in the study, as study population should be similar to general population. It was also clarified that patients with active (chronic or acute) HCV **or** HBV (HBV DNA test positive or HCV RNA test positive) will be excluded.

Requirement was added that prophylactic antiviral therapy should be given per local standard of care for patients who are positive for HBsAg or HBcAb at screening. Further, monthly monitoring of HBV and HCV (HBV DNA test for patients positive for HBsAg and/or HBcAb; and HCV-RNA test for patients positive for anti-HCV antibody) was added to the protocol; also included recurrence as withdrawal criteria. The change was made because patients with HBV and HCV are at risk of recurrence while receiving rituximab.

Sections affected by this modification: Synopsis, 6.2 Exclusion criteria, 6.4.1.1 Withdrawal criteria, 9.1 Tabular schedule of evaluations, 9.2.1.1 Screening period.

15.2.1.8 Modification 8 – clarification of exclusion criterion related to proteinuria

Exclusion criterion was modified to clarify that laboratory method used to assess proteinuria is not limited to UPCR only. Based on investigator feedback, the criterion was amended to make the patient evaluation more flexible and feasible.

In addition, it was clarified how the tests should be performed and reported to avoid misunderstandings and errors in collection.

Section affected by this modification: 6.2 Exclusion criteria, 9.1 Tabular schedule of evaluations, 9.2.1.1 Screening period, 9.6.3.1 Laboratory.

15.2.1.9 Modification 9 – language on corticosteroid therapy clarified

It was clarified in the protocol that previous corticosteroid therapy must be stopped or reduced to the allowed dose at least 7 days prior to the screening tumor scan, and again at least 7 days prior to the first study drug administration. This modification was made to eliminate a bias in the tumor response assessment; as to not potentially change the lesion status from time of baseline scan to study treatment start.

It was also clarified that short term systemic corticosteroids will be allowed as premedication prior to bendamustine infusions. This change was made based on investigator's feedback of the use of corticosteroids as premedication due to infusion reactions in the standard of care.

Guidance was added in case the use of corticosteroids as premedication leads to increases of glucose or blood pressure.

Sections affected by this modification: 6.2 Exclusion criteria, Section 8.1.1 Prohibited concomitant therapy, 8.1.2 Permitted concomitant therapy.

15.2.1.10 Modification 10 – prior treatment with copanlisib prohibited

Copanlisib was included to the list of prohibited previous therapies and medications. Inclusion criterion for prior line of therapy was revised accordingly. Modification was done because prior treatment with copanlisib could jeopardize the clinical assessment of the study drug.

Sections affected by this modification: 6.1 Inclusion criteria, 6.2 Exclusion criteria.

15.2.1.11 Modification 11 – updated guidance for management and monitoring of glucose increases

An updated guidance for the management of transient glucose increases was provided to ensure the patient safety. These changes were made based on updated clinical data and the feedback from the investigators.

Changes include:

- Management of transient glucose increases should be based on persistent post-infusion blood glucose results.
- Additional guidance regarding meal timing was provided.
- An updated guidance on dose modification for transient glucose increases was provided.
- Additional information regarding glucose monitoring at home was provided.
- The withdrawal criterion *"CTCAE Grade ≥ 3 glucose (and glucose > 250 mg/dL value confirmed by repeated laboratory analysis) despite optimal glucose lowering therapy at 30 mg dose level"* was revised to align with a new guidance for the transient glucose increases management.
- Incorrect sentence regarding high glycemic index foods was removed from Appendix 16.8. High glycemic index foods have a glucose reference index greater than 70.
- Glucose measurements related to rituximab infusion and bendamustine infusion were added to monitor the effects of corticosteroids used as premedication and to monitor the rituximab effect on glucose levels.

Sections affected by this modification: 6.4.1.1 Withdrawal criteria, 7.4 Dosage and administration, 7.4.2.3 Non-hematological toxicity, 7.4.3.1 Management of transient post-infusion glucose increases that can occur with copanlisib, 8.1.2 Permitted concomitant therapy, 9.1 Tabular schedule of evaluations, 9.2.1.2.1 Treatment – Cycle 1, 9.2.1.2.2 Treatment – From Cycle 2 to Cycle 6, 9.2.1.2.3 Treatment – From Cycle 7 onwards (during copanlisib/placebo monotherapy), 9.6.3.2 Glucose measurement on treatment days,

16.8 The average Glycemic Index of common foods derived from multiple studies by different laboratories.

15.2.1.12 Modification 12 – updated guidance for management and monitoring of blood pressure increases

Changes were made to reflect updated copanlisib safety information pertaining to potential drug-related transient blood pressure increases and feedback from investigators/lymphoma specialists regarding hypertension monitoring and management to make the process more feasible without compromising patient safety.

Sections affected by this modification: 7.4.2.3 Non-hematological toxicity, 9.6.3.5 Blood pressure measurement on treatment days.

15.2.1.13 Modification 13 – fasting requirement for lipid panels revised

The 11 h fasting requirement for lipid panels was revised; patients must be fasting prior to lipid sampling according to local standards. This change was made to allow the implementation of local standards for fasting requirements for lipid panel testing.

Sections affected by this modification: 7.4.3.2 Management of hyperlipidemia, 9.1 Tabular schedule of evaluations, 9.2.1.1 Screening period, 9.2.1.2.2 Treatment – From Cycle 2 to Cycle 6, 9.2.1.2.3 Treatment – From Cycle 7 onwards (during copanlisib/placebo monotherapy), 9.2.1.4 End-of-treatment (EOT) visit and 9.6.3.1 Laboratory.

15.2.1.14 Modification 14 – clarification of tumor response language

- ***Table for the CT and/or MRI response assessment criteria was updated***
    - Language in column “Spleen” for PD was updated; a rule was added to minimize any measurements errors, and the value of ≥ 1 cm was used after advice from professor Cheson, the author of the Lugano classification (14). The total value of increase is also in line with the total increase required for the bigger lesions, i.e. lesions > 2 cm.
    - A footnote regarding the longest diameter (LDi) was added to provide more details as was outlined in the table; the rule or the content was not changed.
    - A note was added to further clarify the evaluation provided in the response table, which is especially important for patients who do not have a lesion in the spleen.
- ***Table for the PET-CT response assessment criteria was updated***
    - Guidance was added for the investigator to clarify how to evaluate the response. This modification is based on the webinar content presented by professor Cheson in October 2014.
    - A clarification of PET-avid lesions was added to initiate a common understanding what the general term “PET-avid or PET-positive lesions” means with regard to the scoring system.

  - Rules for the response assessment were added to provide clear guidance as this was not covered by the response table. This modification did not change any overall rules for the assessment.

- In addition, the response assessment based on PET-CT and CT/MRI scans was clarified; in cases where CT shows unequivocal progression, the response is PD, independent from the response of the previous PET-CT response.
- Tumor assessment language was modified; the requirement that tumor assessments should be performed "within 7 days" after the last dose and "starting from Cycle 3" was removed to be feasible with different cycle lengths between R-B (every 4 weeks) and R-CHOP (every 3 weeks).
- It was also clarified that the types of indolent FDG-avid histologies where PET-CT should be considered include follicular lymphoma grade 3 and marginal zone lymphoma (nodal type). This modification was done to be consistent with imaging manual (by GCIS).
- Modifications were also done to harmonize the language across the protocol and with other copanlisib protocols, e.g. in Synopsis, and in Section 9.4.2 "Radiological tumor assessments".
- In general, CT/MRI needs to be performed with i.v. contrast agents. A clarification was added to explain, in which situations the switch from CT to MRI is required and when to proceed after the first treatment without a contrast-enhanced CT/MRI.

Sections affected by this modification: Synopsis, 5.1 Design overview, 9.1 Tabular schedule of evaluations, 9.2.1.3 Tumor assessments, 9.4.2 Radiological tumor assessments, 9.8 Appropriateness of procedures / measurements, 16.5 Evaluation of tumor response.

15.2.1.15 Modification 15 – guidance for management of toxicities added

Guidance for dose modifications for CHOP and bendamustine in case of toxicities was added to Section 7.4.2 Dose modification. This change was made to clarify that dose modifications regarding CHOP and bendamustine can be done according to prescribing information and investigator's experience.

Guidance in Table 7-5 "Dose modification of copanlisib/placebo for hematological toxicity" was updated: language related to dose reduction/ re-escalation of copanlisib/placebo was added to make dose modification more clear, clarification of concomitant medication to treat hematological toxicity was added, and criterion for INR or PTT was revised to update information.

Sections affected by this modification: 7.4.2 Dose modification,7.4.2.2 Hematological toxicity.

15.2.1.16 Modification 16 – usage of verapamil and diltiazem amended

The text was modified to state that verapamil and diltiazem (non-dihydropyridine calcium channel blockers**) should be used with caution** instead of **should be avoided** because itraconazole (a strong CYP 3A4 inhibitor) only increased copanlisib exposure by 1.42 fold.

Sections affected by this modification: 7.4.3.3 Treatment of blood pressure increases associated with copanlisib, 8.1.2 Permitted concomitant therapy.

15.2.1.17 Modification 17 – guidance for metformin use updated

Language related to interruption of metformin when receiving ionidated contrast media was modified; metformin should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast and prescribing information should be checked for further information. This change was made to recommend metformin use according to the prescribing information at the site, because differences regarding the time of temporary discontinuation can occur among metformin prescribing information.

Section affected by this modification: 8.1.2 Permitted concomitant therapy, 9.4.2 Radiological tumor assessments.

15.2.1.18 Modification 18 – recommendation for prednisone administration removed

Recommendation to administer the first dose of prednisone before rituximab infusion on D2 was removed. This change was done to allow the decision to be made by the investigator.

Section affected by this modification: 9.2.1.2.2 Treatment – From Cycle 2 to Cycle 6.

15.2.1.19 Modification 19 – reference to the Declaration of Objection form removed

The reference to the Declaration of Objection to the Collection of Study Data after Withdrawal of Consent was removed from the study protocol since this form is not used anymore according to sponsor's standard operating procedures.

Sections affected by this modification: 6.4.1.1 Withdrawal criteria, 13.4 Patient information and consent.

15.2.1.20 Modification 20 – changes in statistical language

Figure "Confirmatory testing strategy" was replaced with a new one; the new figure is equivalent to the old one statistically, but easier to understand.

Description of the testing hierarchy was revised and clarifications and corrections were made.

Sample size description and time point of measurement for primary variable for the phase III part were updated. This change was made due to a new accrual pattern based on knowledge from a competitor study and site feedback.

Sections affected by this modification: Synopsis, 5.3 Phase III, 5.3.1 Primary variable, 5.3.3 End of study, 10.3.2.5 Primary efficacy analysis, 10.3.2.7 Confirmatory statistical test strategy, 10.4 Determination of sample size.

15.2.1.21 Modification 21 – modification of replacement language

Replacement criterion for the safety run-in part was updated to clarify that patients with insufficient treatment exposure due to voluntary withdrawal in Cycle 1 will be replaced. The

modification was done because patients who discontinue during the first cycle due to reasons other than toxicity need to be replaced in order to ensure adequate number of subjects evaluable for safety.

Section affected by this modification: 6.4.2 Replacement.

15.2.1.22 Modification 22 – central pathology review of bone marrow samples clarified

Language was modified to clarify that central pathology review of bone marrow samples shall be performed for baseline, and after the first complete response if the baseline sample was positive.

Sections affected by this modification: Synopsis, 5.1 Design overview, 9.2.1.3 Tumor assessments.

15.2.1.23 Modification 23 – modification of coagulation language

Inclusion criterion was updated to clarify that INR should be ≤ 1.5 at Screening and PT can be used instead of INR if PTT ≤ 1.5 × ULN. The modification was done because previous language (INR ≤ 1.5 × ULN) allowed patients with INR of 1.8 to be eligible. INR and PT may be used interchangeably, since the INR is a standardized prothrombin time (which was initially designed to account for differences in thromboplastin).

Furthermore, “PT ratio or PT Quick method” was removed from the coagulation panel to avoid redundant testing report on the coagulation method.

Sections affected by this modification: 6.1 Inclusion criteria, 7.4.2.2 Hematological toxicity, 9.6.3.1 Laboratory.

15.2.1.24 Modification 24 – monitoring guidelines for opportunistic infection (OI) prophylaxis

Language provides guidance and clarification to the use of prophylactic treatment in patients at risk for opportunistic infections while on study treatment.

Following Health Authority alerts related to safety issues with Zydelig (idelalisib, a PI3K inhibitor) treatment in clinical trials, Section 7.4.3.6 was added to provide guidance for monitoring and prophylaxis of opportunistic infections in patients who are at risk for opportunistic infection development while on study treatment.

