Document Type:	Clinical Study Protocol
Official Title:	A Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed indolent B-cell non-Hodgkin's lymphoma (iNHL) – CHRONOS-3
NCT Number:	NCT02367040
Document Date:	09-Feb-2023

Cover page of the integrated protocol

A Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed indolent B-cell non-Hodgkin's lymphoma (iNHL) – CHRONOS-3

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

- **Original protocol,** Version 1.0, dated 21 MAY 2014
- **Amendment 01** (global amendment described in Section 13.1) forming integrated protocol Version 2.0, dated 23 JAN 2015
- **Amendment 06** (global amendment described in Section 13.2) forming integrated protocol Version 3.0, dated 18 FEB 2016
- **Amendment 07** (global amendment described in Section 13.3) forming integrated protocol Version 4.0, dated 28 JUL 2016
- **Amendment 09** (global amendment described in Section 13.4) forming integrated protocol Version 5.0, dated 02 FEB 2018
- **Amendment 10** (global amendment described in Section 13.5) forming integrated protocol Version 6.0, dated 08 OCT 2019
- **Amendment 11** (global amendment described in Section 13.6) forming integrated protocol Version 7.0, dated 22 MAY 2020
- **Amendment 12** (global amendment described in Section 13.7) forming integrated protocol Version 8.0, dated 09 FEB 2023

Amendments not included in the consecutive numbering of amendments are local amendments described in Section 13.8 (Country/region-specific requirements) of this integrated global protocol. These are:

- **Amendment 02**, dated 11 MAY 2015 (local amendment valid for Ireland, Germany and Belgium only)
- **Amendment 03**, dated 25 AUG 2015 (local amendment valid for France only)
- **Amendment 04**, dated 01 SEP 2015 (local amendment valid for Denmark only)
- **Amendment 05**, dated 13 OCT 2015 (local amendment valid for Turkey only)
- **Amendment 08**, dated 18 APR 2017 (local amendment valid for Japan only)

Title page

A Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed indolent B-cell non-Hodgkin's lymphoma (iNHL) – CHRONOS-3

Copanlisib and rituximab in relapsed iNHL

Test drug:	BAY 80-6946 / copanlisib		
Clinical study phase:	III	Date:	09 FEB 2023
EudraCT no.:	2013-003893-29	Version no.:	8.0
EU CT no.	2023-503702-37		
Study no.:	BAY 80-6946 / 17067		
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 100 Bayer Boulevard, P.O.box 915 Whippany, NJ, USA Telephone no.: 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 integrated 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.

Synopsis

Title	**A Phase III, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of copanlisib in combination with rituximab in patients with relapsed indolent B-cell non-Hodgkin's lymphoma (iNHL) – CHRONOS-3**
Short title	Copanlisib and rituximab in relapsed iNHL
Clinical study phase	III
Rationale	Rituximab is approved for the treatment of CD20+ relapsed or refractory iNHL and is widely used as a single drug or in combination regimens. Retreatment with rituximab alone or in combination has been shown to be feasible and efficacious. Additional therapeutic options that incorporate novel active drugs are needed to further improve outcomes in relapsed iNHL including augmenting the efficacy of rituximab retreatment. Considering the pre-clinical profile of copanlisib and the promising preliminary efficacy data from the Phase I and II studies, it is expected that in comparison to rituximab with placebo, copanlisib in combination with rituximab will lengthen progression-free survival (PFS) in patients with relapsed iNHL.
Study objective(s)	The primary objective of this study is: To evaluate whether copanlisib in combination with rituximab is superior to placebo in combination with rituximab in prolonging progression-free survival (PFS) in patients with relapsed iNHL who have received one or more lines of treatment, including rituximab, and who either had a treatment-free interval of ≥ 12 months after completion of the last rituximab-containing treatment, or who are unwilling to receive chemotherapy/for whom chemotherapy is contraindicated on reason of age, comorbidities, and/or residual toxicity The secondary objectives of this study are to evaluate: • The following characteristics of disease-related symptoms: "time to deterioration" and "time to improvement" • Other radiological and clinical indicators of treatment efficacy • Safety and tolerability of copanlisib The other objectives of this study are to evaluate: • Pharmacokinetics • Biomarkers • Quality of life
Test drug(s)	Copanlisib
Name of active ingredient	Copanlisib / BAY 80-6946 / phosphatidylinositol-3 kinase (PI3K) inhibitor
Treatment administered	Copanlisib in combination with rituximab
Dose(s)	Copanlisib starting dose: 60 mg. Dose reductions to 45 mg and further to 30 mg are possible, should toxicities occur. Dosing will be administered on Days 1, 8 and 15 of each 28-day cycle. Copanlisib will be administered before rituximab. Rituximab: 375 mg/m^2 body surface weekly during Cycle 1 on Days 1, 8, 15 and 22, and then on Day 1 of Cycles 3, 5, 7 and 9.

Route of administration	Intravenous (IV) infusions
Duration of treatment	Copanlisib treatment will be continued until disease progression (PD) (determined locally) as defined in the 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]), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment. Rituximab treatment will be continued until the same criteria as defined for copanlisib are met, for a maximum of 8 infusions (until Cycle 9).
Reference drug(s)	Placebo
Name of active ingredient	Not applicable
Treatment administered	Placebo in combination with rituximab
Dose(s)	Placebo starting dose: 60 mg. Dummy dose reductions to 45 mg and further to 30 mg are possible should toxicities occur. Dosing will be administered on Days 1, 8 and 15 of each 28-day cycle. Placebo will be administered before rituximab. Rituximab: 375 mg/m^2 body surface weekly during Cycle 1 on Days 1, 8, 15 and 22, and then on Day 1 of Cycles 3, 5, 7 and 9.
Route of administration	IV infusions
Duration of treatment	Placebo treatment will be continued until PD (determined locally), as defined in the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Owen Criteria for patients with WM), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment. Rituximab treatment will be continued until the same criteria as defined for placebo are met, for a maximum of 8 infusions (until Cycle 9).
Indication	Relapsed indolent B-cell non-Hodgkin's lymphoma
Diagnosis and main criteria for inclusion	Histologically confirmed diagnosis of iNHL in CD20 positive patients with histological subtype limited to: • Follicular lymphoma (FL) G1-2-3a • Small lymphocytic lymphoma (SLL) with absolute monoclonal lymphocyte count <$5x10^9$/L at study entry • Lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia (LPL/WM) • Marginal zone lymphoma (MZL) (splenic, nodal, or extra-nodal) Patients must have relapsed (recurrence after complete response or presented progression after partial response) after the last rituximab-, rituximab biosimilars-, or anti-CD20 monoclonal antibody (e.g., obinutuzumab)-containing therapy (other previous treatment lines after rituximab are allowed). A previous regimen is defined as one of the following: at least 2 months of single-agent therapy (less than 2 months of therapy is allowed for patients who responded to single-agent rituximab, rituximab biosimilars, or anti-CD20 monoclonal antibody); at least 2 consecutive cycles of polychemotherapy; autologous transplant; radioimmunotherapy. Previous exposure to PI3K is acceptable (except to copanlisib) provided there is no resistance. Patients with prior intolerance to PI3K inhibitors other than copanlisib are eligible. Non-WM patients must have at least one bi-dimensionally measurable lesion (that has not been previously irradiated) according to the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: 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 ≥ 2x 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 for central pathology (obtained within 5 years of the consent date) at Screening. Adequate baseline laboratory values as assessed within 7 days before starting study treatment. Left ventricular ejection fraction ≥ 45%. Patients must either • have had a progression-free and treatment-free interval of ≥ 12 months after completion of the last rituximab-containing treatment OR • be considered unfit to receive chemotherapy on reason of age, concomitant morbidities, and/or residual toxicity from previous treatments, or unwillingness to receive chemotherapy. These patients must also have had a progression-free and treatment free interval of ≥ 6 months after completion of the last rituximab-containing treatment. Patients in whom chemotherapy is contraindicated are defined by one of the following features: o Age ≥ 80 years o Age < 80 years and at least 1 of the following conditions: ▪ at least 3 grade 3 CIRS-G comorbidities OR ▪ at least 1 grade 4 CIRS-G comorbidity (if considered compatible with participation in the study).
Main criteria for exclusion	Follicular lymphoma grade 3b or transformed disease, or chronic lymphocytic leukemia. Progression-free interval or treatment-free interval of less than 12 months since the last rituximab-, rituximab biosimilars-, or anti-CD20 monoclonal antibody (e.g., obinutuzumab)-containing treatment (including maintenance with these drugs). For patients considered unwilling/unfit to receive chemotherapy: progression-free interval or treatment-free interval of less than 6 months since the last rituximab-, rituximab biosimilars-, or anti-CD20 monoclonal antibody-containing treatment (including maintenance with these drugs), as assessed by the investigator. History or concurrent condition of interstitial lung disease and/or severely impaired lung function. Known lymphomatous involvement of the central nervous system. Patients with HbA1c > 8.5% at Screening. Known history of human immunodeficiency virus (HIV) infection. Hepatitis B (HBV) or hepatitis C (HCV). Patients positive for HBsAg or HBcAb will be eligible if they are negative for HBV-DNA, these patients should receive prophylactic antiviral therapy. 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. Prior treatment with copanlisib.
Study design	A randomized, double-blind, placebo-controlled, 2-arm phase III study to evaluate the efficacy and safety of copanlisib in combination with rituximab, in comparison to placebo in combination with rituximab in patients with relapsed iNHL. Approximately 450 FL and other iNHL patients who meet the eligibility criteria will be randomly assigned in a 2:1 ratio to the double-blinded treatment arms: copanlisib plus rituximab or placebo plus rituximab, respectively. Patients will be stratified by a combination of NHL histology (FL vs. other iNHL), inclusion criteria (progression-free and treatment-free interval of $\geq$ 12 months after the last rituximab-containing treatment vs. unwilling/unfit to receive chemotherapy), presence of bulky disease (yes vs. no) and previous treatment with PI3K inhibitors (yes vs. no). If the patient fulfills both entry criteria, the criterion "unwilling/unfit to receive chemotherapy" should be selected. After the 30th randomized patient has completed the first cycle of treatment, the Data Monitoring Committee will review the unblinded safety data accumulated up to that time and provide recommendation on whether it is safe to continue in the combination arm at the initial dose of copanlisib. The investigators, patients and the sponsor will remain blinded.
Methodology	The primary efficacy variable is PFS, defined as the time (in days) from randomization to PD as assessed by central review or death from any cause (if no progression is documented). Secondary efficacy variables are objective tumor response rate (ORR), duration of response (DOR), complete response rate (CRR), time to progression (TTP), overall survival (OS), time to improvement and the time to deterioration in disease-related symptoms - physical (DRS-P) of at least 3 points as measured by the FLymSI-18 questionnaire (FLymSI = NCCN-FACT Lymphoma Symptom Index). Other efficacy variables are FLymSI-18 subscale, total score analyses and time to onset of physical symptoms of lymphoma based on DRS-P, and ECOG performance status. The study is composed of the following periods: Screening, Treatment, Safety follow-up, Active follow-up (if applicable) and Survival follow-up. Patients randomized to copanlisib + rituximab arm will receive 60 mg copanlisib IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle, and 375 mg/m^2 rituximab during Cycle 1 on Days 1, 8, 15 and 22, and then on Day 1 of Cycles 3, 5, 7 and 9. Patients randomized to placebo + rituximab arm will receive placebo IV infusion on Days 1, 8 and 15 of each 28-day treatment cycle, and 375 mg/m^2 rituximab during Cycle 1 on Days 1, 8, 15 and 22, and then on Day 1 of Cycles 3, 5, 7 and 9. 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 (window of +5 days allowed) after the last administration of study treatment. Patients who discontinue study treatment because of PD will enter Safety follow-up period and patients who 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 follow-up tumor assessments performed locally 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 intervals during the Survival follow-up period (up to 7 years after the last patient started study treatment), except for patients who object to follow-up data collection. Study participants may be offered the option to transition into a roll-over study (ROS) or receive further treatment through any other mechanism in accordance with local legal and compliance rules. Safety evaluations will be done at Screening, on the first day of study treatment administration (Cycle 1 Day 1), at each clinic visit during treatment, and at the safety follow-up visit. The first radiological tumor assessments with IV (and oral, if indicated, per Imaging Manual) contrast-enhanced computed tomography / magnetic resonance imaging (CT/MRI) scans of neck, chest, abdomen and pelvis 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 the screening CT/MRI (if a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the screening). The method chosen at baseline 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 period as well as during the Active follow-up period, tumor assessments with the same modality will be performed every 8 weeks (± 7 days) during Year 1, every 12 weeks (± 7 days) during Year 2, and every 24 weeks (± 7 days) during Year 3 and onwards, starting from Cycle 1 Day 1. CT/MRI scans are not required at the EOT visit if the patient discontinues because of PD which has been radiologically confirmed within the 4 weeks preceding the EOT. Central independent blinded review of tumor scans will not be performed. 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. 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. Biopsies taken up to 28 days prior to first dose are acceptable. If the baseline biopsy is positive for lymphoma infiltration at Screening, it will be mandatory to perform it 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. No central review of bone marrow biopsy will be performed during treatment or Active follow-up.
Type of control	Inactive control: placebo
Number of patients	Assuming 30% screening failure rate, 643 patients (including FL and other iNHL) need to be enrolled to have 450 randomized patients. Patients will not be replaced.
Primary variable	The primary variable is PFS, defined as the time (in days) from randomization to PD as assessed by central review or death from any cause (if no progression is documented).
Plan for statistical analysis	**Efficacy analysis**: The primary efficacy variable is PFS, as assessed by central review in the full analysis set (FAS), which is defined as all patients who were randomized. Patients alive without documented progression at the time of analysis will be censored at the date of their last tumor evaluation. Copanlisib in combination with rituximab vs. placebo in combination with rituximab will be compared in the