Also exclusion and withdrawal criteria were modified: patients with cytomegalovirus (CMV) infection are to be excluded from the study (re-screening is allowed once), and delay in test drug administration due to reactivation of CMV can be up to 2 months. These criteria were modified to avoid worsening of CMV infection in patients with active CMV and to harmonize the protocol with other CHRONOS studies.

Laboratory tests for OI were added and tabular schedule of evaluations was modified to be consistent with the OI guidance.

Sections affected by this modification: Synopsis, 6.2 Exclusion criteria, 6.4.1.1 Withdrawal criteria, 6.4.1.2 Screening failure, 7.4.2.3 Non-hematological toxicity, 7.4.3.6 Guidance for

monitoring and prophylaxis of opportunistic infection (OI), 9.1 Tabular schedule of evaluations, 9.2.1.1 Screening period, 9.2.1.2 Treatment period, 9.2.1.2.1 Treatment - Cycle 1, 9.2.1.2.2 Treatment - From Cycle 2 to Cycle 6, 9.2.1.2.3 Treatment – From Cycle 7 onwards (during copanlisib/placebo monotherapy), 9.6.3.1 Laboratory, 9.6.3.3.2 Brief physical examination and status check.

15.2.1.25 Modification 25 – clarification of reporting period of adverse events during safety follow-up

Language was modified to clarify that adverse events should be collected and recorded until 30 days after last treatment with study drug though safety follow-up visit may occur 30 days (a time window of +5 days is allowed) after last treatment.

Sections affected by this modification: 5.1 Design overview, 9.1 Tabular schedule of evaluations, 9.2.1.5.1 Safety follow-up, 9.6.1.3 Assessments and documentation of adverse events.

15.2.1.26 Modification 26– modification of absolute neutrophil count (ANC) criteria for copanlisib dosing

ANC laboratory test criteria were modified for copanlisib/placebo dosing; the ANC limit was lowered to ≥1000/mm^3 for Day 1 (from Cycle 2 onwards) and to ≥500/mm^3 for Day 8 and 15. G-CSF was added to be mandatory if ANC<1000/mm^3 as per label. Neutropenia can be managed by G-CSF in many cases and data shows that the ANC nadir coincides with copanlisib administration (Days 8 and 15), therefore, a strict ANC dosing criteria may be unnecessarily limiting for copanlisib dosing and therefore compromise the potential efficacy of the drug. Table 7-5 Dose modification for hematological toxicity was also modified accordingly.

Sections affected by this modification: 7.4 Dosage and administration, 7.4.2.2 Hematological toxicity, 8.1.2 Permitted concomitant therapy.

15.2.1.27 Modification 27– modification of withdrawal criterion and dose adjustment in case of non-infectious pneumonitis

To allow patients with low grades of NIP (CTCAE Grade 1 and 2) to pursue treatment and to align the protocol with other CHRONOS studies, the withdrawal criterion was modified to withdraw only patients with NIP ≥ CTCAE Grade 3. A new table was added to Section 7.4.2.3 for guidance of dose adjustment in cases of NIP.

Sections affected by this modification: 6.4.1.1 Withdrawal criteria, 7.4.2.3 Non-hematological toxicity.

15.2.1.28 Modification 28 – change in the timing of the IVRS/IWRS randomization transaction

The timing of IVRS/IWRS randomization transaction before the first dose (Cycle 1 Day 1) was increased from maximum 48 to maximum 72 hours, to allow more flexibility.

Sections affected by this modification: 7.3.2 Phase III part, 9.1 Tabular schedule of evaluations, 9.2.1.2.1 Treatment – Cycle 1.

15.2.1.29 Modification 29 – clarification on DLT language and transition from safety run-in phase to phase III part

It was clarified that in the safety-run in part, dose reduction is only allowed after Cycle 1 and that the DLTs are evaluated during Cycle 1. The DLT definition on abnormal lab values was also added.

The specific laboratory values were removed from the defined hematologic DLTs to avoid redundancy.

Clarification was added that the evaluation of the RP3D of copanlisib by DMC could be performed separately for R-B and for R-CHOP since recruitment speed for these cohorts is different. This change was made to avoid a potential delay to the start of the phase III part.

Sections affected by this modification: Synopsis, 5.2 Safety run-in part, 7.4.1 Definition of dose-limiting toxicities (DLTs).

15.2.1.30 Modification 30– modification to criteria for CT-based response assessment

It was clarified that in addition to a negative IHC confirmation for CR, a negative PCR is also acceptable for evaluation of the bone marrow.

Section affected by this modification: 16.5 Evaluation of tumor response.

15.2.1.31 Modification 31 – other clarifications and corrections

- It was clarified in the Section 7.4 “Dosage and administration - Dosing criteria” that in addition to the investigator, laboratory results can be also assessed by the treating physician or sub-investigator prior to administration of planned dose. It was also emphasized that on D8 and D15, laboratory test criteria described in Table 7-3 must be met before copanlisib/placebo will be administered.
- References to footnotes in Table 9-3 for procedures “Plasma for tumor genetics” and “Plasma for non-genetic biomarker analysis” were corrected for consistency.
- The word “Less than” was replaced with word “Within” in Section 9.2.1.1 “Screening period” to clarify the maximum allowed time for procedures performed before first study drug administration.
- The exclusion criterion “HIV infection” was changed to “Known history of HIV infection” to keep language consistent across the program.
- It was clarified in Section 6.4.1.1 “Withdrawal criteria” that patients **must** (not may) be withdrawn from the study at the specific request of the sponsor and in liaison with the investigator. Duplicate criterion regarding withdrawal in the case when investigator considers the study harmful to patient was removed.
- The withdrawal criterion regarding delay in test drug administration was clarified; patient must be withdrawn from study treatment if the delay due to toxicities is >28 days instead on >21 days (21 days plus 1 week of washout is 28 days).

- Language was clarified without changing the content in the Table 7-6 “Dose modification of copanlisib/placebo for non-hematological toxicity” to harmonize the language with other dose modification tables.
- It was clarified in Section 5.1 “Design overview” that the evaluation of WM patients without radiological disease will be performed by investigators based on the laboratory/clinical tests.
- Text regarding the examination of skin was combined with the examination of hand and feet in Section 9.6.3.3.1 and Section 9.6.3.3.2 to avoid repetition.
- An adjustment was made to Tables 9-1, 9-2 and 9-3 in Section 9.1 “Tabular schedule of evaluation” stating that acceptable deviation of -1 days to + 2 days is applicable to all visits during the treatment unless otherwise specified. This change was made to be more flexible and feasible for the sites to perform the procedures. Footnote “dd” was added to flowcharts in Section 9.1 to clarify the timing for laboratory tests prior to each infusion.
- Wording “dose reductions” for CHOP and bendamustine was changed to “dose modifications” in Section 7.4.2.3 “Non-hematological toxicity” as there can be also other modifications than reductions.
- It was clarified in Section 7.5 “Blinding” that also placebo is given in combination with R-B/R-CHOP.
- It was clarified in Section 7.1 “Treatments to be administered” that there will be no rituximab maintenance therapy administered from C7 onwards.
- Administrative change was done; the study medical expert was changed.
- Due to sponsor name change, sponsor information and sponsor logo were changed on Title page.
- It was clarified in Section 7.4.3.3 “Treatment of blood pressure increases associated with copanlisib” that nitrates instead of topical nitrates should be considered for the management of acute blood pressure increases following copanlisib/placebo administration.
- Clarification was made in Section 9.7.2 that time to improvement and the time to deterioration in disease-related symptoms –physical are measured by the DRS-P subscale of the FLymSI-18 questionnaire.

15.2.2 Changes to the protocol text

Changes to the protocol text done in Amendment 2 are provided in Section 15.2.2 of the Amendment 2.

15.3 Amendment 3

Amendment 3 is a global amendment dated 30 MAR 2017.

15.3.1 Overview of changes

15.3.1.1 Modification 1 – change in the inclusion criterion: prior therapies

The study eligibility criteria were modified to include patients who have received prior treatment with rituximab-based immunochemotherapy and alkylating agents. The change was done since the previous criterion (rituximab and R-B, R-CVP or R-CHOP) was considered as too restrictive. There is for example lack of vincristine in some countries and it is being replaced with other agents, such as vindesine.

Treatment allocation language was changed accordingly: patients who never received prior treatment with R-B will be randomized to study drug + R-B treatment group.

Sections affected by this modification: Synopsis, 4.2 Phase III part, 5.1 Design overview, 5.3 Phase III, 6.1 Inclusion criteria, 7.3.2 Phase III part

15.3.1.2 Modification 2 – combination with study drug and R-B allowed for patients who have received prior treatment with R-B

The study design was modified to allow patients who have received R-B as a previous line of therapy to be randomized to study drug plus R-B group in case there is ≥ 24 months progression-free interval after the last R-B treatment. The change was done because patients who relapse within 24 months but more than 6 months would be eligible for copanlisib plus R-CHOP. These patients are also more likely to be treated by R-CHOP. Patients who relapse ≥ 24 months after first R-B treatment respond well to R-B treatment. These patients are more likely to be treated with other treatment options rather than R-CHOP.

The following exclusion criterion was removed as a result of the change: “Patients who received R-B and R-CHOP or R-B and R-CVP as previous lines of therapy”.

Sections affected by this modification: Synopsis, 5.3 Phase III, 6.2 Exclusion criteria, 7.3.2 Phase III part

15.3.1.3 Modification 3 – changes in the statistical analysis and sample size

There is no regulatory obligation of powering on a specific subtype of iNHL. As a result, the total sample size was reduced from 676 patients to 520 patients and primary efficacy analysis will be performed in the FAS instead of both FAS and FL subgroup. Additionally, the recruitment ramp up period increase from 6 months to 15 months based on more updated site information.

A clarification was added that patients recruited into the safety run-in part will not be evaluated as part of the phase III part.

Sections affected by this modification: Synopsis, 5.2 Safety run-in part, 5.3 Phase III, 5.3.1 Primary variable, 5.3.3 End of study, 10.3.2.1 Population characteristics, 10.3.2.5 Primary efficacy analysis, 10.3.2.6 Secondary efficacy analysis,

10.3.2.7 Confirmatory statistical test strategy (section removed), 10.3.2.8 Other efficacy analysis, 10.3.2.10 Safety variables and analysis, 10.4 Determination of sample size

15.3.1.4 Modification 4 – RP3D for copanlisib in combination with R-B determined

The protocol was updated to include new information on the RP3D of copanlisib in combination with R-B. The dose was determined as 60 mg in the safety run-in part of the protocol in accordance with the DMC.

It was also further clarified that it is possible to start the phase III part for the treatment combination to which RP3D has already been determined even though the safety run-in part for the other treatment combination is still ongoing. See also amendment 2, in Section 15.2.1.29. This change was made to avoid a potential delay of the start of the phase III part.

Sections affected by this modification: Synopsis, 3.3 Benefit-risk assessment, 5.2 Safety run-in part

15.3.1.5 Modification 5 – changes in exclusion criteria

New exclusion criterion was added: patients who have received live vaccination, including virus vaccination and yellow fever vaccination, within 6 months before start of study treatment will not be eligible. According to the Centers for Disease Control and Prevention guidance on the timing of receiving the live vaccines, live vaccines may cause infections in patients receiving immunochemotherapy and patients with weak immune system.

The definition of rituximab resistance was modified for clarification. It was clarified that the last course of treatment with a rituximab containing regimen includes rituximab maintenance.

For other changes in exclusion criteria, see Modification 2.

Section affected by this modification: Synopsis, 6.2 Exclusion criteria

15.3.1.6 Modification 6 – patients experiencing disease progression may continue on treatment

The language was modified to allow patients to continue treatment with copanlisib if, in the investigator's opinion, treatment is providing clinical benefit.

Sections affected by this modification: Synopsis, 5.1 Design overview, 5.3 Phase III

15.3.1.7 Modification 7 – changes to the safety evaluation schedule

The safety evaluations to be performed on Day 22 were removed for patients in the copanlisib/placebo + R-B combination therapy group (from C1 to C6) and for all patients during copanlisib/placebo monotherapy (from C7 onwards). The modification was done since study treatment is not administered on Day 22 of any treatment cycle, and therefore, there is no harm for patient safety.

Similarly, the safety evaluations to be performed on Day 15 were removed for patients in the copanlisib/placebo + R-CHOP combination therapy group (from C1 to C6) since study treatment is not administered on those days.

Sections affected by this modification: Synopsis, 9.1 Tabular schedule of evaluations, 9.2.1.2.1 Treatment – Cycle 1, 9.2.1.2.2 Treatment – From Cycle 2 to Cycle 6, 9.2.1.2.3 Treatment – From Cycle 7 onwards (during copanlisib/placebo monotherapy)

15.3.1.8 Modification 8 – clarifications related to bone marrow assessments

The text was modified to clarify that bone marrow biopsy can be used for histological confirmation of WM diagnosis and for biomarker analyses in patients with WM. The IgM monoclonal gammopathy and confirmed invasion at bone marrow biopsy are the requirements for WM diagnosis and no lymph node biopsies are necessary. In case of lymphadenomegaly, the measurable lesions will only contribute for the tumor radiological assessment and will not have an impact on WM diagnosis. Therefore there is no need to expose the patient to lymph node biopsy. Also, for biomarker analysis in patients with WM, bone marrow biopsy can be used as the tumor tissue samples.