	FAS, using a one-sided log-rank test stratified by the same factors as used for randomization: FL vs. other iNHL histologies and progression-free and treatment-free interval of ≥ 12 months after completion of the last rituximab-containing treatment vs. unwilling/unfit to receive chemotherapy. Kaplan-Meier estimates and survival curves will also be presented for each treatment group, as well as the hazard ratios with their confidence intervals. Separate statistical test strategies will be conducted for the United States and Europe For the US, if the null hypothesis in the primary efficacy variable is rejected in the FAS, PFS in the combined FL and MZL population, ORR in the combined FL and MZL population, time to deterioration and time to improvement in DRS-P in the combined FL and MZL population will be tested sequentially. For the EU, if the null hypothesis in the primary efficacy variable is rejected in the FAS, ORR in the FAS population, time to deterioration and time to improvement in DRS-P in the FAS population will be tested sequentially. OS, TTP, DOR, time to deterioration and time to improvement in DRS-P of at least 3 points will be analyzed using a stratified log-rank test similar to that for the primary endpoint, PFS. ORR and CRR will be analyzed using the Cochran-Mantel-Haenszel test. The tests will be adjusted for the same stratification factors as used for PFS. Other efficacy endpoints will be analyzed descriptively. **Safety analysis**: Safety variables will be summarized by means of descriptive statistics and/or frequency tables as appropriate. Summaries will be given by treatment group.

Table of contents

Table of tables

Table of figures

List of abbreviations

Ab	Antibody
AE	Adverse event
AESI	Adverse event of special interest
Ag	Antigen
AKT	Protein kinase B
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
BfS	Federal Office for Radiation Protection
BP	Blood pressure
BTK	Bruton's tyrosine kinase
BUN	Blood urea nitrogen
C	Cycle
CBC	Complete blood count
CD	Cluster of differentiation
c-KIT	Proto-oncogen c-KIT (CD117)
CHGRAO	China Human Genetic Resources Administration Office
CHOP	Cyclophosphamide, hydroxydaunorubicin, vincristine, prednisolone
CI	Confidence interval
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum drug concentration
CMV	Cytomegalovirus
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CRR	Complete response rate
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVP	Cyclophosphamide, vincristine, prednisolone
CYP3A4	Cytochrome P450 isoenzyme 3A4
D	Day
dL	Deciliter
DLBCL	Diffuse large B-cell lymphoma
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
DPP4	Dipeptidyl peptidase-4
DRS-E	Disease-related symptoms – emotional (subscale)
DRS-P	Disease-related symptoms – physical (subscale)
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
e.g.	For example (*exempli gratia*)
EGFR	Epidermal growth factor receptor

EOT	End of treatment
ePRO	Electronic patient-reported outcome
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin-fixed paraffin-embedded
FL	Follicular lymphoma
FLIPI	Follicular lymphoma International Prognostic Index
FLymSI-18	NCCN-FACT Lymphoma Symptom Index-18
FND	Fludarabine, mitoxantrone, dexamethasone
FSH	Follicle stimulating hormone
FU	Follow-up
FWB	Functional and well-being (subscale)
g	Gram
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
GPV	Global Pharmacovigilance
h	Hour(s)
Hb	Hemoglobin
HbA1c	Glycated hemoglobin
HBcAb	Hepatitis B core antibody
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCG	β-human chorionic gonadotropin
HCV	Hepatitis C Virus
HCVAb	Anti-HCV antibody
HDL	High-density lipoprotein
HER	Human epidermal growth factor receptor
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonization
IDMS	Isotope dilution mass spectroscopy
i.e.	That is (*id est*)
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
IRB	Institutional review board
ISO	International Organization for Standardization
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS	Interactive Voice Response System

IWRS	Interactive Web Response System
kg	Kilogram
LDH	Lactate dehydrogenase
LDi	Longest diameter
LDL	Low-density lipoprotein
LPL	Lymphoplasmacytoid lymphoma
LVEF	Left ventricular ejection fraction
M-1	Metabolite 1
MALT	Marginal-zone lymphoma of mucosa-associated lymphoid tissue
MD	Medical Doctor
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minutes
mmHg	Millimeter of mercury
mL	Milliliter
MR	Minor response
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
MUGA	Multiple gated acquisition
MZL	Marginal-zone lymphoma
NaOH	Sodium hydroxide
NCCN	National Comprehensive Cancer Network
NCCN-FACT	National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy
NCI	National Cancer Institute
NHL	Non-Hodgkin's Lymphoma
NIP	Non-infectious pneumonitis
nM	Nanometer
NMZL	Nodal marginal-zone lymphoma
NYHA	New York Heart Association
OI	Opportunistic infection
ORR	Objective tumor response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Disease progression
PDGFR	Platelet-derived growth factor receptor
PDK1	Phosphoinositide-dependent kinase 1
PET	Positron emission tomography
PFS	Progression-free survival
pH	Negative log of hydrogen ion concentration
PI-4,5-P2	Phosphatidylinositol-4,5-bisphosphate
PID	Patient identification number
PI3K	Phosphatidylinositol-3-kinase
PIP3	Phosphatidylinositol-3,4,5-trisphosphate
PK	Pharmacokinetic(s)
PPD	Product of perpendicular diameters
PR	Partial response
PRO	Patient-reported outcomes
PT	Prothrombin time
PTEN	Phosphatase and tensin homolog

PTT	Partial thromboplastin time
PV	Pharmacovigilance
QoL	Quality of life
RBC	Red blood cell count
RNA	Ribonucleic acid
ROS	Roll-over study
RR	Response rate
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SCR	Serum creatinine
SDi	Shortest diameter
SFU	Safety follow-up
SGLT-2	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
SUSAR	Suspected, unexpected, serious adverse reaction
TEAE	Treatment-emergent adverse event
TSE	Treatment side effects (subscale)
TTP	Time to progression
ULN	Upper limit normal
UPCR	Urine protein to creatinine ratio
vs.	Versus
VEGF	Vascular endothelial growth factor
VGPR	Very good partial response
WBC	White blood cell count
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary
WM	Waldenström macroglobulinemia
WOCBP	Woman of childbearing potential

Definitions of terms

Throughout this protocol, prior rituximab therapy covers treatment with rituximab, rituximab biosimilars, or anti-CD20 monoclonal antibody (e.g. obinutuzumab).

Lugano Classification – criteria for tumor response assessment as defined in the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma (27).

Owen Criteria – criteria for tumor response assessment applicable for patients with Waldenström macroglobulinemia (WM), as defined in the Response Assessment in Waldenström macroglobulinemia: update from the VIth International Workshop (35).

1. Introduction

1.1 Background

Non-Hodgkin's lymphomas (NHLs) are a heterogeneous group of lymphoproliferative malignancies arising either from B lymphocytes (85–90%) or from T/NK lymphocytes. These malignancies typically originate in the lymph nodes, but can involve almost any organ tissue (1).

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 (1).

NHLs can be divided according to their clinical behavior into two main prognostic groups: indolent NHL and aggressive NHL. Aggressive lymphomas are characterized by an aggressive clinical course and may evolve into a lethal presentation if not immediately treated. However, with modern chemo-immunotherapy regimens and stem cell transplant consolidation a definitive cure can be reached in 50-60% of patients. Indolent NHLs have a relatively good prognosis with a median survival longer than 10 years, but they are incurable with current available therapeutic options, especially in advanced stages. While they are highly responsive to standard chemotherapy regimens and to radiotherapy, their natural history is characterized by a continuous pattern of relapses, which can be generally treated with success, but the time to next relapse progressively decreases each time, finally evolving into a refractory disease or into a transformation into an aggressive histologic type. The risk of transformation has been estimated to be 2-3% per year.

Indolent NHLs encompass the following low-grade histologic subtypes of B-cell NHL included in the 2008 WHO classification of lymphoid neoplasm: 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) (3). FL is the second most common subtype of NHL (22% of newly diagnosed cases) (4), 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.

Optimal treatment of advanced stages of indolent NHL is controversial because of low cure rates with the current therapeutic options. The first-line standard therapy includes rituximab, usually administered together with cytotoxic combinations (CHOP, CVP) or single agents (alkylators, e.g. bendamustine, or purine nucleoside analogs such as fludarabine or 2-chlorodeoxyadenosine).

There is no acknowledged standard treatment for patients with recurrent disease. As long as disease appears to be responsive to rituximab (treatment-free intervals of > 6 months after the previous rituximab-containing treatment), a rituximab-based chemoimmunotherapy using non-cross-resistant cytotoxic agents would be administered at the next relapse.

While the good tolerability of rituximab makes repeated administration possible, alkylating agents and purine nucleoside analogs can progressively reduce the bone marrow reserve (5)

and cause secondary malignancies (6, 7). Doxorubicin is associated with dose-dependent cardiac toxicity. Cardiac abnormalities can occur in patients treated with doxorubicin for lymphoma in the absence of congestive heart failure, even in patients who received moderate anthracycline doses (8, 9). More than half of all lymphomas occur in patients older than 65 years (10). Acute and residual toxicities of chemotherapy are particularly important in an elderly patient population because they interfere with the ability of the patient to tolerate treatment at optimum dose and schedule, and reduce the number of options for subsequent treatments. In addition, these elderly patients will frequently have various comorbidities, which further limit their ability to cope with toxicity.

As patients will invariably relapse, further active and well-tolerated agents are needed. Copanlisib has a molecular target and mechanism of action different from those of cytotoxic agents, a non-overlapping safety profile, and single-agent activity in patients with relapsed/refractory iNHL. Therefore, copanlisib could represent an adequate partner for rituximab in a cytotoxic-free combination that could be offered to patients expected to derive a benefit from rituximab-based treatment.

1.1.1 Copanlisib (BAY 80-6946)

The phosphatidylinositol 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway is one of the prominent pathways that promote cellular survival and constitutively is activated in many types of cancers (11, 12). Class I PI3K is downstream of most cancer-associated tyrosine kinase growth factor receptors (such as epidermal growth factor receptor [EGFR]/ human epidermal growth factor receptor [HER], insulin-like growth factor 1 receptor [IGF-1R], platelet-derived growth factor receptor [PDGFR], vascular endothelial growth factor [VEGF], c-KIT or mesenchymal epithelial transition factor [Met]). Once PI3K is activated, it activates Pleckstrin Homology Domain (PH-domain) proteins including 3-phosphoinositide-dependent protein kinase-1 (PDK-1) and AKT as well as guanine nucleotide exchange factor by generation of phosphoinositol-3-phosphate (PIP3). The tumor suppressor phosphatase and tensin homolog (PTEN) antagonizes PI3K by dephosphorylating PIP3, and its activity is frequently lost in cancer cells (13). In addition to mediating cancer associated signals, activation of the PI3K/AKT pathway is also one of the major mechanisms by which tumors escape from, and become resistant to, the effects of cytotoxic chemotherapy, targeted agents such as trastuzumab (12), and radiation (12, 14).

Four of these PI3K isoforms (PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ) are categorized as class I enzymes because they can use phosphatidylinositol-4,5-bisphosphate (PI-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. The clinical relevance of PI3K inhibition has been demonstrated by the activity of idelalisib (PI3Kδ-targeted compound) in patients with refractory iNHL (15).

As expected from its pharmacological properties, copanlisib, a small molecule PI3K inhibitor, showed excellent anti-tumor activity in pre-clinical models with up-regulated PI3Kα pathway. However, copanlisib not only inhibits PI3Kα with IC_{50} of 0.5 nM, but also PI3Kδ with IC_{50} of 0.7 nM. Copanlisib also potently regulates nuclear localization of the forkhead family members resulting in the induction of transcriptional programs that lead to rapid cell death by

apoptosis. In addition, copanlisib exhibits anti-angiogenesis activity by effectively blocking VEG-stimulated endothelial cell proliferation (for details see Investigator's Brochure [IB])**.**

1.1.2 Clinical experience

Copanlisib is currently under investigation in various trials enrolling cancer patients.

As of 01 FEB 2016, approximately 627 patients with advanced cancer have been treated with copanlisib in Phase I, Phase II and Phase III clinical trials as a single agent or in combination with other agents.

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 (MTD) 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. In AUG 2013, the enrollment in study 12871 was completed. Dose-limiting toxicity was observed at 1.2 mg/kg with MTD established at 0.8 mg/kg when administered intravenously (IV) over 1 h, on Days 1, 8 and 15 of every 28 days as a single agent. The flat dose of 65 mg correlates with 0.8 mg/kg (MTD level) dose and was selected in order to control copanlisib exposure in obese patients.

In the NHL expansion cohort of Study 12871, a total of 6 non-diabetic patients with FL and 3 patients with diffuse large B-cell lymphoma (DLBCL) were treated, all initially dosed at 0.8 mg/kg. As of 01 FEB 2014, according to investigator's assessment, 7 patients (77.8%) with NHL experienced partial response (PR) as best overall response and 2 patients (22.2%) had progressive disease. Partial responders included 6 patients with FL and 1 patient with DLBCL. A retrospective independent review performed in 8 of the 9 NHL patients (excluding the clinical assessment) concluded that a complete response (CR) was the best overall response in the 2 FL long-term responders (assessed as partial responders by the investigators).

The most common treatment-emergent adverse events (TEAEs), regardless of seriousness, severity, and causality, occurring in ≥20% of the 57 subjects 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%).

Pharmacokinetic (PK) results indicate nearly dose proportional increase in maximum concentration (C_{max}) and area under curve ($AUC_{(0-25)}$) values in the 0.1 to 1.2 mg/kg dose range and lack of significant accumulation after once weekly dosing. At the maximum tolerated dose of 0.8 mg/kg, the geometric mean half-life, ($t_{1/2}$) was approximately 36-42 h (preliminary data), supporting a once weekly dosage regimen. To date, one metabolite, the morpholinone derivate M-1, showing approximately 4 to 16% of the $AUC_{(0-25)}$ of copanlisib has been identified and is currently being investigated in clinical studies. Results of a preliminary population PK analysis of copanlisib in studies 12871, 15205 (Phase I monotherapy study in Japanese subjects) and Phase II study 16349 (part A) showed no correlation between body weight and copanlisib clearance, indicating that body weight-based dosing does not reduce between-subject variability in copanlisib PK. The use of a fixed dose regimen for all patients was therefore considered suitable. Using the available data on preliminary safety and efficacy of copanlisib monotherapy, a fixed dose of 60 mg copanlisib has been defined as the recommended dose for use in all patients in future clinical studies.

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%). A t 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.

1.2 Rationale for the study

Rituximab is approved for the treatment of CD20+ relapsed or refractory iNHL, and is widely used as a single drug or in combination regimens (16-20). Retreatment with rituximab alone or in combination has been shown to be feasible and efficacious (21, 22) also in a large comparative trial involving rituximab retreatment in relapsed patients with FL initially responsive to rituximab-containing therapy (23).

To further improve outcomes in relapsed iNHL including augmenting the efficacy of rituximab retreatment, additional therapeutic options that incorporate novel active drugs are needed.

Considering the pre-clinical profile of copanlisib and the promising preliminary efficacy data from the Phase I study 12871 and the ongoing Phase II study 16349, it is expected that in comparison to rituximab with placebo, copanlisib in combination with rituximab will lengthen progression-free survival (PFS) in patients with relapsed iNHL who have received one or more lines of treatment, have been exposed to rituximab and who either had a treatment-free interval of ≥ 12 months after completion of the last rituximab-containing treatment, or who are unwilling to receive chemotherapy/for whom chemotherapy is contraindicated.

The prolonged rituximab treatment (4 weekly infusions + 4 bimonthly) has proved to be associated with a longer event-free survival and response duration compared to the standard 4 weekly infusions schedule, without additional clinical toxicity in both relapsed iNHL (24, 25) and as front line therapy (26), and this is the reason why it was chosen as a reference drug in this study.

1.3 Benefit-risk assessment

The proposed indication is a serious and, in the long-term, life-threatening disease. Advanced iNHL can be controlled with the current treatments for a relatively long time, but remains an incurable disease of which the patient would ultimately die. While at the early stages of advanced iNHL effective treatments are available (e.g. rituximab + CHOP and rituximab + bendamustine), the efficacy of subsequent lines of treatment tends to diminish, with progressively decreasing response rate and PFS. There are no guideline recommendations, or widely accepted standards of care for patients beyond first relapse. The treatment given depends on patient's condition, physician's preference, and availability of drugs not already used with other in previous lines of treatment. In patients with limited ability to cope with toxicity the number of options is further reduced. There is therefore a need for drugs with new targets and mechanisms of action that are effective and have a safety profile different from that of drugs used in earlier lines of treatment.

Copanlisib showed activity in patients with relapsed or refractory iNHL (see Section 1.1.2). Hyperglycemia and hypertension, the most frequently observed and expected toxicities with copanlisib, proved to be manageable, without CTCAE Grade 4 events. Toxicities will be carefully monitored during the course of the study with a detailed and tailored program of management. Rituximab and copanlisib have different targets and mechanisms of action, and their safety profiles indicate that no major overlapping toxicities are expected. Furthermore, the safety and feasibility of combination will be evaluated after the first 30 patients have been treated for at least one cycle. A Data Monitoring Committee (DMC) will be instituted to ensure the safety of patients participating in the study.

Considering the existing evidence of the efficacy of copanlisib treatment in patients with iNHL and the manageable toxicities, the benefit/risk ratio of the copanlisib treatment is assessed as positive.

2. Study objectives

The primary objective of this study is:

- To evaluate whether copanlisib in combination with rituximab is superior to placebo in combination with rituximab in prolonging progression-free survival (PFS) in patients with relapsed iNHL who have received one or more lines of treatment, including rituximab, and who either had a treatment-free interval of ≥ 12 months after completion of the last rituximab-containing treatment, or who are unwilling to receive chemotherapy/for whom chemotherapy is contraindicated on reason of age, comorbidities, and/or residual toxicity

The secondary objectives of this study are to evaluate:

- The following characteristics of disease-related symptoms: “time to deterioration” and “time to improvement”
- Other radiological and clinical indicators of treatment efficacy
- Safety and tolerability of copanlisib

The other objectives of this study are to evaluate:

- Pharmacokinetics
- Biomarkers
- Quality of life

3. Investigator 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 sheet before patient recruitment may start at the respective center. Likewise, all protocol amendments/integrated protocols must be signed and dated by the principal investigator 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 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 or under supervision of the study statistician. 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.

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 pathology review

The retrospective confirmation of histopathological diagnosis will be performed centrally.

4. Study design

Design overview

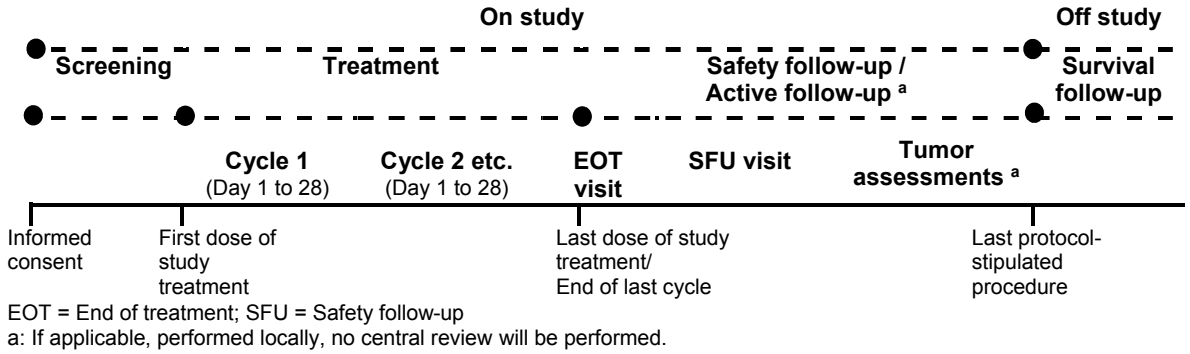
This is a randomized, double-blind, placebo-controlled, two-arm, Phase III study to evaluate efficacy and safety of copanlisib in combination with rituximab, in comparison to placebo in combination with rituximab, in patients with relapsed iNHL.

Approximately 450 (including FL and other iNHL) patients who meet the eligibility criteria will be randomly assigned in a 2:1 ratio to one of the double-blinded treatment arms: copanlisib plus rituximab or placebo plus rituximab. Patients will be stratified by a combination of NHL histology (FL vs. other iNHL), inclusion criteria (progression-free and treatment-free interval of ≥ 12 months after completion of the last rituximab-containing treatment vs. unwilling/unfit to receive chemotherapy), presence of bulky disease (yes vs. no) and previous treatment with PI3K inhibitors (yes vs. no). For details see Section 6.3.

After the 30th patient has completed the first cycle of treatment the Data Monitoring Committee will review the unblinded safety data of all patients treated up to that timepoint and provide recommendation on whether it is safe to continue recruitment into the combination arm at the initial dose of copanlisib. The investigators, patients and the sponsor will remain blinded.

The overview of study periods is presented in Figure 4–1.

Figure 4–1 Study periods



EOT = End of treatment; SFU = Safety follow-up
a: If applicable, performed locally, no central review will be performed.

The start of the study period is defined by signing of the informed consent form (ICF). Patients who meet the eligibility criteria as defined in Section 5.1 will be randomized to one of the two arms and will start treatment (see Section 6.3).

The start of the treatment period is defined by the first administration of study treatment. Treatment with copanlisib or placebo will be continued until the occurrence of PD (determined locally) as defined in the Lugano Classification (for patients with WM according to the Owen Criteria), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment (see Section 5.2.1.1) For the definitions of Lugano Classification and Owen Criteria please refer to the Definitions of terms. Rituximab treatment will be continued until the same criteria as defined for copanlisib are met, for a maximum of 8 infusions (until Cycle 9).

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 (window of +5 days allowed) after the last administration of study treatment.

Patients who discontinue study treatment because of PD will enter the Safety-follow up period and patients who discontinue study drug 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 performed locally 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. During the Active follow-up period, serious adverse events (SAEs) and AEs assessed as related to study procedures by the investigator will be reported. AE pages of the electronic Case Report Form (eCRF) and the SAE Form should be completed in the usual manner and forwarded to the applicable sponsor's PV department.

All patients will be followed off study for overall survival at 3-monthly intervals during the Survival follow-up period (up to 7 years after the last patient started study treatment), except for patients who object to follow-up data collection. During this period, patients are not considered to be "on-study".

Safety evaluations will be done at Screening, on the first day of study treatment administration (Cycle 1 Day 1), at each clinic visit during the 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 6.4.1).