It was also clarified that bone marrow biopsy needs to be assessed locally before providing it to central pathology review.

In addition, the text related to platelet count values for patients with lymphomatous bone marrow infiltration was modified to take into account the bone marrow infiltration result based on local assessment performed at study entry. This change was also done for clarification.

Sections affected by this modification: Synopsis, 5.1 Design overview, 6.1 Inclusion criteria, 7.4 Dosage and administration, 9.1 Tabular schedule of evaluations, 9.2.1.1 Screening period, 9.2.1.3 Tumor assessments, 9.7.1 Biomarker investigations

15.3.1.9 Modification 9 – clarifications to the OI guidance

The blood test schedule for CMV was modified. The tests were aligned with study treatment schedule and visits (i.e. cycles) instead of months. It was also clarified that CMV can be analyzed retrospectively to avoid study drug interruptions in case the results are not immediately available.

Since all patients have lymphoma at study entry, clarification was added that lymphoma should not be considered a risk factor for enhanced monitoring of OI (history of immunodeficiency in the last 12 months).

It was also clarified that additional assessments indicated for patients with identified risk factors and those who developed OI on study treatment are not mandatory.

Sections affected by this modification: 7.4.3.6.1 Monitoring guidelines for OI, 9.1 Tabular schedule of evaluations, 9.2.1.2 Treatment period, 9.6.3.1 Laboratory

15.3.1.10 Modification 10 – clarification to urinalysis examinations (dipstick)

The modification was done to clarify that bilirubin test is not mandatory at urinalysis (dipstick).

Bilirubin test is not standard test at urinalysis and has no clinical impact since bilirubin is already analyzed as part of the complete chemistry panel.

Section affected by this modification: 9.6.3.1 Laboratory.

15.3.1.11 Modification 11 – changes and clarifications to radiological tumor assessments

The requirement that tumor assessments must be performed within 7 days after the last dose (previous cycle) of study drug and before Day 1 of the subsequent cycle was removed. The change was done to guarantee that tumor assessments will be performed at the same time for both copanlisib and placebo treatment groups and to ensure that results are comparable irrespective of patient receiving the drug or not.

Further clarification was added that calculation of tumor assessment time points (e.g. every 12 weeks) starts from Cycle 1 Day 1.

Recommendations related to the use of PET-CT imaging were added to the protocol. It was recommended to perform a PET-CT, if at a previous imaging visit the tumor response was derived from PET-CT and CT/MRI alone shows any change in the response assessment on subsequent imaging visits. As PET-CT trumps CT in most cases, the recommendation to perform PET-CT in case CT/MRI alone shows any change was added in order to be able to upgrade the response.

The language was clarified to state that all sites of disease selected as target lesions “should be preferably” PET positive instead of “must be”. Target lesions can be only selected and identified with CT/MRI. If the PET scan is done but is negative, target lesions would be still identified with CT/MRI.

Withdrawal criterion was modified to clarify that disease progression leading to discontinuation of study treatment should be based on the assessment of independent central review.

Language in Appendix 16.5 was also modified since conversion of lymphoma from PET negative to PET positive would be a valid PD assessment.

Sections affected by this modification: Synopsis, 9.1 Tabular schedule of evaluations, 9.2.1.3 Tumor assessments, 9.2.1.4 End-of-treatment visit, 9.2.1.5.2 Active follow-up, 9.4.2 Radiological tumor assessments, 16.5 Evaluation of tumor response

15.3.1.12 Modification 12 – reporting of medical device failures of imported and non-approved third-party device

According to a new regulatory requirement in Japan, Bayer Japan has to report medical device failures of imported and non-approved third-party device used in Bayer-sponsored clinical trials in Japan to the PMDA, IECs/IRBs and investigators. A new section was added to include this requirement.

Section affected by this modification: 9.6.3.9 Reporting of medical device failures (new section)

15.3.1.13 Modification 13 – change in the PK sampling schedule

The PK samples that were to be collected on Cycle 9 and Cycle 12 were removed from the protocol. The number of samples was reduced based on the feedback from the investigators.

Sections affected by this modification: 9.1 Tabular schedule of evaluations, 9.2.1.2.2 Treatment – From Cycle 2 to Cycle 6, 9.2.1.2.3 Treatment – From Cycle 7 onwards (during copanlisib/placebo monotherapy), 9.5.1 Sampling

15.3.1.14 Modification 14 – a minimum length for the screening period added

A minimum screening period of 7 days was added to the protocol to ensure timely supply of the study drug to the sites.

Sections affected by this modification: 5.1 Design overview, 9.2.1.1 Screening period

15.3.1.15 Modification 15 – changes based on drug-drug interaction data

The guidance text regarding the use of drugs that are substrates of P-gp and/or BCRP was removed from the protocol since the potential for drug-drug interactions appears to be very low based on the observed clinical C_{max} (~ 1µM) for copanlisib at the recommended clinical dose of 60 mg vs. in vitro IC_{50} for P-gp (7.0 and 7.6 µM) and BCRP (11µM). As a result of this change, Appendix 16.2 was removed from the protocol and all information regarding the use of MATE2K substrates was transferred to Section 8.1.2.

The language stating that non-dihydropyridine calcium channel blockers (verapamil and diltiazem) should be used with caution due to a potential CYP3A4 interaction was removed from the protocol as there is a low drug-drug interaction liability based on the current clinical knowledge with copanlisib.

It was also further clarified that the use of strong inhibitors of CYP3A4 and strong inducers of CYP3A4 is not permitted.

Sections affected by this modification: 6.2 Exclusion criteria, 7.4.3.3 Treatment of blood pressure increases associated with copanlisib, 8.1.1 Prohibited concomitant therapy, 8.1.2 Permitted concomitant therapy, 16.1 CYP3A4 inhibitors and inducers, 16.2 Pg-p substrates, BCRP substrates and MATE2K-substrates

15.3.1.16 Modification 16 – possibility to use paper QoL questionnaire in case ePRO device is not available

Language regarding the use of the paper version of PRO was added so that sites have the option to use this version if and when the ePRO device is not available and only if the Sponsor approves.

Section affected by this modification: 9.7.3 Electronic patient-reported outcomes evaluation

15.3.1.17 Modification 17 – other clarifications and corrections

- It was clarified that dose modifications are allowed during all treatment cycles in the phase III part of the study but only starting from Cycle 2 in the safety run-in part.
- Language was modified to further clarify that in countries where prednisone is not available, prednisolone can be administered instead.
- Since comparators will either be sourced centrally or provided locally by the sites/investigators followed by reimbursement, it was clarified that rituximab and chemotherapeutic agents will be sourced centrally or locally.

- The term “unblinded monitor” was changed to “independent monitor” as monitors are only potentially exposed to receive unblinded information from the unblinded pharmacist.
- Glucose monitoring guidance for diabetic patients was clarified to align the protocol with other copanlisib studies. “Non-fasting glucose < 200 mg/dL” was removed and no specific goal for the blood glucose values after 72 h post-infusion was included.

Section affected by this modification: Synopsis, 7.2 Identity of study treatment, 7.4 Dosage and administration, 7.4.2 Dose modification, 7.4.3.1 Management of transient post-infusion glucose increases that can occur with copanlisib, 7.5 Blinding, 7.7 Treatment compliance, 9.1 Tabular schedule of evaluations, 9.2.1.2.1 Treatment – Cycle 1,
9.2.1.2.2 Treatment - From Cycle 2 to Cycle 6

15.3.2 Changes to the protocol text

Changes to the protocol text done in Amendment 3 are provided in Section 15.3.2 of the Amendment 3.

15.4 Amendment 5

Amendment 5 is a global amendment dated 14 AUG 2017.

15.4.1 Overview of changes

Modification 1 – patients experiencing disease progression not allowed to continue on treatment

The language was modified not to allow patients to continue treatment in CHRONOS-4 beyond disease progression. This change was made at the request of French Health Authority, L'Agence nationale de sécurité du médicament et des produits de santé.

Sections affected by this modification: Synopsis, 5.1 Design overview, 5.3 Phase III

15.4.2 Changes to the protocol text

Changes to the protocol text done in Amendment 5 are provided in Section 15.4.2 of the Amendment 5.

15.5 Amendment 6

Amendment 6 is dated 25 SEP 2018.

15.5.1 Overview of changes

15.5.1.1 Modification 1 – updated guidance for management of glucose increases

Based on available safety data on copanlisib and to align with copanlisib prescribing information, the dose reduction guidance and withdrawal criterion for persistent occurrence of post-infusion blood glucose was modified from > 400 mg/dL to > 500 mg/dL.

Based on available safety data, fasting status has no significant clinical impact on post-infusion blood glucose. Fasting requirement at C1D1 and on D1 of subsequent cycles was removed. On infusion days, the timing of meal intake and additional glucose testing (if applicable) is managed and monitored by the investigators.

Based on available data, post-infusion blood glucose increase related to copanlisib treatment is transient and manageable. Home glucose monitoring was modified to allow investigator to determine a need for home glucose monitoring based on post-infusion glucose profile and clinical status of the patient.

On infusion days the allowed time window for post-infusion glucose measurements was changed from ± 5 min to ± 10 min for easier compliance. The time window for glucose measurements on D2 was extended from 5 minutes to 30 minutes to allow more flexibility. In addition, the language related to glucose measurement time points was clarified.

The schedule for HbA1C measurements was updated and an additional measurement of HbA1C 3 months after the EOT visit was implemented in order to assess HbA1C after treatment with copanlisib.

Sections affected by this modification: 6.4.1.1 Withdrawal criteria, 6.4.1.2 Screening failure, 7.4 Dosage and administration, 7.4.2.3 Non-hematological toxicity, 7.4.3.1 Management of transient post-infusion glucose increases that can occur with copanlisib, 9.1 Tabular schedule of evaluations, 9.2.1.1 Screening period, 9.2.1.2.1 Treatment – Cycle 1, 9.2.1.2.2 Treatment – From Cycle 2 to Cycle 6, 9.2.1.2.3 Treatment – From Cycle 7 onwards (during copanlisib/placebo monotherapy), 9.2.1.4 End-of-treatment visit, 9.2.1.5 Follow-up periods, 9.6.3.2 Glucose measurement on treatment days, 16.8 The average Glycemic Index of common foods derived from multiple studies by different laboratories

15.5.1.2 Modification 2 – updated guidance for blood pressure measurements

The guidance related to blood pressure measurements on infusion days was clarified, however, the data points remained unchanged. The time interval for the pre-dose measurement was updated to be aligned with copanlisib labeling information. The requirement to measure blood pressure on D2 (C1-C6) before and after rituximab administration was removed to be aligned with the rituximab label.

Sections affected by this modification: 9.2.1.2.1 Treatment – Cycle 1, 9.2.1.2.2 Treatment – From Cycle 2 to Cycle 6, 9.6.3.5 Blood pressure measurement on treatment days

15.5.1.3 Modification 3 – updated guidance for dermatologic and hematological toxicity

Updated guidance for dose modifications in cases of dermatologic toxicity was added to be aligned with the copanlisib label.

Following the investigator's feedback guidance text for hematological toxicity was modified to clarify that the use of G-CSF is based on local standard of care and that prophylactic treatment with G-CSF is allowed. In addition, it was also clarified G-CSF should be prescribed when ANC <1000/mm^3.

Section affected by this modification: 7.4.2.2 Hematological toxicity, 7.4.2.3 Non-hematological toxicity

15.5.1.4 Modification 4 – clarifications/modifications of inclusion criteria

Inclusion criterion 3 was modified to clarify that if prior line of rituximab-based immunochemotherapy and alkylating agents have been given concomitantly, they are considered one line of therapy. In addition the requirement for the previous regimen was clarified; less than 2 months of therapy with single agent rituximab can be considered a previous regimen in the case the patient responded to it.

The requirement for splenic MZL was clarified in inclusion criterion 4 since this group of patients presents manifestations which usually include only spleen and bone marrow. Nodal and extranodal involvement is rare, and therefore requiring a bi-dimensionally measurable lesion for this subtype is unreasonable.

See Modification 8 for the description of change in inclusion criterion 11.

Sections affected by the modification: Synopsis, 5.1 Design overview, 6.1 Inclusion criteria

15.5.1.5 Modification 5 – clarifications/modifications of exclusion criteria

Exclusion criterion 3 was removed, patients with close affiliation with the investigational site are no longer excluded from the study. This change was made to per site feedback to remove study participation restriction for these patients and to harmonize language within copanlisib protocols.