The first radiological tumor assessments with IV (and oral, if indicated, per Imaging Manual) contrast-enhanced CT/MRI scans of neck, chest, abdomen and pelvis 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 the screening CT/MRI (if a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the screening). The method chosen at baseline 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 (for further details see Section 7.3.2).

During the treatment period as well as during the Active follow up period tumor assessments with the same modality will be performed every 8 weeks (± 7 days) during Year 1, every 12 weeks (± 7 days) during Year 2, and every 24 weeks (± 7 days) during Year 3 and onwards, starting from Cycle 1 Day 1. CT/MRI scans are not required at the EOT visit if the patient discontinues due to PD, which has been radiologically confirmed within the 4 weeks preceding EOT.

The response assessment will be done according to the Lugano Classification, and, for patients with WM, according to the Owen Criteria. Central independent blinded review of tumor scans will not be performed.

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. 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. Biopsies taken up to 28 days prior to first dose are acceptable. If the baseline biopsy is positive for lymphoma infiltration at Screening, it will be mandatory to perform it again to confirm the first CR, and also at the investigator's discretion if clinical evaluation leads to suspicion of bone marrow infiltration without further radiological findings. No central review of bone marrow biopsy will be performed during treatment or Active follow-up.

Tumor tissue collection will be mandatory at Screening for central pathology review.

In addition, additional 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 7.6.1).

Blood samples for PK analysis will be collected from all patients to characterize the PK of copanlisib and rituximab (see Section 7.4). Plasma samples for biomarker analyses will be collected from every patient, according to the schedule specified in Section 7.1. Blood samples for exploratory genetic biomarker analysis will be collected on Cycle 1 Day 1 from patients who provide "genetic research" consent (voluntary).

PK and biomarker samplings are not applicable to sites who cannot obtain approval by competent Health Authority.

Primary variable

The primary efficacy variable is PFS, defined as the time (in days) from randomization to PD as assessed by central review or death from any cause (if no progression is documented). The main analysis of the study will be performed when at least 190 PFS events (PD by central review or death before PD) are observed in the study.

Justification of the design

Single-agent rituximab represents a valid therapy option for patients who had a long response following the last rituximab-based treatment, as well as for non-refractory patients with responses of shorter duration in whom chemotherapy is contraindicated for medical reasons (see Section 1.2).

The 2:1 randomization in favor of the treatment arm increases the probability for a study participant to receive the study drug.

The use of placebo in this study is justified for the following reasons:

- 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 (PRO).
- Although treatment with copanlisib is associated with two specific AEs, hyperglycemia and hypertension, the risk of inadvertent unblinding is low. In the majority of the cases, the intensity of both symptoms is low; both symptoms are relatively frequently found in the age group to which the majority of iNHL patients belong; and most investigators will treat 1-2 patients only due to the rarity of patients with the requested profile.

End of study

For each participating European Union (EU) country, the end of the study will be reached when the last visit of the last patient for all centers in the respective country has occurred. The end of study 17067 as a whole will be reached as soon as the last visit of the last patient (LPLV) has been reached in all centers in all participating countries (EU and non-EU).

If the study is stopped, but benefits are observed for patients on treatment, options for treatment continuation will be discussed and agreed between the investigator, sponsor, and the patients. Study participants may be offered the option to transition into a roll-over study (ROS) or any other mechanism to supply drug post-study. In the event that a ROS or any new mechanism to supply drug post-study is established, the present study will end when all patients, as applicable, have transitioned or discontinued from this study for another reason (e.g., consent withdrawn, lost to follow-up, death). Until the transition, patients will continue to follow all the procedures and visits required in the current version of the protocol.

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

The end of study notification to Health Authorities will be based on the completion of the collection of survival data.

5. Study population

5.1 Eligibility

5.1.1 Inclusion criteria

1. Ability to understand and willingness to sign written informed consent. Signed informed consent must be obtained before any study specific procedure [1].
2. Histologically confirmed diagnosis of iNHL in CD20 positive patients, with histological subtype limited to:
   - Follicular lymphoma (FL) grade 1-2-3a
   - Small lymphocytic lymphoma (SLL) with absolute monoclonal lymphocyte count $<5x10^9$/L at study entry
   - Lymphoplasmacytoid 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) after the last rituximab-, rituximab biosimilars-, or anti-CD20 monoclonal antibody (e.g. obinutuzumab)-containing therapy (other previous treatment lines after rituximab are allowed). A previous regimen is defined as one of the following: at least 2 months of single-agent therapy (less than 2 months of therapy is allowed for patients who responded to single-agent rituximab, rituximab biosimilars, or anti-CD20 monoclonal antibody); at least 2 consecutive cycles of polychemotherapy; autologous transplant; radioimmunotherapy. Previous exposure to PI3K is acceptable (except to copanlisib) provided there is no resistance (see also exclusion criterion 40). Patients with prior intolerance to PI3K inhibitors other than copanlisib are eligible.
4. Non-WM patients must have at least one bi-dimensionally measurable [2] lesion (which 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.
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 x upper limit of normal (ULN) and positive immunofixation test.

---

[1] 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, CT/MRI scans, bone marrow sample, MUGA/echocardiogram and hepatitis testing which may be used provided they fall into the protocol specified 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. CT/MRI must also meet the quality standards of the Imaging Manual.

[2] Minimum measurements for measurable disease according to the Lugano Classification:
- nodal lesions > 1.5 cm LDi
- extranodal lesions > 1 cm LDi

6. Male or female patients ≥ 18 years of age.
7. ECOG performance status ≤ 2 (ECOG: Eastern Cooperative Oncology Group).
8. Life expectancy of at least 3 months
9. Availability of fresh tissue and/or archival tumor tissue for central pathology (obtained within 5 years of the consent date) 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 5 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 (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 baseline laboratory values collected no more than 7 days before starting study treatment:
    - Total bilirubin ≤ 1.5 x ULN (< 3 x ULN for patients with Gilbert-Meulengracht syndrome or for patients with cholestasis due to compressive adenopathies of the hepatic hilum).
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN (≤ 5 x ULN for patients with liver involvement by lymphoma).
    - Lipase ≤ 1.5 x ULN.
    - Glomerular filtration rate (GFR) ≥ 30 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 later 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 x ULN. PT can be used instead of INR if ≤ 1.5 x ULN.
    - Platelet count ≥ 75,000 /mm^3. For patients with confirmed lymphomatous bone marrow infiltration, 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.
      Packed red blood cell transfusion or erythropoietin should not be given less than 7 days before the exam collection.

- Absolute neutrophil count (ANC) ≥ 1,000/mm^3. For patients with confirmed lymphomatous bone marrow infiltration, ANC count ≥ 750 /mm^3.
  Myeloid growth factors should not be given less than 7 days before the exam collection.

12. Left ventricular ejection fraction (LVEF) ≥ 45%.
13. Patients must either:

- have had a progression-free and treatment-free interval of at least 12 months after completion of the last rituximab-, rituximab biosimilars-, or anti-CD20 monoclonal antibody-containing treatment (see exclusion criterion 4)

  OR

- be considered unfit to receive chemotherapy on reason of age, concomitant morbidities, and/or residual toxicity from previous treatments, or unwillingness to receive chemotherapy. These patients must also have had a progression-free and treatment-free interval of at least 6 months after completion of the last rituximab-, rituximab biosimilars-, or anti-CD20 monoclonal antibody-containing treatment (see exclusion criterion 4). Patients in whom chemotherapy is contraindicated are defined by one of the following features:
  - Age ≥ 80 years
  - Age < 80 years and at least 1 of the following conditions:
    - at least 3 grade 3 CIRS-G comorbidities (see Appendix 14.7)

    OR

    - at least 1 grade 4 CIRS-G comorbidity (if compatible to participation in the study - see exclusion criterion no. 26).

5.1.2 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. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site).

Excluded medical conditions:

3. FL grade 3b or transformed disease, or chronic lymphocytic leukemia.
4. Progression-free interval or treatment-free interval of less than 12 months since the last rituximab-, rituximab biosimilars-, or anti-CD20 monoclonal antibody (e.g. obinutuzumab)-containing treatment (including maintenance with these drugs). For patients considered unwilling/unfit to receive chemotherapy (see inclusion criterion 13): progression free-interval or treatment-free interval of less than 6 months since the last rituximab-, rituximab biosimilars-, or anti-CD20 monoclonal antibody-containing treatment (including maintenance with these drugs), as assessed by the investigator.
5. Previous or concurrent cancer that is distinct in primary site or histology from indolent B-cell NHL(as described in inclusion criterion 2) within 5 years prior to treatment start **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]), and asymptomatic prostate cancer without known metastatic disease and with no requirement for therapy or requiring only hormonal therapy and with normal prostate-specific antigen for ≥1 year prior to randomization.
6. Known lymphomatous involvement of the central nervous system.
7. Congestive heart failure > New York Heart Association (NYHA) class 2.
8. 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.
9. Uncontrolled arterial hypertension despite optimal medical management (per investigator's assessment).
10. Patients with HbA1c > 8.5% at Screening.
11. 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 treatment.
12. Non-healing wound, ulcer, or bone fracture.
13. Active, clinically serious infections > CTCAE Grade 2.
14. Known history of human immunodeficiency virus (HIV) infection.
15. Hepatitis B (HBV) or hepatitis C (HCV). 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 HBsAg or HBcAb will be eligible if they are negative for HBV-DNA, these patients should receive prophylactic antiviral therapy. Patients positive for anti-HCV antibody will be eligible if they are negative for HCV-RNA.
16. Patients with seizure disorder requiring medication.
17. Patients with evidence or history of bleeding diathesis. Any hemorrhage or bleeding event ≥ CTCAE Grade 3 within 4 weeks prior to the start of study treatment.
18. *Criterion 18 was removed by amendment 1.*

19. Proteinuria ≥ CTCAE Grade 3 as assessed by either a 24 h total urine protein quantification or a urine protein to creatinine ratio (UPCR) > 3.5 on a random urine sample.
20. History or concurrent condition of interstitial lung disease of any severity and/or severely impaired lung function (as judged by the investigator).
21. Concurrent diagnosis of pheochromocytoma.
22. Pregnant or breast-feeding patients. Women of childbearing potential must have a serum pregnancy test performed a maximum of 7 days before start of treatment, and a negative result must be documented before start of treatment.
23. Unresolved toxicity higher than CTCAE Grade 1 attributed to any prior therapy/procedure, excluding alopecia, peripheral neuropathy, and bone marrow parameters.
24. Known hypersensitivity to any of the test drugs, test drug classes, or excipients in the formulation.
25. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the study or evaluation of the study results.
26. Any illness or medical conditions that are unstable or could jeopardize the safety of patients and their compliance in the study.

Excluded previous therapies and medications:

27. *Criterion 27 removed by amendment 1.*
28. Treatment with investigational drugs other than PI3K inhibitors less than 28 days before start of treatment, unless evidence of progression since last treatment.
29. Ongoing immunosuppressive therapy.
30. Radiotherapy or immuno-/chemotherapy less than 4 weeks before start of treatment, unless evidence of progression since last treatment.
31. Radioimmunotherapy or autologous transplant less than 3 months before start of treatment, unless evidence of progression since last treatment.
32. Myeloid growth factors less than 7 days before start of treatment.
33. Blood or platelet transfusion less than 7 days before start of treatment.
34. Ongoing systemic corticosteroid therapy at a daily dose higher than 15 mg prednisone or equivalent. Previous corticosteroid therapy must be stopped or reduced to the allowed dose at least 7 days before performing the screening CT/MRI. If a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the screening. Patients may be using topical or inhaled corticosteroids.
35. History of having received an allogeneic bone marrow or organ transplant.
36. Major surgical procedure or significant traumatic injury (as judged by the investigator) less than 28 days before start of treatment, open biopsy less than 7 days before start of treatment.

37. Anti-arrhythmic therapy (beta blockers or digoxin are permitted).
38. Use of strong inhibitors of CYP3A4 is prohibited from Day -14 of Cycle 1 until the Safety follow up visit (see Appendix 14.1).
39. Use of strong inducers of CYP3A4 is prohibited from Day -14 of Cycle 1 until the Safety follow up visit (see Appendix 14.1).
40. 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.
41. Prior treatment with copanlisib.

Other exclusions:

42. Cytomegalovirus (CMV) infection. Patients who are CMV PCR positive at baseline will not be eligible.

For prohibited concomitant therapy please see Section 6.9.1.

5.1.3 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-refractory. The combination of rituximab and copanlisib is expected to be sufficiently well tolerated when administered to patients in whom chemotherapy is contraindicated on reason of age and comorbidities. These patients will be selected according to the CIRS-G score, which has been validated with respect to the clinical outcome in older patients (28) and proved to be useful in the assessment of NHL patients as well (29, 30). 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.

5.2 Withdrawal of patients from study

5.2.1 Withdrawal

A patient who discontinues study participation prematurely for any reason is defined as a "dropout" if the patient has already been randomized. A patient who, for any reason (e.g., failure to satisfy the selection criteria), terminates the study before randomization is regarded a "screening failure".

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.

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/MRI scans, bone marrow sample, 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 for HbA1c.

5.2.1.1 Withdrawal of study treatment

Patients *must* be withdrawn from the study treatment for the following reasons:

- 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 (see Section 11.2).
- If, in the investigator's opinion, continuation of the study would be harmful to the patient's well-being.
- Disease progression as defined in the Lugano Classification and, for patients with WM, according to the Owen Criteria.
- Occurrence of unacceptable toxicity.
- CTCAE Grade 4 arterial hypertension.

- 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.
- CTCAE Grade 4 dermatologic toxicity.
- CTCAE Grade ≥3 (or recurrent Grade 2) non-infectious pneumonitis.
- 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.
- The patient does not tolerate copanlisib/placebo dose of 30 mg.
- 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 test drug (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 an SAE via the Pregnancy Monitoring Form.

The patient *must* be withdrawn from the study for the following reasons*:*

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

Any patient removed from the study will remain under medical supervision until discharge or transfer is medically acceptable.

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.

In all cases, the reason for discontinuing study treatment and the completion of the follow-up periods must be clearly documented in the eCRF and in the patient's medical records.

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.

Details for the premature termination of the study are provided in Section 10.

5.2.1.2 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 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 to determine survival status (up to 7 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

5.2.2 Replacement

Patients will not be replaced.

5.3 Patient identification

At Screening upon signing the ICF, each patient will be assigned a unique patient identification number (PID) by the IVRS/IWRS for unambiguous identification. The PID will be constructed as follows:

a. Digits 1 to 2: Unique country code

b. Digits 3 to 5: Center code (unique within each country)

c. Digits 6 to 9: Unique patient code (unique within each center)

Within the unique patient code, the first digit (digit 6) represents the study a patient is participating in.

Patients participating in study 17067 (this study) have a "7" as the 6th digit. As an example, PIDs in this study have the structure "aabbb**7**ccc".

Once allocated, the patient's PID number will identify the patient throughout the study and will be entered into the Site Enrollment Log and in the eCRF.

6. Treatments

6.1 Treatments to be administered

The study treatment (=study drugs) will comprise the following:

- The combination of the test drug copanlisib (BAY 80-6946) and rituximab, to be administered as combination therapy. Copanlisib will be administered before rituximab.
- The combination of placebo and rituximab, to be administered as combination therapy. Placebo will be administered before rituximab.

For the dosage and administration please see Section 6.4.

6.2 Identity of investigational medicinal products

All 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 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 study treatment 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.

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 infusions is obtained after reconstitution of the lyophilisate with normal saline 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

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 6.5.

Rituximab

Rituximab will be sourced centrally or locally by the sponsor depending on the local law and requirements. For full details on rituximab and instructions for dilution, please refer to the current prescribing information / Summary of Product Characteristics (SmPC).

6.3 Treatment assignment

At the end of the screening period, eligible patients will be randomly assigned in a 2:1 ratio to the two double-blinded treatment arms: copanlisib + rituximab or placebo + rituximab, respectively.

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

IVRS/IWRS will stratify patients according to four factors based on baseline characteristics*:*

- NHL histology
  - FL histology
  - Other iNHL histology (SLL, MZL, LPL/WM)
- Entry criterion:
  - progression-free and treatment-free interval of ≥ 12 months after completion of the last rituximab-containing treatment
  - considered unwilling/unfit to receive chemotherapy for age or comorbidities (see inclusion criterion 13 for further details)

  If the patient fulfills both entry criteria, please select the criterion “considered unwilling/unfit to receive chemotherapy for age or comorbidities”.
- Presence of bulky disease (as defined by the presence of a nodal or extranodal mass ≥ 7 cm in the longest diameter, with the exception of spleen):
  - yes
  - no
- Previous treatment with PI3K inhibitors
  - yes
  - no

Resulting from the combination of these 4 stratification factors, patients will be randomized into 16 different strata. The randomization must be performed up to maximum 72 h before the first dose of study treatment.

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.

6.4 Dosage and administration

Copanlisib and placebo

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

Dosing is weekly for the first 3 weeks of a 28-day cycle (on Days 1, 8, and 15), followed by a 1-week break (i.e., no infusion on Day 22).

The requirements for fasting state and pre-dose glucose levels are presented in Table 6–1.

Table 6–1 Fasting requirements and pre-dose glucose levels

Period	Fasting ≥ 8 h required before first glucose measurement	Pre-dose glucose levels (first glucose measurement)
Cycle 1 Day 1	Yes [a]	≤125 mg/dL (non-diabetic patients) <160 mg/dL (diabetic patients)
Subsequent infusions after Cycle 1 Day 1	No [b]	<160 mg/dL (fasting) < 200 mg/dL (non-fasting)

[a] Diabetic patients who take insulin treatment at any cycle visit: Timing and content of meal intake will be managed by the investigator. Consultation with treating physician or diabetologist/endocrinologist is advised.

[b] The decision regarding meal timing and fasting can be made by the investigator based on glucose response patterns during prior treatment days.

- Fasting refers to a ≥ 8 h fast.
- Non-fasting status includes any caloric intake such as meals and also juice, snacks, and other caloric intake not consistently called a meal.

From Cycle 1 Day 1 onwards, 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 temporary increase in blood glucose. Addition of meal in close proximity to copanlisib/placebo infusion may exacerbate glucose increase.

On infusion days, a low calorie or 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.

Rituximab

Rituximab will be given IV at 375 mg/m^2 body surface weekly during Cycle 1 (on Days 1, 8, 15 and 22). Although the dose is calculated by the IVRS/IWRS, a minor variation (±5%) of the recommended dose is allowed due to the local standard of care disbursing requirements. However, a +5% variance is only permitted if a new vial is not required. For those patients who are still on treatment after evaluation at the end of Cycle 2 (not in PD), rituximab will be administered once in each of Cycles 3, 5, 7 and 9 (on Day 1). It 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.

Dosing criteria

Starting from Cycle 1 Day 8, laboratory tests prior to each infusion may be performed either the day before or on the planned date of infusion, with the exception of glucose, which must be performed on the day of copanlisib/placebo infusion. All laboratory results must be assessed by the investigator and/or appropriate site personnel prior to administration of the planned dose.

On Day 1 of each subsequent cycle, the dose of study treatment will be given only if the criteria described in Table 6–2 are met.

Table 6–2 Laboratory test criteria for Day 1 dose of subsequent cycles

Laboratory Test	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. For patients with confirmed lymphomatous bone marrow infiltration at screening and ANC ≥ 750/mm^3 - < 1000/mm^3: ANC ≥ 750/mm^3. [b]
Platelets	≥ 50,000/mm^3
ALT	≤ 5 X ULN
AST	≤ 5 X ULN
Total bilirubin	≤ 3 X ULN
GFR (MDRD)	≥ 30 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 h 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] For patients with lymphomatous bone marrow infiltration:

- If ANC ≥ 1000/mm^3 during screening, the limit of ANC ≥ 1000/mm^3 should be applied during the study.
- If after screening the ANC raises to levels above 1000/mm^3, it is recommended to confirm the result of the test within 1 day. Unconfirmed single assessment or confirmed double assessment of ANC > 1000/mm^3 warrants ANC ≥ 1000/mm^3 to receive further doses of study drugs for this patient for the remainder of the study.

A blood count will be performed and assessed prior to the subsequent doses in each cycle of copanlisib/placebo on Days 8 and 15. The study drug will not be administered if, on the day of scheduled dosing, any of the following criteria is met:

- CTCAE Grade 4 neutrophil count decreased (ANC < 500/mm^3)
  (G-CSF is mandatory if ANC < 1000/mm^3 and should be administered as per label)
- CTCAE Grade ≥ 3 platelets count decreased (platelets < 50,000/mm^3)
- CTCAE Grade ≥ 3 anemia (hemoglobin < 8 g/dL), see footnote [a] in Table 6–2

Doses 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 copanlisib/placebo is 5 days.

6.4.1 Dose modification

Dose modifications due to toxicities described below apply to copanlisib and placebo for copanlisib ("dummy dose modification").There will be no dose reduction of rituximab. If severe (life-threatening) reaction to rituximab infusion occurs despite supportive treatment patients should be withdrawn from the study treatment. Patients must have received at least 4 complete rituximab infusions until Cycle 3 Day 1 (included) to continue the treatment with single agent copanlisib/placebo.

It is recognized that attribution of causality of any AE to the test drug specifically may be difficult. However, certain toxicities were seen only in relation to copanlisib in Phase I and II trials: 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 must be done according to the guidelines in Section 6.4.1.1 and 6.4.1.2. The investigator may judge a more conservative dose modification 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.

The dose modification levels of copanlisib and placebo are outlined in Table 6–3:

Table 6–3 Dose levels of copanlisib and placebo

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, with the exception of non-infectious pneumonitis (NIP).

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

6.4.1.1 Hematological toxicity

Neutropenia and febrile neutropenia are listed in the current version of IB as expected adverse events. If the guidelines given in Table 6–4 are not followed, the rationale for other measures is to be documented in detail in the patient's medical record.

Table 6–4 Dose modification of copanlisib/placebo for hematological toxicity

Hematological toxicity (any of the following)	Test drug 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 [e] • CTCAE Grade ≥ 3 anemia (Hb < 8 g/dL)	Delay infusion until criteria displayed in Table 6–2 are met.[d] Patient can be treated at one dose level lower at the investigator's discretion.[b] 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; G-CSF = Granulocyte colony stimulating factor; Hb = hemoglobin; INR = international normalized ratio, PTT = partial thromboplastin time

[a] For patients who develop CTCAE Grade ≥ 3 neutropenia, a blood count after 3 days is recommended. For patients with CTCAE Grade 3 neutropenia and no bone marrow infiltration, consider reducing the dose of copanlisib until recovery to Grade 2 and also consider the use of myeloid stimulating factor as long as the patient responds or does not progress. G-CSF is mandatory if ANC < 1000/mm^3 and should be administered as per label).

[b] 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.

[c] *Footnote c deleted by amendment 7.*

[d] Treatment with transfusion or growth factors is allowed at the investigator's discretion.

[e] INR and PTT should have returned to ≤ 1.5 and ≤ 1.5 x ULN, respectively, with no signs of bleeding.

6.4.1.2 Non-hematological toxicity

Dose modifications for non-hematologic toxicities except glucose increases, dermatologic toxicity, non-infectious pneumonitis and arterial hypertension are outlined in Table 6–5.

Table 6–5 Dose modification of copanlisib/placebo for non-hematological toxicity (except glucose increases, dermatologic toxicity, non-infectious pneumonitis and arterial hypertension)

		Test 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	–

[a] Toxicities according to CTCAE version 4.03
[b] Despite maximum supportive therapy
[c] Not applicable for 30 mg dose level (*footnote [d] deleted by amendment 1*)
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 cytomegalovirus (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 6–6. If these guidelines are not followed, the rationale for other measures will be documented in detail in the patient's medical record.

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

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

[a] Toxicities according to CTCAE version 4.03
[b] Despite maximum supportive therapy
[c] Not applicable for 30 mg dose level (*footnote [d] deleted by amendment 1*)
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 (NIP)

In the event of suspected NIP of any grade, copanlisib/placebo treatment should be adjusted according to the guidance in Table 6–7.