The definition of rituximab resistance was clarified in exclusion criterion 5 to explain that it is progression within 6 months of the last date of rituximab administration, including rituximab maintenance.

Please see Modification 8 for the change in exclusion criterion 10, 22 and 41.

Exclusion criterion 14 on excluding patients with history of current autoimmune disease was removed. Ongoing immunosuppressive treatment is already prohibited in exclusion criterion 30.

Sections affected by the modification: Synopsis, 5.1 Design overview, 6.2 Exclusion criteria

15.5.1.6 Modification 6 – clarification of the administration of study treatment

It was clarified that if any of the study treatment (copanlisib/placebo or immunochemotherapy) must be permanently discontinued, all other study treatment must be discontinued as well (excluding the planned discontinuation of R-B or R-CHOP after Cycle 6). In addition, it was emphasized, that if any drug administration is delayed, all drug combinations must be delayed.

It was also clarified that rituximab biosimilars cannot be prescribed in this study to avoid introducing any more variables to the study.

Sections affected by the modification: 7.2 Identity of study treatment, 7.4.2 Dose modification

15.5.1.7 Modification 7 – clarification of time window for assessments

It was clarified that the -1 to + 2 days time window for study drug administration in the tabular schedule of evaluations does not apply to visits at CxD2.

It was also clarified that starting from Cycle 1 Day 8 all laboratory tests performed prior to infusion including complete blood count with the exception of blood glucose may be done and assessed either the day before or on the planned day of infusion. This change was made to be aligned with the SOC and to make the test feasible for the sites.

At screening, an extended window of 14 days for diagnostic tests (if approved by the sponsor) was added. This change was made to increase flexibility at the sites and prevent unnecessary testing if historic test results are available.

It was clarified that IVRS/IWRS transactions for medication dispensing at Cycle 2 and above will be on Day 1 of each cycle or as described in the Pharmacy Manual. Individual sites may be permitted to perform the IVRS/IWRS transactions for medication dispensing up to 48 hours earlier than Day 1 of each Cycle due to logistics involved in medication being stored at main site and transported to a satellite location for dose administration.

Sections affected by the modification: 7.4 Dosage and administration, 9.1 Tabular schedule of evaluations (Tables 9-1, 9-2 and 9-3), 9.2.1.1 Screening period, 9.2.1.2.1 Treatment – Cycle 1, 9.2.1.2.2 Treatment – From Cycle 2 to Cycle 6, 9.2.1.2.3 Treatment – From Cycle 7 onwards (during copanlisib/placebo monotherapy)

15.5.1.8 Modification 8 – modification of the laboratory assessments

The requirement for total bilirubin level was changed from normal limit to $< 1.5 \times$ ULN for inclusion criterion 11 and for laboratory test criteria for Day 1 dose (in Cycle 2 and higher). This change was made because the review of safety data allows more flexibility to enroll patients with $< 1.5 \times$ ULN and to be aligned with other Chronos trials. It was also clarified that conjugated and unconjugated bilirubin must be calculated only if bilirubin $> 1.5 \times$ ULN). This change was made to be aligned with clinical practice and local SOC.

Guidance on how to consider a PCR test positive for CMV was added and a time window of -1 day was added. It was also emphasized that treatment of CMV should be initiated based on local SOC. The timing of the PCR test for CMV was also clarified.

The timing for HBV DNA PCR and HCV RNA test was clarified, these tests should be performed every cycle (±7 days) through treatment, not monthly. For consistency, these tests were added also to Day 1 of Cycle 2 - Cycle 6, Day 1 of C7 onwards and to the Active FU. In addition, it was clarified that patients positive for HBsAg or HBcAb and negative for HBV-DNA should receive prophylactic antiviral therapy as per rituximab label to be eligible.

The criterion to perform blood cultures when ANC CTCAE grade 4 occurs was removed to align the protocol language with the current SOC, since ANC grade 4 alone is not usually a mandatory criterion to perform blood cultures.

It was clarified that UPCR > 3.5 is equivalent to > 396 mg / mmol. This change was made to avoid unit conversion by the site when checking the excluded medical condition. In addition, the units of total urine protein and urine creatinine were removed as it should not be specified which unit the site will enter.

Sections affected by the modification: 6.1 Inclusion criteria, 6.2 Exclusion criteria 7.4 Dosage and administration, 7.4.3.6.1 Monitoring guidelines for OI, 9.1 Tabular schedule of evaluations, 9.2.1.1 Screening period, 9.2.1.2 Treatment period, 9.2.1.2.2 Treatment – From Cycle 2 to Cycle 6, 9.2.1.2.3 Treatment – From Cycle 7 onwards (during copanlisib/placebo monotherapy), 9.2.1.5.2 Active follow-up, 9.6.3.1 Laboratory

15.5.1.9 Modification 9 – clarification of tumor assessments

It was clarified that bone marrow biopsy should be provided to central pathology review also at the investigator discretion if clinical evaluation leads to suspicion of bone marrow infiltration without further radiological findings. Protocol was also modified to remind about the need for bone marrow evaluation for those patients who had previous lymphoma in the bone marrow. The text was aligned with other copanlisib protocols.

It was clarified that PET functional imaging is preferred modality and should be done based on institutional standards.

It was also clarified that CT/MRI scans are starting from Cycle 1 Day each year, not only in Year 1.

Language on CT/MRI scans at EOT visit was modified; these scans are not required, if the patient has been radiologically evaluated within the 4 weeks preceding EOT. This change was made to avoid unnecessary radiological exposure in all patients despite of the reason for drug withdrawal.

Sections affected by the modification: Synopsis, 5.1 Design overview, 9.2.1.3 Tumor assessments, 9.2.1.4 End-of-treatment visit, 9.2.1.5.2 Active follow-up, 9.4.2 Radiological tumor assessments, 9.8 Appropriateness of procedures / measurements

15.5.1.10 Modification 10 – clarification of stratification factor related to treatment-free interval

Due to feedback from sites and to be aligned with the exclusion criterion 5, it was clarified that patients will be stratified by the duration of progression-free interval from the last rituximab containing regimen.

Given the recognition that some sites are using progression-free interval for stratification, the change of stratification factor is considered beneficial for correct stratification of future patients.

Sections affected by this modification: Synopsis, 5.3 Phase III, 7.3.2 Phase III part

15.5.1.11 Modification 11 – administrative change

The contact information of sponsor's medical expert was changed. One of the co-ordinating investigators was changed. In addition, the sponsor's medically responsible person was changed.

Sections affected by this modification: Title page, 13.1 Investigator(s) and other study personnel, and Signature of the sponsor's medically responsible person

15.5.1.12 Modification 12 – changes to prohibited concomitant therapy

The use of Biotin is prohibited for at least 72 hours prior to immunoassay test collection as requested in the FDA Safety communication/recommendations on the use of Biotin. Since the use of Biotin produce high levels of the vitamin, these can interfere with the result of the immunoassay test.

Section affected by this modification: 8.1.1 Prohibited concomitant therapy

15.5.1.13 Modification 13 – other clarifications and corrections

- HBV DNA and HCV RNA test was added also to tabular schedule of evaluations (Tables 9-1 and 9-2) for consistency.
- For this protocol, it was clarified in Section 5 (Study design) that one month is considered to have 30 days.
- The reference to the version number of the NCCN-FACT Lymphoma Symptom Index-18 (FLymSI-18) questionnaire was corrected in Section 9.7.2, it should be version 4 instead of 2. The actual FLymSI-18 questionnaire was removed from the Appendix 16.6 to be consistent with protocol guidelines and to avoid potential amendments in the future.
- It was clarified that the EOT visit must take place also when the patient completes 12 months of treatment (maximum duration of therapy) if the patient has not discontinued treatment due to other reasons.
- It was explained in the study flow chart footnote "o" that Active follow-up period includes all patients who discontinued treatment due to any other reason than PD.
- "Evaluation of any new onset or worsening of pulmonary symptoms" was removed from the study flow charts Table 9-1, Table 9-2 and Table 9-3 to avoid overlap as brief and complete physical examinations already include lung examination.
- A reference to DMC charter was added instead of mentioning a specific timepoint for the DMC review to avoid protocol deviations.
- It was clarified that the enrollment period of 33 months and follow-up of 19 months are approximations. The terminology for progression was clarified for better readability.

In addition, minor editorial corrections to language were done throughout for consistency and to improve readability

15.5.2 Changes to the protocol text

Changes to the protocol text are provided in a separate track changes version.

15.6 Amendment 8

Amendment 8 is a global amendment dated 14 AUG 2019.

15.6.1 Protocol amendment summary of changes table

Section # and name	Description of changes	Brief rationale
Section 2 Synopsis, Section 4.2 Phase III part, Section 5.1 Design overview, Section 5.3 Phase III, Section 6.1 Inclusion criteria, Section 6.2 Exclusion criteria, Section 6.3 Justification of selection criteria, Section 7.3.2 Phase III part	Addition of prior anticancer therapies with rituximab biosimilars, and/or anti-CD20 monoclonal antibody	Considering the current iNHL treatment landscape and following the investigator's feedback, the eligibility criteria was modified to allow prior anticancer therapies with rituximab biosimiliars, and/or anti-CD20 monoclonal antibody.
Section 7.2 Identity of study treatment, Section 7.6 Drug logistics and accountability	Clarification of the local and central drug supply batch number tracking requirements for sites	In order to maintain consistency throughout the protocol, the requirement on how to handle background treatments was added.
Section 9.1 Tabular schedule of evaluations, Section 9.2.1.2.1 Treatment – Cycle 1, Section 9.2.1.2.2 Treatment – From Cycle 2 to Cycle 6, Section 9.2.1.2.3 Treatment – From Cycle 7 onwards (during copanlisib/placebo monotherapy), Section 9.2.1.4 End-of-treatment visit, Section 9.2.1.5.1 Safety follow-up, Section 9.7.2 Quality of life questionnaire – Phase III part only, Section 9.7.3 Electronic patient reported outcomes evaluation, Section 11.3 Data processing	Removal of PRO electronic device, Correction of version number of FLymSI-18	Due to technical issues with the devices at the start of the study, paper PRO is being used instead of ePRO.
Section 9.2.1.2.1 Treatment – Cycle 1	Deletion of descriptive text of excluding blood count test at CxD8	Correction of error

Section 9.1 Tabular schedule of evaluations	Deletion of BP measurement at D2 (C1-C6)	Correction of error
Section 1 Title page, Signature of the sponsor's medically responsible person, Section 13.1 Investigator(s) and other study personnel	Update contact information of sponsor's medical expert	Administrative changes

15.6.2 Changes to the protocol text

Changes to the protocol text are provided in a separate tracked-changes version.

15.7 Amendment 9

Amendment 9 is a global amendment dated 21 MAR 2023.

15.7.1 Protocol amendment summary of changes table

Section # and name	Description of changes	Brief rationale
2. Synopsis 5.3.1. Primary variable 5.3.3. End of study 10.3.2.5. Primary efficacy analysis 10.3.2.6. Secondary efficacy analysis 10.3.2.7. Confirmatory statistical test strategy 10.4. Determination of sample size	Changed the number of PFS events for primary completion from approximately 256 events to approximately 280 events Provided that confirmatory statistical testing strategies will be provided in the SAP.	To address the US FDA comment for the primary endpoint to include the FL subpopulation
9.1. Tabular schedule of evaluations 9.2.1.5.2. Active follow-up	Changed the end of the active follow up period to extend up to 2 years after study primary completion	To clarify the end of the active follow up period after study primary completion
2. Synopsis 5.1. Design overview 6.4.1.1. Withdrawal criteria 9.1. Tabular schedule of evaluations 9.2.1.5.3. Survival follow-up	Changed the time for collecting survival follow up data from 5 to 10 years after the last patient started study treatment	The extension of survival follow-up period from 5 years up to 10 years would allow long-term assessment of OS as both a safety and efficacy endpoint.
2. Synopsis Section 4.2. Study Objectives – Phase III Part 10.3.2.3 Secondary efficacy variables 10.3.2.6. Secondary efficacy analysis	Added disease control rate as a secondary objective and defined its respective analyses	Considered to be an informative secondary endpoint.
9.1. Tabular schedule of evaluations Section 9.2.1.5.2 Active follow-up Section 9.7.2 Quality of life questionnaire	Provided that FLyMSi questionnaire will be completed during the active follow up period for up to at least 1 year after study primary completion or until the sponsor advises termination of its collection	To extend a QOL assessment beyond the study primary completion allowing more data collection for the treatment evaluation.