Table 6–7 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.

Pneumonitis is to be reported as such only in the event of NIP. The investigator is requested to differentiate between non-infectious pneumonitis (NIP) and infectious pneumonitis (viral, bacterial, fungal), aspiration pneumonitis, or other 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 6.4.2.1.

- 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 5.2.1.1).

b) Arterial hypertension

The guidelines for dose modifications of copanlisib/placebo in case of arterial hypertension are given in Table 6–8.

No dose should be given if blood pressure is ≥ 150/90 mmHg. Instructions for blood pressure measurement are given in Section 7.5.3.3. Antihypertensive medication may be given to

control the arterial hypertension. 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 blood pressure increases are given in Section 6.4.2.3. Patients with a hypertension of CTCAE Grade 4 must permanently discontinue the study drug (see Section 5.2.1.1).

Table 6–8 Dose modification of copanlisib/placebo for arterial hypertension

Toxicity (CTCAE)	Study drug action	Recommendation
Pre-dose measurements BP ≥ 150/90 mmHg	No dose should be given until recovery to < 150/90 mmHg.	Consider 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, delay dosing until next visit.
During infusion: CTCAE hypertension of grade 3 or ≥ 160/100 mmHg	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 CTCAE hypertension of grade 3 or ≥ 160/100 mmHg [a]	–	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	–

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

6.4.2 Treatment of toxicities

Recommendations for the treatment of toxicities described below apply to copanlisib and placebo. For monitoring and management of adverse reactions following rituximab administration please refer to rituximab SmPC.

6.4.2.1 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 6–9.

Table 6–9 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 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
On subsequent days:		
Max post-infusion glucose > 200 mg/dL noted on subsequent days	• Oral glucose lowering medication recommended on subsequent days • 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 already monitors his/her blood glucose as part of routine antidiabetic care, the routine measurements should not be replaced by the study specific measurements.

6.4.2.2 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 (31). 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 fasting requirements, the evaluation of lipid-panels including triglycerides is considered as not feasible.

6.4.2.3 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 arterial hypertension following copanlisib/placebo will need to be individualized for each patient, but the 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. In the event of the occurrence of arterial hypertension ≥ 150/90 mmHg during infusion of copanlisib/placebo at any cycle antihypertensive treatment is suggested as indicated above. In the event of the occurrence of CTCAE Grade 3 arterial hypertension (≥ 160/100 mmHg) during infusion of copanlisib/placebo, the infusion should be interrupted and antihypertensive treatment as suggested above is administered. Infusion can be resumed when blood pressure has returned to <150/90 mmHg.

6.4.2.4 Treatment of vomiting and diarrhea

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 or Lomotil, which contains diphenoxylate plus atropin might also be used. In the event of CTCAE Grade 3 diarrhea with maximal pharmacological support, the administration of the test drug should be delayed.

6.4.2.5 Treatment of dermatologic toxicity

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

Table 6–10 can be used as guidance.

Table 6–10 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

[a] Cross check with short-term corticosteroid administration (see Section 6.9).
Bid = twice daily, CTCAE = Common Terminology Criteria for Adverse Events
Source: Lacouture ME.,2008 (32)

6.4.2.6 Special considerations for patients unfit for chemotherapy

By definition patients unfit for chemotherapy are vulnerable to toxicities. A structure covering for adequate support at home should be present. Special consideration has to be paid to:

- Quality of outpatient glucose monitoring and management
- New onset/worsening of dyspnea or cough
    - Check oxygen saturation
    - Consider further diagnostic steps early
- Adequate hydration and electrolyte balance: generally in a population with likely reduced sense of thirst and in patients with transient glucose increases, polyuria, nausea, vomiting or diarrhea:
    - Consider unscheduled checks of electrolytes
    - Consider parenteral fluids early

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

6.4.2.7.1 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/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 or when ANC of CTCAE grade 4, PCR for CMV (every cycle on Cycle X Day 1 for the first 6 months of study treatment and every 3 cycles thereafter). 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. 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 myelosupressive cytotoxic therapy)
- History of CMV, herpes
- History of lower respiratory tract infection, history of immunodeficiency (excluding lymphoma) in the last 12 months
- 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, C-reactive protein (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 or CT scans)
    - Note: Treatment of developed OI should be based on local SOC.

6.4.2.7.2 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 6.4.2.7.1).

6.5 Blinding

Patients will be randomized to receive copanlisib in combination with rituximab or placebo in combination with rituximab, 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.

The DMC will review the safety data of the first 30 patients after their first cycle in an unblinded manner, to assess the safety of the copanlisib + rituximab combination. However, 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. 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 7.5.1.5), the patient's treatment code will usually be unblinded before reporting to the health authorities, ethic committees and investigators (see Section 7.5.1.4) if the SUSAR was related to the blinded treatment.

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.

6.6 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with Good Clinical Practice (GCP) and 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 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 study drug via IVRS/ IWRS and 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.

6.7 Treatment compliance

The administration of intravenous copanlisib/placebo and rituximab will be performed in the clinic on a weekly basis and must be recorded in the eCRF.

6.8 Post-study therapy

If the study is stopped, but continuous benefits are observed for certain patients, treatment options will be discussed and agreed upon between the investigators, the sponsor, and the patients.

Patients may receive further treatment, assessments and/or be followed either via a ROS (subject to approval by the competent health authority and EC/IRB) or through any other mechanism in accordance with local legal and compliance rules. See Section 4, End of study.

The supply of commercially available drugs in a ROS or any other mechanism to supply drug post-study will be at the discretion of the sponsor and can potentially change from central to local supply by the sponsor, to supply per prescription or any other available option.

6.9 Prior and concomitant therapy

For prohibited prior therapy please refer to Section 5.1.2.

6.9.1 Prohibited concomitant therapy

- CYP3A4 inhibitors and inducers (see Appendix 14.1): copanlisib is primarily metabolized by CYP3A4. Therefore, concomitant use of **strong** inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir), and **strong** inducers of CYP3A4 (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) is not permitted from Day -14 of Cycle 1 until the Safety follow-up visit.
- Grapefruit and grapefruit juice (CYP3A4 inhibitor) consumption is not permitted during the study treatment until the Safety follow-up visit.
- Anti-arrhythmic therapy other than beta blockers or digoxin
- Systemic corticosteroid therapy at a daily dose higher than 15 mg prednisone or equivalent. Previous corticosteroid therapy must be stopped or reduced to the allowed

dose at least 7 days prior to the screening CT/MRI. If a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the screening. Patients may be using topical or inhaled corticosteroids. Short-term systemic corticosteroids above 15 mg prednisolone or equivalent will be allowed for the management of acute conditions and as premedication prior to rituximab infusion and for radiological contrast infusion. The use of corticosteroids as antiemetics prior to copanlisib/placebo administration will not be allowed.

- *Myeloid growth factors removed by amendment 1*
- Ongoing immunosuppressive therapy
- Concomitant radiotherapy (it is assumed that radiation would be indicated only in case of progression, when the patient would come off study medication anyway)
- Use of biotin (vitamin B7) produces high levels of the vitamin, which can interfere with the result of the immunoassay tests including biomarker analysis, HBcAb, HBeAg, HBsAg, HCVAb, HIV-Ag/Ab combo, HIV combo. Therefore, refrain from the use of biotin for at least 72 hours prior to immunoassay test collection.

6.9.2 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, including5-HT3 blockers, such as granisetron, ondansetron, or an equivalent agent, is allowed as needed. The use of corticosteroids as antiemetics prior to copanlisib/placebo administration will be not allowed.
- Palliative and supportive care for the other disease-related symptoms (with the exception of radiotherapy) 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 (with the exception of radiotherapy).
- 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.

7. Procedures and variables

7.1 Schedule of procedures

7.1.1 Tabulated overview

Schedule of procedures are presented in Table 7–1 and Table 7–2.

Table 7–1 Study flow chart

	Screening maximum days before C1D1			**Treatment**									**EOT**	**Safety FU**	**Active FU** [z]	**Survival FU** [aa]
				Cycle 1					**Cycle 2 and higher**				Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	**D4**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22** [x]	**7**	**30 + 5** days window [y]		every 3 months
Acceptable deviation (in days)				-1 to + 2 days					-1 to + 2 days				Decision to stop	Last dose		±14 days
Screening and enrollment																
Patient informed consent (including genetic)	Written patient informed consent must be obtained prior to any study-specific procedures [ab]															
Check in- and exclusion criteria		X	X	X												
Medical history [a]		X														
IVRS/IWRS transaction [b]	X			X[b]					X				X			
HBsAg, HBcAb, anti-HCV antibody [ac]	X															
CMV PCR test [ad]	X			X [ad]					X [ad]							
Beta-2-microglobulin (for patients with WM/FL)	X															
Serum pregnancy test (if applicable) [c]			X						X [c]				X [c]			
UPCR / 24 h total urine protein quantification			X													
GFR calculation (MDRD abbreviated formula)			X						X							
Safety																
Toxicity / AE assessment [d]		X		X		X	X	X	X	X	X		X	X	X	
Concomitant medication [d]		X		X		X	X	X	X	X	X		X	X		
Complete physical examination [e]		X		X					X				X			
Brief physical examination [f]						X	X	X		X	X			(X)		
12-lead ECG [g]	X			X					X [g]				X			
MUGA scan or echocardiogram [h]		X			(X)[h]				X [h]				X			
Hemoglobin A1c [i]			X						X [i]				X			
Complete blood count [j]			X			X	X	X	X	C2 only	C2 only		X	(X)		
Hemoglobin, ANC and platelet counts (from Cycle 3 onwards)										X	X					
Chemistry panel [k]			X [k]			X	X	X	X [k]	C2 only	C2 only		X [k]	(X)		
Coagulation panel: PTT, PT and INR			X				X		X				X	(X)		

Table 7–1 Study flow chart

	Screening maximum days before C1D1			**Treatment**									**EOT**	**Safety FU**	**Active FU** [z]	**Survival FU** [aa]
				Cycle 1					**Cycle 2 and higher**				Within (days) after			
Days	**-28**	**-14**	**-7**	**D1**	**D4**	**D8**	**D15**	**D22**	**D1**	**D8**	**D15**	**D22** [x]	**7**	**30 + 5** days window [y]		every 3 months
Acceptable deviation (in days)				-1 to + 2 days					-1 to + 2 days				Decision to stop	Last dose		±14 days
CD4 (for patients with signs of infection) and cultures if febrile neutropenia [ae, af]																
Glucose [l]				X		X	X		X	X	X					
Blood pressure [n]				X		X	X		X	X	X					
Efficacy																
CT / MRI and tumor evaluations [o]	X											X [o]	(X)		X [o]	
Bone marrow biopsy [q]	X											X [q]				
For LPL/WM patients only																
Serum protein electrophoresis [r]	X[r]											X [r]	(X) [r]		X [r]	
Immunofixation [r]	X[r]											X [r]	(X) [r]		X [r]	
Serum quantitative IgM test [r]	X[r]											X [r]	(X) [r]		X [r]	
Serum or plasma viscosity [r]	X[r]								(X) [r]				(X) [r]			
Pharmacokinetic sample (see Table 7–2)						X	X	X								
Biomarkers																
Tumor tissue (central pathology and biomarkers)[s]	X												(X) [s]			
Plasma for tumor genetics [t]				X									X			
Plasma for non-genetic biomarker analysis [u]				X		X	X		C2 only	C2 only	C2 only		X			
Whole blood for biomarkers [v]				X												
Drug administration																
Copanlisib/placebo IV infusion, before rituximab infusion				X		X	X		X	X	X					
Rituximab IV infusion [w]				X		X	X	X	C3,5,7,9							
Survival status, new anticancer therapy																X

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C = cycle; CBC = complete blood count; CD = cluster of differentiation; CIRS-G = Cumulative Illness Rating Scale for Geriatrics; CMV = cytomegalovirus; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events, version 4.03; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology

Group; 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; HCV = Hepatitis C virus; HDL = high-density lipoprotein; INR = international normalized ratio; IV = intravenous; ; IVRS = Interactive Voice Response System; IWRS = Interactive Web Response System; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; LPL/WM = Lymphoplasmacytoid lymphoma/Waldenström macroglobulinemia; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multiple gated acquisition; NYHA = New York Heart Association; OI = opportunistic infection; PCR = polymerase chain reaction; PD = disease progression; PT = prothrombin time; PTT = partial thromboplastin time, QoL = quality of life; RBC = red blood cell count; SAE = serious adverse event; SOC = standard of care; UPCR = urine protein to creatinine ratio; WBC = white blood cell count; WM = Waldenström macroglobulinemia

[a] Complete medical and surgical history including demographics, relevant medical history findings, concomitant illnesses, CIRS-G if applicable, 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. Information on patient's smoking history will also be collected and recorded.