Section 9.7.2 Quality of life questionnaire	Corrected the version of the FLyMSi-18 form from version 4 to version 2.	The paper version number of the FLyMSi-18 form was down-versioned from version 4 to version 2
2. Synopsis 5.1. Design overview 9.1. Tabular schedule of evaluations 9.2.1.3. Tumor assessments 9.4.2. Radiological tumor assessments	Provided guidance to specify the tumor assessments beyond Year 5 study period. Increased the time window to ±14 days for performing radiological tumor assessments beyond Year 5.	To provide guidance for tumor assessments beyond Year 5 of the study period.
2. Synopsis 3.3. Benefit-risk assessment 5.2 Safety run-in part	Added text confirming the completion of the safety run-in part of the study for copanlisib in combination with R-CHOP	The safety run-in part of the study was completed and the DMC determined that copanlisib in combination with R-CHOP is a recommended and approved dose used in the phase III part of the study
9.1. Tabular schedule of evaluations 9.2.1.4 End-of-treatment visit 9.7.1. Biomarker investigations	Removed text that required submission of a tumor sample from a biopsy or excision occurring during the study based on medical need	The text is removed due to completion of the biomarker analysis.
9. Procedures and Variables	Added text for participant visits, assessments, and monitoring in the event of study continuity issues	To provide general mitigation strategies in the event of a pandemic or other major study disruption
2. Synopsis 5.1 Design overview 9.1. Tabular schedule of evaluations 9.2.1.1. Screening period 9.7.1. Biomarker investigations 13.1 Investigator(s) and other study personnel	Added text to clarify that central pathology will be analyzed only as an exploratory analysis	For the study eligibility evaluation, a histologically confirmed diagnosis per local assessment was used. A clarification is added that central pathology will be analyzed only as an exploratory analysis.
2. Synopsis 5.1 Design overview 9.2.1.3. Tumor assessments 9.2.1.5.2 Active follow-up	Changed the post-baseline bone marrow biopsy assessment central review to local assessment to confirm the first complete response.	Having the study treatment period completed in April 2021, the likelihood of the first complete response is decreasing significantly in time. Therefore, a local bone marrow biopsy assessment will be allowed for the first CR confirmation.
13.5. Publication policy	Text regarding disclosure of study results added	Clarification to comply with the requirement of the European Union Clinical Trials Regulation (EU-CTR) 536/2014.

7.2. Identity of study treatment	Added guidance for study drug storage, accountability, reconciliation, and record maintenance	Clarification to comply with the requirement of the EU-CTR 536/2014.
2. Synopsis	Included the study rationale in the synopsis.	Clarification to comply with the requirement of the EU-CTR 536/2014.
2. Synopsis 5.1 Design overview 5.3.1. Primary variable 5.3.3. End of study 6.4.4.1 Withdrawal criteria 9.4.1 Primary efficacy variable 9.4.3 Tumor assessments in patients with WM 10.3.2.2 Primary efficacy variable 10.3.2.5 Primary efficacy analysis 10.4 Determination of sample size 11.4 Missing data	Aligned text throughout to state that disease progression is assessed by blinded independent central review.	Clarification to ensure consistency throughout.
13.1. Investigator(s) and other study personnel	Names of sponsor's medical expert and coordinating investigators removed.	This information is identified in a separate personnel list that is not part of this clinical study protocol.
Title Page Sponsor Signatory	Removed Sponsor Signatory page from the protocol	The signature of the Sponsor's medically responsible person is generated separately from the protocol as a standalone document filed with the protocol in the Trial Master File.
Throughout	Minor and editorial changes, corrections, and clarifications.	In addition to the modifications described above, protocol text was revised to address changes of editorial nature, clarifications for existing content, corrections based on inconsistencies, and typos or updates according to external guidance.

15.7.2 Changes to the protocol text

Changes to the protocol text are provided in a separate track changes version.

15.8 Country-specific requirements

Amendment 9 is a global amendment dated 21 MAR 2023.

15.8.1 Japan

Local Amendment 4 dated 11 MAY 2017 is specific to Japan.

15.8.1.1 Overview of Changes

15.8.1.1.1 Modification 1 – Japanese safety run-in (J-SRI) cohort added

According to the administrative notice by Ministry of Health, Labour and Welfare (MHLW)*, Japanese safety run-in (J-SRI) cohort is necessary because the increase safety risk associated with copanlisib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) / rituximab and bendamustine (R-B) cannot be ruled out.

The J-SRI cohort was added to confirm that the recommended phase III dose (RP3D) of copanlisib in combination with R-B and R-CHOP is safe and tolerable in Japanese subjects. The J-SRI is to be performed instead of the safety run-in part of main study (original protocol), and started after the RP3D of each combination (copanlisib+R-B or copanlisib+R-CHOP) is determined. Once the safety and tolerability of the RP3D of copanlisib in either combination with R-CHOP or R-B has been confirmed in Japanese subjects, the enrollment of Japanese subjects with the combination in the phase III part will start. The J-SRI of the other combination will continue until the safety and tolerability of the RP3D is confirmed.

*: "Basic Principles on Global Clinical Trials (Reference Cases)" issued by MHLW on 5 Sep. 2012

Clinical study protocol sections affected by this modification:

2. Synopsis, List of abbreviations, 3.3 Benefit-risk assessment, 4.1 Safety run-in part (New section added: 4.1.1 Japanese safety run-in cohort), 5.1 Design overview, 5.2 Safety run-in part (New section added: 5.2.1 Japanese safety run-in cohort), 5.3 Phase III, 5.3.1 Primary variable, 5.3.2 Justification of the design, 6. Study population, 6.4.1.1 Withdrawal criteria, 6.4.1.3 Drop out, 6.4.2 Replacement, 7.1 Treatments to be administered, 7.3.1 Safety run-in part (Section title changed), 7.4 Dosage and administration, 7.4.1 Definition of dose-limiting toxicities (DLTs), 7.4.2 Dose modification, 7.4.2.1 Safety run-in part and phase III part (Section title changed), 7.4.2.2 Hematological toxicity, 7.5 Blinding, 9.1 Tabular schedule of evaluations, 9.2.1 Visit descriptions in safety run-in part and phase III part (Section title changed), 9.5.1 Sampling, 9.5.2 Analysis, 10.1 General considerations, 10.2 Analysis sets, 10.3.1 Safety run-in part (Section title changed), 10.3.2.11 Further variables and their analysis, 10.4 Determination of sample size

15.8.1.2 Changes to the protocol text

In the sections on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version.

In the display of modifications, the "*old text*" refers to the protocol version preceding this amendment. Deletions are ~~crossed out~~ in the "*old text*". Additions are underlined in the "*new text*". Corrections of typos or omissions are not highlighted.

15.8.1.2.1 Section 2. Synopsis

Old text:

[…]	[…]
Study objective(s)	[…] • Biomarkers of efficacy, mode-of-action-related effect, safety, and / or the pathomechanism of the disease **<u>Phase III part (randomized, controlled trial)</u>** **Primary objective is:** […]
[…] **Dose(s)**	[…] […] After Cycle 1, dose reductions to 45 mg (if starting dose is 60 mg) and further to 30 mg are possible, should toxicities occur. **Phase III part**: Dosing of copanlisib: […]
[…] **Duration of treatment**	[…] […] The maximum duration of treatment with copanlisib/placebo is 12 months (including combination therapy and monotherapy). The duration of treatment in the safety run-in part will be the same as in the phase III part.
[…] **Dose(s)**	[…] **Safety run-in part**: Not applicable […]
[…]	[…]
Study design	The study has two parts: safety run-in / dose finding part and double-blind, controlled, two-arm phase III part. **Safety run-in part:** […] Patients recruited into the safety run-in part are treated in an unblinded fashion and will thus not be evaluated as part of the phase III part. **Phase III part:** […] The study (applicable to safety run-in part and phase III part) is composed of the following periods:

	[…]
Methodology	The primary safety variable in the safety run-in part is occurrence of dose-limiting toxicities in Cycle 1. The primary efficacy variable in the phase III part is PFS (for the definition, see below). […]
[…]	[…]
Number of patients	**Safety run-in part**: maximum 2 x 6 patients per combination evaluable for the primary endpoint. **Phase III part**: approximately 520 (including FL and other iNHL). Patients recruited into the safety run-in part will not be evaluated as part of the phase III part.
Primary variable(s)	**Safety run-in part**: The primary safety variable is the occurrence of DLTs in Cycle 1. […]
Time point/frame of measurement for primary variable(s)	**Safety run-in part**: Approximately 6-8 months […]
Plan for statistical analysis	**Safety run-in part**: Safety data will be summarized or listed per dose level. […]

New text:

[…]	[…]
Study objective(s)	[…] • Biomarkers of efficacy, mode-of-action-related effect, safety, and / or the pathomechanism of the disease **Japanese safety run-in (J-SRI) cohort** For Japanese subjects, the Japanese safety run-in (J-SRI) cohort is to be performed instead of the safety run-in part. It will start after the RP3D of copanlisib with each combination (R-B and R-CHOP) has been determined by the safety run-in part. Once the safety and tolerability of the RP3D of copanlisib in either combination (copanlisib+R-CHOP or copanlisib+R-B) has been confirmed, the enrollment of Japanese subjects with the combination in the phase III part will start. The J-SRI of the other combination will continue until the safety and tolerability of the RP3D is confirmed. **Primary objective is to confirm:** • Safety and tolerability of the RP3D of copanlisib determined by the safety run-in part in each combination (R-B and R-CHOP) in Japanese subjects **Further objectives are to evaluate:** • Radiological and clinical indicators of treatment efficacy in Japanese subjects

	(for subjects that stay on treatment after Cycle 1) • Safety and tolerability of copanlisib in combination with R-B/R-CHOP in Japanese subjects **(for subjects that stay on treatment after Cycle 1)** • PK of copanlisib in Japanese subjects • Biomarkers of efficacy, mode-of-action-related effect, safety, and/or the pathomechanism of the disease **Phase III part (randomized, controlled trial)** **Primary objective is:** […]
[…] **Dose(s)**	[…] […] After Cycle 1, dose reductions to 45 mg (if starting dose is 60 mg) and further to 30 mg are possible, should toxicities occur. **J-SRIcohort:** Dosing of copanlisib in this cohort: • in combination with R-B: RP3D of copanlisib (60 mg) determined by the safety run-in part, on Days 1, 8 and 15 of each 28-day cycle or • in combination with R-CHOP: RP3D of copanlisib (60 mg or 45 mg) determined by the safety run-in part, on Days 1 and 8 of each 21-day cycle. After Cycle 1, dose reductions to 45 mg (if starting dose is 60 mg) and further to 30 mg are possible, should toxicities occur. **Phase III part**: Dosing of copanlisib: […]
[…] **Duration of treatment**	[…] […] The maximum duration of treatment with copanlisib/placebo is 12 months (including combination therapy and monotherapy). The duration of treatment in the safety run-in part and the J-SRI cohort will be the same as in the phase III part.
[…] **Dose(s)**	[…] **Safety run-in part and J-SRI cohort**: Not applicable […]
[…]	[…]
Study design	The study has two parts: safety run-in (For Japanese subjects, J-SRI cohort will be used instead) / dose finding part and double-blind, controlled, two-arm phase III part. **Safety run-in part:**

	[…] Patients recruited into the safety run-in part are treated in an unblinded fashion and will thus not be evaluated as part of the phase III part. **J-SRI cohort:** The study for Japanese subjects will start with a J-SRI cohort, where the RP3D of copanlisib determined by the safety run-in part in combination with each regimen (R-B or R-CHOP) will be confirmed safe and tolerable in Japanese subjects. During the J-SRI cohort, two treatment combinations (copanlisib with R-B and copanlisib with R-CHOP) will be tested at the RP3D for safety and tolerability in Japanese subjects. All data available from J-SRI cohort will be reviewed in accordance with the predefined DLT evaluation procedures for J-SRI cohort attached to DMC charter and evaluated whether protocol specified treatment combinations are safe and tolerable. The outcome of the assessment will be reported to DMC. Once the safety and tolerability of the RP3D of copanlisib in either combination (R-B and R-CHOP) in Japanese subjects has been confirmed by investigators and sponsor in parallel with reporting outcome to the DMC, the enrollment of Japanese subjects with the combination in the phase III part will start. The J-SRI of the other combination will continue until the safety and tolerability of the RP3D is confirmed. Subjects recruited into the J-SRI cohort are treated in an unblinded fashion and will thus not be evaluated as part of the phase III part. **Phase III part:** […] The study (applicable to safety run-in part, J-SRI cohort and phase III part) is composed of the following periods: […]
Methodology	The primary safety variable in the safety run-in part and the J-SRI cohort is occurrence of dose-limiting toxicities in Cycle 1. The primary efficacy variable in the phase III part is PFS (for the definition, see below). […]
[…]	[…]
Number of patients	**Safety run-in part**: maximum 2 x 6 patients per combination evaluable for the primary endpoint. **J-SRI cohort**: 3 or 6 subjects per combination evaluable for the primary endpoint (2 combinations). **Phase III part**: approximately 520 (including FL and other iNHL). Patients recruited into the safety run-in part and J-SRI cohort will not be evaluated as part of the phase III part.
Primary variable(s)	**Safety run-in part and J-SRI cohort**: The primary safety variable is the occurrence of DLTs in Cycle 1. […]
Time point/frame of measurement for primary variable(s)	**Safety run-in part**: Approximately 6-8 months **J-SRI cohort**: This cohort runs after the RP3D determined in the safety run-in part

	of each combination (R-B and R-CHOP) to early phase III part. […]
Plan for statistical analysis	**Safety run-in part**: Safety data will be summarized or listed per dose level. **J-SRI cohort**: Safety data will be summarized or listed per dose level, which are independent from the safety run-in part. […]

15.8.1.2.2 List of abbreviations

New text:

J-SRI	Japanese safety run-in

15.8.1.2.3 Section 3.3 Benefit-risk assessment

Old text:

[…]

Safety run-in part for copanlisib in combination with R-B has been completed. DMC has reviewed the safety data and decided that **copanlisib dose of 60 mg plus R-B** is safe to be used in the phase III part. Safety run-in for copanlisib in combination with R-CHOP remains open for enrollment, and DMC will review the safety data upon completion.

New text:

[…]

Safety run-in part for copanlisib in combination with R-B has been completed. DMC has reviewed the safety data and decided that **copanlisib dose of 60 mg plus R-B** is safe to be used in the phase III part. Safety run-in for copanlisib in combination with R-CHOP remains open for enrollment, and DMC will review the safety data upon completion.

For Japanese subjects, the Japanese safety run-in (J-SRI) cohort is to be performed instead of the safety run-in part.

15.8.1.2.4 Section 4.1.1 Japanese safety run-in (J-SRI) cohort

Old text:

Not applicable (this is a new section)

New text:

4.1.1 Japanese safety run-in (J-SRI) cohort

For Japanese subjects, the J-SRI cohort is to be performed instead of the safety run-in part. The J-SRI will start after the RP3D of copanlisib with each combination (R-B and R-CHOP) has been determined by the safety run-in part. Once the safety and tolerability of the RP3D with either combination in Japanese subjects has been confirmed by investigators and sponsor in parallel with reporting the outcome to DMC, the enrolment of Japanese subjects with the combination in the phase III part will start. The J-SRI of the other combination will continue until the safety and tolerability of the RP3D is confirmed.

The primary objective is to confirm:

- Safety and tolerability of the RP3D of copanlisib determined by the safety run-in part in each combination (R-B and R-CHOP) in Japanese subjects.

Further objectives are to evaluate:

- Radiological and clinical indicators of treatment efficacy in Japanese subjects **(for subjects that stay on treatment after Cycle 1)**.
- Safety and tolerability of copanlisib in combination with R-B/R-CHOP in Japanese subjects **(for subjects that stay on treatment after Cycle 1)**.
- PK of copanlisib in Japanese subjects.
- Biomarkers of efficacy, mode-of-action-related effect, safety, and/or the pathomechanism of the disease.

15.8.1.2.5 Section 5.1 Design overview

Old text:

[…]

The study includes two parts. The safety run-in part will determine the RP3D of copanlisib in combination with standard immunochemotherapy (R-B or R-CHOP) to be used in the subsequent phase III part. The primary objective of the phase III part is to evaluate whether copanlisib in combination with standard immunochemotherapy, is superior to standard immunochemotherapy in prolonging progression-free survival (PFS) in patients with relapsed, rituximab-sensitive iNHL. The study will accrue patients with FL, MZL, SLL, and LPL/WM. In view of the prevalence of various histological types, it is expected that the large majority of study participants will be patients with FL.

[…]

The following design applies to ~~both~~ safety run-in part and the phase III part unless otherwise specified.

[…]

New text:

[…]

The study includes two parts. The safety run-in part will determine the RP3D of copanlisib in combination with standard immunochemotherapy (R-B or R-CHOP) to be used in the subsequent phase III part. For Japanese subjects, the J-SRI cohort is to be performed instead of the safety run-in part to confirm the safety and tolerability of the RP3D of copanlisib determined by the safety run-in part in each combination (R-B and R-CHOP) in Japanese subjects. The primary objective of the phase III part is to evaluate whether copanlisib in combination with standard immunochemotherapy, is superior to standard immunochemotherapy in prolonging progression-free survival (PFS) in patients with relapsed, rituximab-sensitive iNHL. The study will accrue patients with FL, MZL, SLL, and LPL/WM.

In view of the prevalence of various histological types, it is expected that the large majority of study participants will be patients with FL.

[…]

The following design applies to safety run-in part, J-SRI cohort and the phase III part unless otherwise specified.

[…]

15.8.1.2.6 Section 5.2.1 Japanese safety run-in (J-SRI) cohort

Old text:

Not applicable (this is a new section)

New text:

5.2.1 Japanese safety run-in (J-SRI) cohort

The study for Japanese subjects will start with a J-SRI cohort, which is based on an open-label, one dose level, 3+3 design.

During the J-SRI cohort, two treatment combinations (copanlisib with R-B and copanlisib with R-CHOP) will be tested at the RP3D determined in the safety run-in part for safety and tolerability in Japanese subjects. Each treatment combination with one dose level will have a minimum of 3 and maximum of 6 patients evaluable for DLT during Cycle 1.

The dose level of copanlisib in the Japanese safety run-in cohort will be tested as follows:

Dose level:	The RP3D of copanlisib determined by the safety run-in part in combination with either R-B or R-CHOP

For the dosing of R-B and R-CHOP, please see Section 7.4. For the treatment assignment, please see Section 7.3.1.

The dose-finding steps are presented in Figure 5–2J.

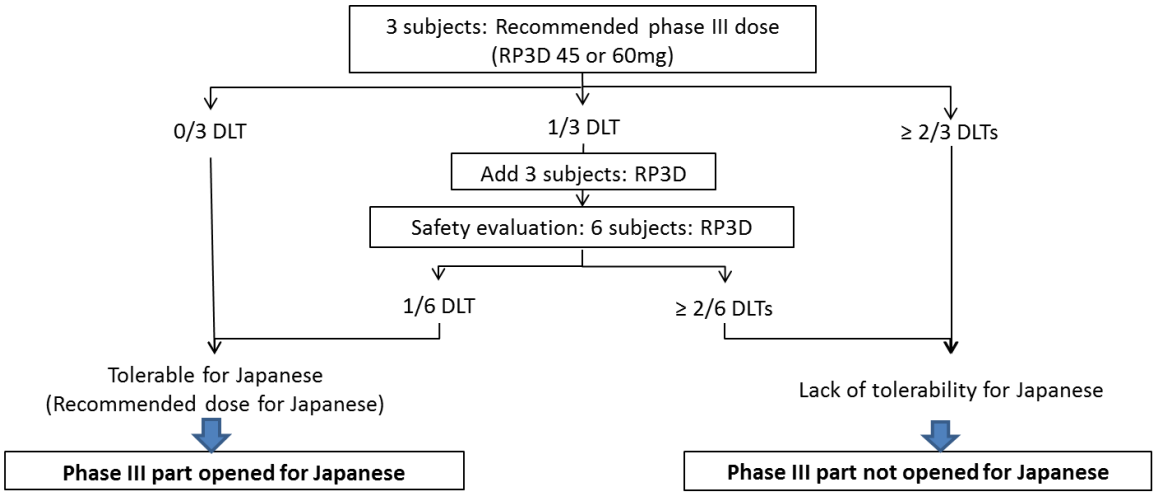
Three subjects will receive the RP3D of copanlisib.

- If 2 or more of the first 3 subjects experience DLT (see Section 7.4.1 for DLT definitions) at the RP3D, the J-SRI cohort would be closed and the participation of Japanese subjects in the phase III part considered to be not feasible.
- If 1 out of the first 3 subjects experiences a DLT at the RP3D, 3 additional subjects will need to be enrolled at this dose level.
  - If 1 or more of the additional 3 subjects experience DLT at the RP3D, then the J-SRI cohort would be closed and the participation of Japanese subjects in the phase III part considered to be not feasible.
  - If none of the additional 3 subjects experiences DLT at the RP3D, the RP3D will be the recommended dose for Japanese subjects.

- If none of the first 3 subjects experience DLT at the RP3D, the RP3D will be the recommended dose for Japanese subjects.

Subjects treated within the J-SRI cohort and who in the investigator's opinion benefit from treatment can continue combination therapy (copanlisib plus R-B or R-CHOP) for a maximum of 6 cycles followed by copanlisib monotherapy with the same dose of copanlisib administered with immunochemotherapy. The maximum duration of treatment with copanlisib is 12 months (including combination therapy and monotherapy).

Figure 5-2J Overall study design of the J-SRI cohort



All subjects enrolled in the J-SRI cohort need to be evaluated for occurrence of DLTs during the first cycle. Subjects not fully evaluable for occurrence of DLTs during the first cycle of therapy will be replaced unless the reason for dropout is a DLT (see Section 6.4.2). Any subjects who experiences a DLT during the first cycle of therapy should not receive further administration of copanlisib or any other study treatment. The investigator must notify the sponsor immediately of any CTCAE Grade 3 or 4 AEs or clinically relevant laboratory abnormalities.

Transition from J-SRI cohort to phase III part

All data available from the J-SRI cohort will be reviewed in accordance with the predefined DLT evaluation process for J-SRI cohort attached to DMC and evaluated whether protocol specified treatment combinations are safe and tolerable in Japanese subjects. Outcome of the review of each combination (R-B and R-CHOP) will be reported to the DMC, respectively. Once the safety and tolerability of the RP3D of copanlisib in either combination in Japanese subjects has been confirmed by investigators and sponsor in parallel with reporting outcome to the DMC, the enrolment of Japanese subjects with the combination in the phase III part will start. The J-SRI of the other combination will continue until the safety and tolerability of the RP3D is confirmed.

Subjects recruited into the J-SRI cohort are treated in an unblinded fashion and will thus not be evaluated as part of the phase III part.

15.8.1.2.7 Section 5.3 Phase III

Old text:

[…]

Patients will be stratified by: prior to base treatment regimen (R-chemotherapy to R-B, R-B to R-CHOP, and R-B to R-B), NHL histology (FL vs. other iNHL) and duration of treatment-free interval (6-12 months vs. >12 months). If the copanlisib immunochemotherapy combinations are deemed safe in the safety run-in part of the trial, approximately 520 (including FL and other iNHL) patients who meet the eligibility criteria will be randomly assigned in a 1:1 ratio to one of the double-blinded treatment arms (approx. 260 patients per arm) in the phase III part: **Arm 1**: copanlisib plus R-CHOP or R-B and **Arm 2**: placebo plus R-CHOP or R-B, see Figure 5–3.

[…]

New text:

[…]

Patients will be stratified by: prior to base treatment regimen (R-chemotherapy to R-B, R-B to R-CHOP, and R-B to R-B), NHL histology (FL vs. other iNHL) and duration of treatment-free interval (6-12 months vs. >12 months). If the copanlisib immunochemotherapy combinations are deemed safe in the safety run-in part of the trial (for Japanese subjects, the J-SRI cohort will be used instead), approximately 520 (including FL and other iNHL) patients who meet the eligibility criteria will be randomly assigned in a 1:1 ratio to one of the double-blinded treatment arms (approx. 260 patients per arm) in the phase III part: **Arm 1**: copanlisib plus R-CHOP or R-B and **Arm 2**: placebo plus R-CHOP or R-B, see Figure 5–3.

[…]

15.8.1.2.8 Section 5.3.1 Primary variable

Old text:

- The primary variable for the safety run-in part is the occurrence of DLTs in Cycle 1.

[…]

New text:

- The primary variable for the safety run-in part and the J-SRI cohort is the occurrence of DLTs in Cycle 1.

[…]

15.8.1.2.9 Section 5.3.2 Justification of the design

Old text:

[…]

The safety run-in part uses the standard design of dose-finding study, with 3-6 patients per dose level, and occurrence of dose-limiting toxicity as primary endpoint. The intensity and frequency of AEs as well as the occurrence of new and unexpected AEs will be carefully monitored. Those patients who have benefit and will stay on treatment after the 1st Cycle will be also evaluated for treatment efficacy, safety and tolerability of copanlisib in combination with R-CHOP/R-B, pharmacokinetics and biomarkers. All these information will be taken into account when assessing the performance of the study in the phase III part.