[b] IVRS/IWRS transaction to register the patient in the system will be at Screening. IVRS/IWRS randomization transaction will take place maximum 72 h before the first dose (Cycle 1 Day 1). IVRS/IWRS transactions for medication dispensing will be on Day 1 of each cycle. IVRS/IWRS transaction to register end of treatment will be at the EOT visit.

[c] After Cycle 1 serum pregnancy test is mandatory at every cycle and at the EOT visit for countries where it is required by local regulations.

[d] After Screening: AE assessment and concomitant medication review must be updated before each dose and 30 days after last dose. 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.

[e] Complete physical examination to include: ECOG performance status, NYHA classification, height (only at Screening), weight, vital signs (temperature, pulse and blood pressure), and complete review of body systems, including lung examination. After the patient signs the informed consent, any new finding discovered not present in the patient's medical history or a worsening of a prior medical history finding must be recorded as an AE.

[f] Brief physical examination to include: ECOG performance status, vital signs (temperature, pulse and blood pressure), examination of pertinent organ systems, and brief interim history (change of symptoms), including lung examination.

[g] 12-lead ECG (including QT cB 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 infusion and at the end of infusion (window of up to 2 h prior to and post- infusion is allowed). On the days of rituximab administration, ECG will be measured after rituximab infusion. 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), within 7 days prior to dosing on Day 1 of every 3rd cycle (3, 6, 9 etc.), and at the EOT (if not previously done within 4 weeks). Same modality must be used throughout the study. For patients with LVEF below lower level of normal for the institution at Screening: one additional assessment should be made at any time between 5 h after the first dose and before the second dose of copanlisib.

[i] Hemoglobin A1c (HbA1c) at Screening, on Day 1 of every 3 cycles (4, 7, 10 etc.) starting from Cycle 4 and at the EOT visit. The testing is not required if the previous test was performed within 4 weeks preceding EOT visit. HbA1C testing should also be performed approximately 3 months after the EOT visit whenever possible.

[j] CBC: Hemoglobin, hematocrit, RBC, WBC (with differential to include neutrophil, lymphocyte, monocyte, basophil and eosinophil counts), and platelet count. From Cycle 3 onwards, only hemoglobin, platelet and ANC will be performed on Day 8 and Day 15 prior to each copanlisib/placebo infusion. Differential blood count in percentage can be provided when absolute count is not available per standard of care of the local lab.

[k] Complete chemistry panel: calcium, sodium, potassium, chloride, phosphorous, magnesium, bicarbonate (or carbon dioxide, if bicarbonate is not routinely measured at the site), total protein, albumin, glucose, BUN (or urea if BUN is not routinely measured at the site), serum creatinine, uric acid, total bilirubin, ALT, AST, LDH, alkaline phosphatase, creatine phosphokinase, lipase, amylase (or pancreatic amylase, if total amylase is not routinely measured at the site), cholesterol (total and LDL) and triglycerides. Laboratory tests prior to each infusion may be performed either the day before or on the planned date of infusion, with the exception of glucose, which must be performed on the day of infusion. Triglycerides, LDL cholesterol and total cholesterol will be tested only at Screening, on Day 1 of every second cycle (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.

[l] Glucose will be measured prior to copanlisib/placebo infusion. Additional measurements to be performed at the clinic as clinically indicated. For details on fasting requirements and pre-dose glucose levels see Section 6.4.

[m] *Home glucose monitoring removed by amendment 9.*

[n] 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. On copanlisib/placebo infusion days, blood pressure will be measured at pre-dose. Blood pressure can be measured during or after copanlisib/placebo infusion if clinically indicated/based on the investigator´s discretion.

[o] The first IV (and oral, if indicated, per Imaging Manual) contrast enhanced CT/MRI scans of neck, chest, abdomen and pelvis must be performed at Screening (including WM patients). Corticosteroids must stopped or reduced to the allowed dose (≤ 15 mg of prednisone or equivalent) at least 7 days before performing the screening CT/MRI (if a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the screening). During treatment and Active follow-up periods, tumor scans will be done with the same modality every 8 weeks (± 7 days) during Year 1, every 12 weeks (± 7 days) during Year 2, and every 24 weeks (± 7 days) during Year 3 and onwards, starting from Cycle 1 Day 1. CT/MRI scans are not required at the EOT visit if the patient discontinued due to PD which has been radiologically evaluated within the 4 weeks preceding EOT. Tumor scans will be done until PD is documented or new anti-tumor treatment is administered. MRI shall be performed instead of CT when local regulations do not permit the use of CT as requested per protocol schedule (see Section 7.3.2). 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. 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 (see footnote [r], and Sections 7.1.2.3 and 7.3.3). No central independent blinded review will be done.

[p] *As of Amendment 12, no further data collection is required for the QoL questionnaires.*

[q] Bone marrow biopsy is 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 at Screening, it will be mandatory to perform it again to confirm the first CR, and also at the investigator's discretion if clinical evaluation leads to suspicion of bone marrow infiltration without further radiological findings. No central review of bone marrow biopsy will be performed during treatment or Active follow-up.

[r] 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 tumor evaluation 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.

[s] Tumor tissue collection will be mandatory for central pathology review. 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. A tumor biopsy is encouraged at the time of progression (optional) to allow investigation of copanlisib resistance. In addition, if a tumor biopsy/excision occurs during the course of the study based on medical need, a sample should be submitted (though no biopsy is required during treatment) (see Section 7.6.1).

[t] Plasma for tumor genetics: On Cycle 1 Day 1, blood for plasma preparation should be drawn prior to drug administration.

[u] 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 drug administration.

[v] Whole blood for biomarkers: On Day 1 of Cycle 1 (prior to drug administration), whole blood will be taken only from patients who have provided genetic consent.

[w] Rituximab infusions during Cycle 1 on Days 1, 8, 15 and 22. For those patients who are still on treatment after evaluation at the end of Cycle 2 (not in PD), rituximab will be administered once at each of Cycles 3, 5, 7 and 9 (on Day 1). Rituximab is administered after copanlisib/placebo IV infusion.

[x] After Cycle 1, there are no mandatory procedures on Day 22 of subsequent cycles. Day 22 from Cycle 2 onwards is the earliest time for procedures due at latest on Day 1 of the next cycle.

[y] The post-treatment follow-up 30 days (window of +5 days is allowed) after the last dose can be conducted via telephone if the patient is no longer being actively seen at the clinic or has started another therapy. Procedures marked with “(X)” are only to be performed, if clinically indicated.

[z] Patients who discontinue study drug for reasons other than PD will enter Active follow-up period (except for patients who object to FU data collection). These patients should have follow-up tumor assessments as outlined in this protocol from the day of randomization until PD is documented or new anti-tumor treatment is administered, whichever occurs first.

[aa] Patients or their health care providers will be contacted either in person or by telephone (except for patients who object to FU data collection). The contacts will be made every 3 months (± 14 days), until death or until the end of the trial (up to 7 years after the last patient started study treatment), whichever comes first. Information to be recorded: Date of contact, survival status, the first new anti-cancer regiment (if applicable), and date and cause of death (if applicable).

[ab] 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, CT/MRI scans, bone marrow sample, MUGA/echocardiogram and hepatitis testing which may be used provided they fall into the protocol specified 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. CT/MRI must also meet the quality standards of the Imaging Manual. 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 (up to additional 14 days permitted).

[ac] 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 and should perform HBV DNA test with PCR monthly 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 monthly through treatment and 6 months thereafter. If viral load becomes positive, patient should be withdrawn from the study.

[ad] Blood test for CMV. Should be performed in all patients prior to IV infusion of copanlisib/placebo. Every cycle on Cycle X Day 1 for the first 6 months of study treatment and every 3 cycles thereafter. If PCR test is positive for CMV, treatment should be delayed until recovery. 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.

[ae] Blood cultures should be performed as per local SOC if the patient develops febrile neutropenia or ANC of CTCAE grade 4. CD4 count should be performed for patients with signs of infection.

[af] For patients with identified risk factors and those who developed OI, additional assessments will 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. chest X-ray or CT scans) (Note: Treatment of developed OI should be based on local SOC).

Table 7–2 PK sampling schedule

Time point	Copanlisib (Plasma)	Rituximab (Serum)
Cycle 1 Day 8		
pre-infusion copanlisib/placebo	X	---
5 - 15 min	X	---
55 min	X	---
Cycle 1 Day 15		
pre-infusion rituximab *	X	X
end of infusion rituximab *	X	X
Cycle 1 Day 22		
pre-infusion rituximab	---	X
end of infusion rituximab	---	X

* same time points for both copanlisib and rituximab samples

min = minute; PK = pharmacokinetic

For further details, see Section 7.4. Note: PK samplings are not applicable to sites who cannot obtain approval by competent Health Authority.

7.1.2 Timing of assessment

If not stated otherwise, the measurements listed in the following sections will be performed by or under the supervision of an investigator or a delegate.

All procedures during the treatment period should be done according to the relative days mentioned in this study protocol. Deviations of -1 day and +2 days are acceptable with the exception of glucose and blood pressure measurement before copanlisib/placebo infusion.

7.1.2.1 Screening period

Screening examinations will be performed after the patient has given written informed consent. 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, CT/MRI scans, bone marrow sample, MUGA/echocardiogram and hepatitis testing which may be used provided they fall into the protocol specified 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. CT/MRI must also meet the quality standards of the Imaging Manual. 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 (up to additional 14 days permitted).

Within 28 days before the first study drug administration:

- IVRS/IWRS transaction to register the patient in the system (see Section 5.3)
- 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 and should perform HBV DNA test with PCR monthly through treatment and 12 months thereafter (47). 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 monthly through treatment and 6 months thereafter (47). If viral load becomes positive, patient should be withdrawn from the study.
- Blood test for CMV infection. Patients who are CMV PCR positive at baseline will not be eligible.
- 12-lead ECG including QTcB and QTcF evaluation (see Section 7.5.3.4).
- IV (and oral, if indicated, per Imaging Manual) contrast-enhanced CT/MRI of neck, chest, abdomen and pelvis (including WM patients). Only MRI will be performed in countries where CT cannot be used according to local regulations. Corticosteroids must be stopped or reduced to the allowed dose (≤ 15 mg of prednisone or equivalent) at least 7 days before performing the screening CT/MRI (if a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the screening) (see Section 7.3.2).

- Bone marrow biopsy: 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 at Screening, it will be mandatory to perform it again to confirm the first CR, and also at the investigator's discretion if clinical evaluation leads to suspicion of bone marrow infiltration without further radiological findings. No central review of bone marrow biopsy will be performed during treatment or Active follow-up.
- Tumor tissue collection will be mandatory at Screening for central pathology review. In addition, additional 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 7.6.1).
- Only in patients affected by 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 14 days before the first study drug administration:

- Check inclusion and exclusion criteria (see Section 5.1).
- Complete medical and surgical history including demographics, relevant medical history findings, concomitant illnesses, CIRS-G if applicable, 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. Information on patient's smoking history will also be collected and recorded.
- 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 7.5.1).
- 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 including ECOG performance status (see Appendix 14.2, NYHA classification (see Appendix 14.3), height, weight, vital signs (temperature, pulse and blood pressure), and a complete review of body systems (see Section 7.5.3.2).
- MUGA scan or echocardiogram to measure LVEF. The method chosen at baseline must be the same throughout the whole study period (see Section 7.5.3.5).