The phase III part will start after RP3D of copanlisib is defined. The use of placebo can minimize investigator bias in assessing treatment effects beyond tumor shrinkage. This is particularly important when assessing duration endpoints and patient-reported outcomes. Although treatment with copanlisib is associated with infusion-related increases in blood glucose and increases in blood pressure, the risk of inadvertent unblinding is low. In the majority of the cases, the intensity of both symptoms is low, and both symptoms are not infrequent in the age group to which the majority of patients with indolent NHL belong.

New text:

[…]

The safety run-in part uses the standard design of dose-finding study, with 3-6 patients per dose level, and occurrence of dose-limiting toxicity as primary endpoint. The intensity and frequency of AEs as well as the occurrence of new and unexpected AEs will be carefully monitored. Those patients who have benefit and will stay on treatment after the 1st Cycle will be also evaluated for treatment efficacy, safety and tolerability of copanlisib in combination with R-CHOP/R-B, pharmacokinetics and biomarkers. All these information will be taken into account when assessing the performance of the study in the phase III part.

For Japanese subjects, the J-SRI cohort is to be performed instead of the safety run-in part to confirm that the RP3D of copanlisib in each combination determined by the safety run-in part is safe and tolerable in Japanese subjects.

The phase III part will start after RP3D of copanlisib is defined. The use of placebo can minimize investigator bias in assessing treatment effects beyond tumor shrinkage. This is particularly important when assessing duration endpoints and patient-reported outcomes. Although treatment with copanlisib is associated with infusion-related increases in blood glucose and increases in blood pressure, the risk of inadvertent unblinding is low. In the majority of the cases, the intensity of both symptoms is low, and both symptoms are not infrequent in the age group to which the majority of patients with indolent NHL belong.

15.8.1.2.10 Section 6 Study population

Old text:

Criteria for patients' eligibility, withdrawal and, as well as patients' identification apply to ~~both~~ safety run-in part and phase III part, unless otherwise specified.

New text:

Criteria for patients' eligibility, withdrawal and, as well as patients' identification apply to safety run-in part, J-SRI cohort and phase III part, unless otherwise specified.

15.8.1.2.11 Section 6.4.1.1 Withdrawal criteria

Old text:

[…]

- Phase III part: The patient does not tolerate copanlisib/placebo dose of 30 mg.

  Safety run-in part: The patient does not tolerate copanlisib dose of 30 mg after Cycle 1.

[…]

New text:

[…]

- Phase III part: The patient does not tolerate copanlisib/placebo dose of 30 mg.

  Safety run-in part and J-SRI cohort: The patient does not tolerate copanlisib dose of 30 mg after Cycle 1.

[…]

15.8.1.2.12 Section 6.4.1.3 Drop out

Old text:

A patient who discontinues study participation prematurely for any reason is defined as a "dropout" if the patient has already been randomized (phase III part) /assigned to treatment (safety run-in part).

New text:

A patient who discontinues study participation prematurely for any reason is defined as a "dropout" if the patient has already been randomized (phase III part) /assigned to treatment (safety run-in part, J-SRI cohort).

15.8.1.2.13 Section 6.4.2 Replacement

Old text:

Safety run-in part

[…]

New text:

Safety run-in part and J-SRI cohort

[…]

15.8.1.2.14 Section 7.1 Treatments to be administered

Old text:

[…]

The maximum duration of treatment with copanlisib/placebo is 12 months (including combination therapy and monotherapy). The duration of treatment in the safety run-in part will be the same as in the phase III part. For the dosage and administration please see Section 7.4.

New text:

[…]

The maximum duration of treatment with copanlisib/placebo is 12 months (including combination therapy and monotherapy). The duration of treatment in the safety run-in part and the J-SRI cohort will be the same as in the phase III part. For the dosage and administration please see Section 7.4.

15.8.1.2.15 Section 7.3.1 Safety run-in part

Old text:

7.3.1 Safety run-in part

During the open-label safety run-in part patients who have given written informed consent and who satisfy the entry criteria will be assigned to the combination therapy (copanlisib + R-B or copanlisib + R-CHOP):

[…]

New text:

7.3.1 Safety run-in part and J-SRI cohort

During the open-label safety run-in part patients and J-SRI cohort subjects who have given written informed consent and who satisfy the entry criteria will be assigned to the combination therapy (copanlisib + R-B or copanlisib + R-CHOP):

[…]

15.8.1.2.16 Section 7.4 Dosage and administration

Old text:

Copanlisib and placebo

Copanlisib and placebo for copanlisib (only in phase III part) administration described below applies to all patients in the safety run-in part and patients in the phase III part, for as long as patients are on treatment with copanlisib or placebo.

[…]

New text:

Copanlisib and placebo

Copanlisib and placebo for copanlisib (only in phase III part) administration described below applies to all patients in the safety run-in part, subjects in the J-SRI cohort and patients in the phase III part, for as long as patients are on treatment with copanlisib or placebo.

[…]

15.8.1.2.17 Section 7.4.1 Definition of dose-limiting toxicities (DLTs)

Old text:

Dose-limiting toxicity – safety run-in part

[…]

New text:

Dose-limiting toxicity – safety run-in part and the J-SRI cohort

[…]

15.8.1.2.18 Section 7.4.2 Dose modification

Old text:

Dose modifications due to toxicities described below apply to copanlisib and placebo for copanlisib ("dummy dose modification"). There will be no dose reductions for rituximab in any cycle. For the safety run-in part, there will be no dose reductions of any components of CHOP or bendamustine in the first cycle. Modifications for CHOP and bendamustine (safety run-in part: Cycle 2 and subsequent cycles, phase III part: all cycles) will be performed according to the measures of precaution and toxicity management per local standards of care, local prescribing information, and according to investigator's experience.

[…]

New text:

Dose modifications due to toxicities described below apply to copanlisib and placebo for copanlisib ("dummy dose modification"). There will be no dose reductions for rituximab in any cycle. For the safety run-in part and the J-SRI cohort, there will be no dose reductions of any components of CHOP or bendamustine in the first cycle. Modifications for CHOP and bendamustine (safety run-in part and the J-SRI cohort: Cycle 2 and subsequent cycles, phase III part: all cycles) will be performed according to the measures of precaution and toxicity management per local standards of care, local prescribing information, and according to investigator's experience.

[…]

15.8.1.2.19 Section 7.4.2.1 Safety run-in part and phase III part

Old text:

7.4.2.1 Safety run-in part and phase III part

Dose modification levels are outlined in Table 7–4. In the safety run-in part, dose modification rules of copanlisib will apply to patients who stay on treatment beyond 1st cycle and present toxicities that will need dose adjustments. Dose modification of placebo applies only to phase III part.

Table 7–4 Dose levels of copanlisib and placebo

If RP3D dose is **45 mg**:

Dose level 1 (starting dose):	45 mg of copanlisib or placebo
Dose level -1:	30 mg of copanlisib or placebo

If RP3D dose is **60 mg**:

Dose level 1 (starting dose):	60 mg of copanlisib or placebo
Dose level -1:	45 mg of copanlisib or placebo
Dose level -2:	30 mg of copanlisib or placebo

[…]

New text:

7.4.2.1 Safety run-in part, J-SRI cohort and phase III part

Dose modification levels are outlined in Table 7–4. In the safety run-in part and the J-SRI cohort, dose modification rules of copanlisib will apply to patients who stay on treatment beyond 1st cycle and present toxicities that will need dose adjustments. Dose modification of placebo applies only to phase III part.

Table 7–4 Dose levels of copanlisib and placebo

If RP3D dose* is **45 mg**:

Dose level 1 (starting dose):	45 mg of copanlisib or placebo
Dose level -1:	30 mg of copanlisib or placebo

If RP3D dose* is **60 mg**:

Dose level 1 (starting dose):	60 mg of copanlisib or placebo
Dose level -1:	45 mg of copanlisib or placebo
Dose level -2:	30 mg of copanlisib or placebo

*: Copanlisib dose of the J-SRI cohort is equal to the RP3D dose defined in the safety run-in part of the main study

[…]

15.8.1.2.20 Section 7.4.2.2 Hematological toxicity

Old text:

Neutropenia and febrile neutropenia are listed in the current version of IB as expected adverse events. If the guidelines given in Table 7–5 are not followed, the rationale for other measures is to be documented in detail in the patient's medical record. The use of myeloid growth factors in the therapeutic setting is allowed during study treatment at investigator's discretion for safety run-in part and phase III part.

[…]

New text:

Neutropenia and febrile neutropenia are listed in the current version of IB as expected adverse events. If the guidelines given in Table 7–5 are not followed, the rationale for other measures is to be documented in detail in the patient's medical record. The use of myeloid growth factors in the therapeutic setting is allowed during study treatment at investigator's discretion for safety run-in part, J-SRI cohort and phase III part.

[…]

15.8.1.2.21 Section 7.5 Blinding

Old text:

Blinding measures are only applicable for the phase III part which follows double-blind design. The safety run-in part ~~is~~ open-label.

[…]

New text:

Blinding measures are only applicable for the phase III part which follows double-blind design. The safety run-in part and the J-SRI cohort are open-label.

[…]

15.8.1.2.22 Section 9.1 Tabular schedule of evaluations

Old text:

This section contains three tabular schedule of evaluations which are valid to ~~both~~ safety run-in part and phase III part of the study (unless otherwise specified):

[…]

New text:

This section contains three tabular schedule of evaluations which are valid to safety run-in part, J-SRI cohort and phase III part of the study (unless otherwise specified):

[…]

15.8.1.2.23 Section 9.2.1 Visit descriptions in safety run-in part and phase III part

Old text:

9.2.1 Visit descriptions in safety run-in part and phase III part

[…]

New text:

9.2.1 Visit descriptions in safety run-in part, J-SRI cohort and phase III part

[…]

15.8.1.2.24 Section 9.5.1 Sampling

Old text:

[…]

Table 9–4 PK assessments in the safety run-in part and phase III part

[…]

New text:

[…]

Table 9–4 PK assessments in the safety run-in part, J-SRI cohort and phase III part

[…]

15.8.1.2.25 Section 9.5.2 Analysis

Old text:

[…]

Concentration data of copanlisib, its metabolite M-1, and other metabolites, as needed, from this study will be analyzed to estimate the individual maximum drug concentration (C_{max}) and area under the curve (AUC), and to measure the variability of the PK of copanlisib, its metabolite M-1 and other metabolites, as needed, in the safety run-in part and phase III population. A population pharmacokinetic approach will be used for the analysis.

[…]

New text:

[…]

Concentration data of copanlisib, its metabolite M-1, and other metabolites, as needed, from this study will be analyzed to estimate the individual maximum drug concentration (C_{max}) and area under the curve (AUC), and to measure the variability of the PK of copanlisib, its metabolite M-1 and other metabolites, as needed, in the safety run-in part, J-SRI cohort and phase III population. A population pharmacokinetic approach will be used for the analysis.

[…]

15.8.1.2.26 Section 10.1 General considerations

Old text:

[…]

Statistical analyses will be performed using Statistical Analysis System (SAS); the version used will be specified in the statistical analysis plan (SAP). As a general principle, the safety run-in part and phase III part will be analyzed separately.

[…]

New text:

[…]

Statistical analyses will be performed using Statistical Analysis System (SAS); the version used will be specified in the statistical analysis plan (SAP). As a general principle, the safety run-in part, J-SRI cohort and phase III part will be analyzed separately.

[…]

15.8.1.2.27 Section 10.2 Analysis sets

Old text:

[…]

Pharmacokinetic analysis set (PKAS): All patients in the safety run-in part with a valid PK profile will be included in the analysis of PK data.

Phase III part:

[…]

New text:

[…]

Pharmacokinetic analysis set (PKAS): All patients in the safety run-in part with a valid PK profile will be included in the analysis of PK data.

J-SRI cohort:

Full analysis set (FAS): All patients in the J-SRI cohort who receive at least one dose of study drug.

Safety analysis set (SAF): All patients in the J-SRI cohort who receive at least one dose of study drug.

Pharmacokinetic analysis set (PKAS): All patients in the J-SRI cohort with a valid PK profile will be included in the analysis of PK data.

Phase III part:

[…]

15.8.1.2.28 Section 10.3.1 Safety run-in part

Old text:

10.3.1 Safety run-in part

The recommended dose of copanlisib in combination with standard immunochemotherapy will be determined based on a 3+3 design. The primary safety variable is the occurrence of DLTs during Cycle 1. Safety variables will include also treatment-emergent AEs, SAEs, laboratory parameters, and vital signs. The safety data will be listed by dose level. The best overall response will be summarized. For further details on PK and biomarker variables and analysis, see Section 10.3.2.11.

New text:

10.3.1 Safety run-in part and J-SRI cohort

The recommended dose of copanlisib in combination with standard immunochemotherapy will be determined based on a 3+3 design. The primary safety variable is the occurrence of DLTs during Cycle 1. Safety variables will include also treatment-emergent AEs, SAEs, laboratory parameters, and vital signs. The safety data will be listed by dose level. The safety data of J-SRI cohort will be summarized, which are independent from the safety run-in part. The best overall response will be summarized. For further details on PK and biomarker variables and analysis, see Section 10.3.2.11.

15.8.1.2.29 Section 10.3.2.11 Further variables and their analysis

Old text:

[…]

The data from the safety run-in part and phase III part will be pooled for PK analysis.

[…]

New text:

[…]

The data from the safety run-in part, the J-SRI cohort and phase III part will be pooled for PK analysis.

[…]

15.8.1.2.30 Section 10.4 Determination of sample size

Old text:

Safety run-in part

Maximum 2 x 6 evaluable patients per combination (dependent on visibility of DLT) will be included into two dose levels to identify the RP3D.

Phase III part

[…]

New text:

Safety run-in part

Maximum 2 x 6 evaluable patients per combination (dependent on visibility of DLT) will be included into two dose levels to identify the RP3D.

J-SRI cohort

Three or 6 evaluable subjects per combination will be included into the RP3D (one dose level) determined by the safety run-in part.

Phase III part

[…]

15.8.2 Germany

Local Amendment 7 dated 12 MAR 2019 is specific to Germany.

15.8.2.1 Overview of Changes

15.8.2.1.1 Modification 1 – Revised blood glucose withdrawal criterion

The withdrawal criterion for persistent occurrence of post-infusion blood glucose was revised from >500 mg/dL to >400 mg/dL.

Supporting the 17833 global protocol amendment 6, a local protocol amendment has been generated to satisfy the German Ethics Committee (EC) request not to modify the withdrawal criterion for persistent occurrence of post-infusion blood glucose. However, the EC has acknowledged that the withdrawal criterion for post-infusion blood glucose increases in the 17833 global CSP 6 was modified following the glucose increase management guidance in the copanlisib program, which was updated based on the available copanlisib integrated safety data, to address investigators' feedback, and to be aligned with the Aliqopa label.

Clinical study protocol sections affected by this modification:

6.4.1.1 Withdrawal criteria, and 7.4.2.3 Non-hematological toxicity / Glucose increases

15.8.2.1.2 Modification 2 – New Sponsor Personnel

Sponsor's medically responsible person and sponsor's medical expert were changed.

Clinical study protocol sections affected by this modification:

1. Title page, Signature of the sponsor's medically responsible person, 13.1 Investigator(s) and other study personnel

15.8.2.2 Changes to the protocol text

In the sections on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the most recent previous protocol version.

In the display of modifications, the "*old text*" refers to the protocol version preceding this amendment. Deletions are ~~crossed out~~ in the "*old text*". Additions are underlined in the "*new text*". Corrections of typos or omissions are not highlighted.

15.8.2.2.1 Section 1. Title page

[...]

Sponsor's medical expert: PPD PPD
~~Rua Cancioneiro de Évora, 255, Prédio E1, 1º andar~~
~~04708-904, São Paulo, Brazil~~
~~Phone:~~ PPD
~~Mobile~~ PPD
~~Fax:~~ PPD

PPD PPD

Address: 100 Bayer Boulevard P.O. Box 915

Phone: PPD

Mobile: PPD

Fax: PPD

(Contact information changed in amendment 6)

15.8.2.2.2 Section Signature of the sponsor's medically responsible person

Name: PPD
PPD PPD

Role: PPD
PPD

Date: .....

Signature: .....

15.8.2.2.3 Section 6.4.1.1 Withdrawal criteria

[…]

- Persistent occurrence of post-infusion blood glucose > ~~500~~ 400 mg/dL based on laboratory analysis which occurred at the lowest copanlisib/placebo dose level despite optimal glucose lowering therapy (after at least one cycle of treatment).

  Definition of persistent occurrence is based on repeated post-infusion blood glucose laboratory analysis taken at different time during the whole cycle of treatment.

[…]

15.8.2.2.4 Section 7.4.2.3 Non-hematological toxicity

[…]

- Persistent occurrence of post-infusion blood glucose > ~~500~~ 400 mg/dL based on laboratory analysis which occurred at the lowest copanlisib/placebo dose level despite optimal glucose lowering therapy (after at least one cycle of treatment) requires permanent discontinuation of the study treatment (see Section 6.4.1.1).

[…]

15.8.2.2.5 Section 13 Investigator(s) and other study personnel

Sponsor's medical expert: (*changed by amendment 2 and 6*)

Name: PPD ~~-~~PPD PPD PPD

Address: ~~Rua Cancioneiro de Évora, 255 | prédio E1 | 1º andar 04708-904 São Paulo, Brazil~~100 Bayer Boulevard P.O. Box 915

Telephone: ~~-~~PPD

Mobile: PPD

Fax: PPD

16. Appendices

16.1 CYP3A4 inhibitors and inducers

A list of strong inhibitors and strong inducers of CYP3A4 (excluded drugs) is shown below.

Strong CYP3A4 inhibitors	Boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, atazanavir, tipranavir, troleandomycin, elvitegravir, danoprevir, conivaptan, boceprevir, suboxone and cobicistat
Strong CYP3A4 inducers	Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum) and enzalutamide

CYP3A4 = Cytochrome P450 isoenzyme 3A4
Source: 23, 24, 25 and 26.

16.2 Section removed by amendment 3.

See Section 15.3.1.15.

16.3 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g. light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

16.4 New York Heart Association (NYHA) Functional Classification

NYHA Class	Symptoms
Not applicable	No cardiac disease
I	No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while **at rest**. Mostly bedbound patients.

Source: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels (19)

16.5 Evaluation of tumor response

Tumor response will be evaluated according to Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (14).

Criteria for CT - based response assessment

	Target lesions (nodal)	Target lesions (extranodal)	Non-target lesions	Spleen	New lesion	Bone marrow
CR	All normal (LDi ≤ 1.5 cm)	All disappeared	All normal	Normal size	No	Normal by morphology; if indeterminate, IHC and/or PCR negative
PR	Decrease ≥ 50% in the SPD of up to 6 target measurable nodes and extranodal sites		All normal or stable	Spleen must have regressed by >50% in extent beyond normal at baseline (=value over 13 cm)	No	Not applicable
SD	Decrease < 50% from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for PD are met		All normal or stable	Normal size or stable size	No	Not applicable
PD	Individual node/lesion: LDi > 1.5 cm AND Increase ≥ 50% in the PPD from nadir AND Increase in LDi or SDi from nadir* ≥ 0.5 cm for lesions ≤ 2 cm ≥ 1.0 cm for lesions > 2 cm		New or increased	New splenomegaly: the splenic length must increase ≥ 2 cm from baseline length and be > 13 cm Recurrent splenomegaly: the splenic length must increase ≥ 2 cm from nadir length and be > 13 cm Progressive splenomegaly: the splenic length must increase by > 50% of the extent beyond normal at baseline (=value over 13 cm) and must increase ≥ 1 cm in total vertical length	Yes: New node > 1.5 cm in any axis New extranodal site > 1.0 cm in any axis (if < 1.0 cm in any axis its presence must be unequivocal and must be attributable to lymphoma)	New or recurrent involvement

CR = complete response; IHC = Immunohistochemistry; LDi = longest diameter; PD = progressive disease; PPD=product of perpendicular diameters; PR = partial response; SD =stable disease; SDi = shortest diameter; SPD = sum of the product of the diameters

* If LDi ≤ 2cm at nadir, absolute increase required for any diameter (LDi or SDi) will be 0.5 cm; if LDi > 2 cm at nadir, absolute increase required for any diameter (LDi or SDi) will be 1.0 cm

Note: In case the patient has only diffuse spleen involvement with splenomegaly careful evaluation of the spleen should be performed as the overall response will be driven by the response for splenomegaly, unless any non-target lesion(s) or a target lesion shows progression or a new lesion/new or recurrent involvement of bone marrow is present.

Criteria for PET-CT response assessment

	Target Lesions (Nodal)	Target lesions (Extranodal)	Non target lesions	Spleen	New lesions	Bone marrow
CMR	Score 1, 2, or 3 with or without a residual mass on 5PS*		N/A	N/A	None	No evidence of FDG-avid disease in marrow
PMR	Score 4 or 5 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		N/A	N/A	None	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed)
NMR	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment		N/A	N/A	None	No change from baseline
PMD	Individual target nodes/nodal masses Score 4 or 5 with an increase in intensity of uptake from baseline **and/or**	Extranodal lesions new FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	None	N/A	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g. infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	New or recurrent FDG-avid foci

CMR= complete metabolic response; FDG = Fluorodeoxyglucose; N/A = not applicable; PMR= partial metabolic response; NMR= no metabolic response, equivalent with stable disease; PMD= progressive metabolic disease, equivalent with progressive disease

Note:

- Most avid lesion will determine final score whereas volume/overall uptake and/or intensity of uptake of lesions should also be considered for response assessments.
- PET-avid lesions must have a minimum score of 4 at baseline in order to be called “PET positive”.
- Only lesions with a score ≥ 4 can be considered a valid measurable target lesion if CT scan is available.
- Lesions with score 1, 2 or 3 are considered “PET negative” and do not qualify for target lesion at baseline
- PET negative patients at BL with a positive histology can be followed-up with CT scan only.

For further details refer to the Imaging Manual.

* 5PS= 5 point score for the visual assessment of PET-CT:

Score 1 = no uptake above background
Score 2=uptake ≤ mediastinum
Score 3 =uptake > mediastinum but ≤ liver
Score 4 = uptake moderately > liver
Score 5=uptake markedly higher than liver and/or new lesions
Score X= new areas of uptake unlikely to be related to NHL

Response assessment based on PET-CT and CT/MRI scans.

Note: a PET-CT response overrides in most cases the response by CT and/or MRI alone: e.g. if PET-CT response = CMR and CT/MRI response = PR, overall response is CR (for further details refer to the Imaging Manual).

Response criteria in patients affected by Waldenström macroglobulinemia (WM):

Complete Response	• Absence of serum monoclonal IgM by immunofixation AND normal serum IgM level • Complete resolution of extramedullary disease • Normal bone marrow
Very Good Partial Response	• IgM M protein still detectable by immunofixation BUT ≥ 90% reduction in serum IgM level from baseline • Complete resolution of extramedullary disease • No new signs/symptoms of active disease
Partial Response	• IgM M protein still detectable by immunofixation BUT ≥ 50% and < 90% reduction in serum IgM level from baseline • Reduction in extramedullary disease • No new signs/symptoms of active disease
Minor Response	• IgM M protein still detectable by immunofixation BUT ≥ 25% and < 50% reduction in serum IgM level from baseline • No new signs/symptoms of active disease
Stable Disease	• IgM M protein still detectable by immunofixation BUT < 25% reduction and < 25% increase in serum IgM level from baseline • No new signs/symptoms of active disease
Progressive Disease	**After Partial Response:** • ≥ 25% increase in serum IgM level from lowest nadir (an absolute value of 5 g/L is required if IgM level is the only criterion) • OR • Progression in clinical features (signs/symptoms) attributable to disease **After Complete Response:** • Reappearance of IgM M protein OR • Recurrence of bone marrow involvement, extramedullary disease, symptoms attributable to disease

IgM = immunoglobulin M
Source: Adapted from Owen RG et al, 2013 (13)

16.6 Quality of life questionnaire: FLymSI-18 *section removed*

Appendix removed by amendment 6 (Section 15.5.1.13).

16.7 Glomerular filtration rate

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the estimated glomerular filtration rate (GFR), calculated using the Modification of Diet in Renal Disease (MDRD) study abbreviated formula.

This equation of 4 variables (serum creatinine level [SCR], age, sex, and ethnicity) is recommended by the National Kidney Foundation for use in individuals 18 years or older.

The formula is as follows:

$$GFR\ (mL/min/1.73m^2) = k \times 186 \times SCR^{-1.154} \times age^{-0.203}$$

where k = 1 (men) or 0.742 (women), GFR indicates glomerular filtration rate, and serum creatinine level is measured in mg/dL.

NOTE: This equation should be used only with those creatinine methods that have not been recalibrated to be traceable to isotope dilution mass spectroscopy (IDMS).

If standardized IDMS-traceable creatinine assay is used, please use the calculator provided in the following link: http://www.kidney.org/professionals/kdoqi/gfr_calculator.

The above result should be multiplied by 1.212 for African-Americans.

Patients with a baseline GFR < 40 mL/min calculated by this method will not be allowed to participate in the study. If not on target, this evaluation may be repeated once after at least 24 hours either according to the MDRD abbreviated formula or by 24-hour sampling. If the later result is within an acceptable range, it may be used to fulfill the inclusion criteria instead.

For further information on assessing renal function using GFR estimates, see references 20, 21, 22.

16.8 The average Glycemic Index of common foods derived from multiple studies by different laboratories *section removed*

Appendix removed by amendment 6 (Section 15.5.1.1)