Within 7 days before the first study drug administration:

- Check inclusion and exclusion criteria (see Section 5.1).
- Serum pregnancy test (if applicable) (see Section 7.5.3.1).
- UPCR/24 h total urine protein quantification (see Section 7.5.3.1).
- GFR calculation according to MDRD abbreviated formula (see Section 7.5.3.1 and Appendix 14.6).
- Blood tests for hemoglobin A1c, complete blood count, complete chemistry and coagulation panels (see Section 7.5.3.1). 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 (see Section 6.4.2.2).
- Urinalysis (dipstick). Microscopy as clinically indicated (see Section 7.5.3.1).

7.1.2.2 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.

The following assessments should be performed at each visit before receiving study treatment

- Monitoring for OI (see Section 6.4.2.7.1):

  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 low ANC of CTCAE grade 4 occurs, PCR for CMV (every cycle on Cycle X Day 1 for first 6 months of treatment and every 3 cycles thereafter). 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. 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.

7.1.2.2.1 Treatment – Cycle 1

Cycle 1, Day 1

On Cycle 1 Day 1 patients should be fasting for at least 8 h prior to the pre-dose glucose measurement. For details on fasting requirements and pre-dose glucose levels, see Section 6.4.

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

- Quality of life (QoL) questionnaire (FLymSI-18): at the start of the infusion day, before the patient sees the physician, to be completed by electronic patient-reported outcome (ePRO) device (see Section 7.6.2).

- Check inclusion and exclusion criteria. No patient may receive treatment unless adherence to all selection criteria as given in Section 5.1 is established.
- IVRS/IWRS randomization transaction. The randomization must be performed up to maximum 72 h before the first dose of study treatment (see Sections 6.3 and 6.5).
- 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 7.5.1).
- 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 including ECOG performance status, NYHA classification, weight, vital signs (temperature, pulse and blood pressure), and complete review of body systems (see Section 7.5.3.2).
- 12-lead ECG including QTcB and QTcF evaluation prior to infusion and at the end of infusion (window of up to 2 h prior to and post-infusion is allowed) (see Section 7.5.3.4).
- Monitoring for OI (see Section 6.4.2.7.1).
- 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 rituximab infusion (window of ± 10 min is allowed except for the pre-dose measurement). See Section 7.5.3.7. Additional measurements to be performed at the clinic as clinically indicated.
  Note: If patient needs to take a meal, then glucose test should be taken prior to meal intake.
- Blood pressure measurements according to guidance provided in Section 7.5.3.3.
- Collection of blood for biomarker analyses prior to infusion (see Section 7.6.1):
  - 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)
- Copanlisib/placebo IV infusion, before rituximab IV infusion.
- Rituximab IV infusion.
- MUGA scan/echocardiogram for patients with LVEF below lower level of normal for the institution at Screening: one additional LVEF assessment should be made at any time between 5 h after the first dose and before the second dose of copanlisib (between Day 1 and Day 8 of Cycle 1).

Cycle 1, Day 4

- Review of blood glucose measurements, meal timing, oral glucose lowering medication and/or insulin administration, if applicable. Patients who might need treatment with glucose lowering medications not only on the day of infusion may be referred to the local diabetes center/endocrinologist for glucose management if appropriate e.g. to be trained to self- administer insulin or oral glucose lowering

medication, and to be provided with glucose lowering medication prescription and an insulin sliding scale regimen, if applicable. Investigators will be free to manage patients in the same way as described in Section 6.4.2.1. If indicated, domiciliary support will be arranged.

Cycle 1, Day 8

- Toxicity/ AE assessment (see Section 7.5.1.3).
- 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, including ECOG performance status, vital signs (temperature, pulse and blood pressure), examination of pertinent organ systems, and brief interim history (change of symptoms) (see Section 7.5.3.2).
- Blood tests for complete blood count and chemistry panel (excluding triglycerides, LDL cholesterol and total cholesterol) (see Section 7.5.3.1).
- Monitoring for OI (see Section 6.4.2.7.1).
- Glucose test prior to copanlisib/placebo infusion and 1 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). See Section 7.5.3.7. Patients are not required to be fasting prior to pre-dose glucose measurement (see Section 6.4).
- Blood pressure measurements according to guidance provided in Section 7.5.3.3.
- PK sampling (see Table 7–2).
- Collection of plasma for non-genetic biomarker analyses prior to copanlisib/placebo infusion (see Section 7.6.1).
- Copanlisib/placebo IV infusion, before rituximab IV infusion.
- Rituximab IV infusion.

Cycle 1, Day 15

- Toxicity/ AE assessment (see Section 7.5.1.3).
- 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, including ECOG performance status, vital signs (temperature, pulse and blood pressure), examination of pertinent organ systems, and brief interim history (change of symptoms) (see Section 7.5.3.2).
- Blood tests for complete blood count, chemistry (excluding triglycerides, LDL cholesterol and total cholesterol) and coagulation panels (see Section 7.5.3.1).
- Monitoring for OI (see Section 6.4.2.7.1).
- Glucose test prior to copanlisib/placebo infusion and 1 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). See Section 7.5.3.7. Patients are not required to be fasting prior to pre-dose glucose measurement (see Section 6.4).

- Blood pressure measurements according to guidance provided in Section 7.5.3.3.
- PK sampling (see Table 7–2).
- Collection of plasma for non-genetic biomarker analyses prior to copanlisib/placebo infusion (see Section 7.6.1).
- Copanlisib/placebo IV infusion, before rituximab IV infusion.
- Rituximab IV infusion.

Cycle 1, Day 22

- Toxicity/ AE assessment (see Section 7.5.1.3).
- 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, including ECOG performance status, vital signs (temperature, pulse and blood pressure), examination of pertinent organ systems, and brief interim history (change of symptoms) (see Section 7.5.3.2).
- Blood tests for complete blood count and chemistry panel (excluding triglycerides, LDL cholesterol and total cholesterol) (see Section 7.5.3.1).
- PK sampling (see Table 7–2).
- Rituximab IV infusion.

After Cycle 1, there are no mandatory procedures on Day 22 of subsequent cycles. Day 22 from Cycle 2 onwards is the earliest time for procedures due at latest on Day 1 of the next cycle.

7.1.2.2.2 Treatment – Cycle 2 and higher

Cycle 2 and higher, Day 1

- IVRS/IWRS transaction for medication dispensing.
- Serum pregnancy test (if applicable): after Cycle 1 serum pregnancy test is mandatory at every cycle for countries where it is required by local regulations.
- Toxicity/ AE assessment (see Section 7.5.1.3).
- 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 including ECOG performance status (see Appendix 14.2, NYHA classification (see Appendix 14.3), weight, vital signs (temperature, pulse and blood pressure), and a complete review of body systems (see Section 7.5.3.2).

- 12-lead ECG 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 infusion (window of up to 2 h prior to and post-infusion is allowed) (see Section 7.5.3.4).
- 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 7.5.3.5).
- Blood tests for complete blood count, chemistry and coagulation panels (see Section 7.5.3.1). Blood test for hemoglobin A1c will be done on Day 1 of every 3 cycles (4, 7, 10 etc.), starting from Cycle 4. Blood tests for triglycerides, LDL cholesterol and total cholesterol will be done 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 (see Section 6.4.2.2).
- GFR measurement (see Section 7.5.3.1 and Appendix 14.6).
- Monitoring for OI (see Section 6.4.2.7.1).
- Glucose test prior to copanlisib/placebo infusion. See Section 7.5.3.7. Patients are not required to be fasting prior to pre-glucose measurement (see Section 6.4).
- Measurement of blood pressure prior to copanlisib/placebo infusion according to guidance provided in Section 7.5.3.3. Blood pressure can be measured during or after copanlisib/placebo infusion if clinically indicated/based on the investigator´s discretion.
- Only in Cycle 2: collection of plasma for non-genetic biomarker analyses prior to copanlisib/placebo infusion (see Section 7.6.1).
- Copanlisib/placebo IV infusion, before rituximab infusion (if applicable).
- Rituximab IV infusion (only at Cycles 3, 5, 7 and 9).
- Only in patients affected by WM:
    - Serum or plasma viscosity: if abnormal at baseline then every 3rd cycle, starting from Day 1 of Cycle 3

Cycle 2 and higher, Day 8

- Toxicity/ AE assessment (see Section 7.5.1.3).
- 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, including ECOG performance status, vital signs (temperature, pulse and blood pressure), examination of pertinent organ systems, and brief interim history (change of symptoms) (see Section 7.5.3.2).
- Blood tests for complete blood count and complete chemistry panel (excluding triglycerides, LDL cholesterol and total cholesterol) (Cycle 2 only). From Cycle 3 onwards, only hemoglobin, platelet and absolute neutrophil count will be performed prior to each copanlisib/placebo infusion (see Section 7.5.3.1).

- Monitoring for OI (see Section 6.4.2.7.1).
- Glucose test prior to copanlisib/placebo infusion. See Section 7.5.3.7. Patients are not required to be fasting prior to pre-dose glucose measurement (see Section 6.4).
- Measurement of blood pressure prior to copanlisib/placebo infusion according to guidance provided in Section 7.5.3.3. Blood pressure can be measured during or after copanlisib/placebo infusion if clinically indicated/based on the investigator´s discretion.
- Only in Cycle 2: collection of plasma for non-genetic biomarker analyses prior to copanlisib/placebo infusion (see Section 7.6.1).
- Copanlisib/placebo IV infusion.

Cycle 2 and higher, Day 15

- Toxicity/ AE assessment (see Section 7.5.1.3).
- 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, including ECOG performance status, vital signs (temperature, pulse and blood pressure), examination of pertinent organ systems, and brief interim history (change of symptoms) (see Section 7.5.3.2)
- Blood tests for complete blood count and chemistry panel (excluding triglycerides, LDL cholesterol and total cholesterol) (Cycle 2 only). From Cycle 3 onwards, only hemoglobin, platelet and absolute neutrophil count will be performed prior to each copanlisib/placebo infusion (see Section 7.5.3.1).
- Monitoring for OI (see Section 6.4.2.7.1).
- Glucose test prior to copanlisib/placebo infusion. See Section 7.5.3.7. Patients are not required to be fasting prior to pre-dose glucose measurement (see Section 6.4).
- Measurement of blood pressure prior to copanlisib/placebo infusion according to guidance provided in Section 7.5.3.3. Blood pressure can be measured during or after copanlisib/placebo infusion if clinically indicated/based on the investigator´s discretion.
- Only in Cycle 2: collection of plasma for non-genetic biomarker analyses prior to copanlisib/placebo infusion (see Section 7.6.1).
- Copanlisib/placebo IV infusion.

7.1.2.3 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 locally during the treatment period as well as during the Active follow up period at the following intervals (see also Section 7.3.2):

- Year 1: Every 8 weeks (± 7 days), starting from Cycle 1 Day 1
- Year 2: Every 12 weeks (± 7 days)
- Year 3 and onwards: Every 24 weeks (± 7 days)

MRI shall be performed instead of CT when local regulations do not permit the use of CT as requested per protocol schedule.

Central independent blinded review of tumor scans will not be performed.

Bone marrow biopsy will be mandatory at baseline and will be sent to central pathology review after local bone marrow assessment. If the baseline biopsy is positive for lymphoma infiltration at Screening, it will be mandatory to perform it again to confirm the first CR, and also at the investigator's discretion if clinical evaluation leads to suspicion of bone marrow infiltration without further radiological findings. No central review of bone marrow biopsy will be performed during treatment or Active follow-up.

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 7.3.3). 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

7.1.2.4 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. They will comprise the following:

- IVRS/IWRS transaction to register end of treatment.
- Serum pregnancy test (if applicable): mandatory for countries where it is required by local regulations (see Section 7.5.3.1).
- Toxicity/AE assessment (see Section 7.5.1.3).
- 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).
- Review of the blood glucose measurements/meal timing/oral glucose lowering medication/insulin doses, if applicable (see Section 6.4.2.1).

- Complete physical examination including ECOG performance status (see Appendix 14.2, NYHA classification (see Appendix 14.3), weight, vital signs (temperature, pulse and blood pressure), and a complete review of body systems, see Section 7.5.3.2).
- 12-lead ECG including QTcB and QTcF evaluation (if not previously done within four weeks) (see Section 7.5.3.4).
- MUGA scan or echocardiogram to measure LVEF (if not previously done within four weeks) (see Section 7.5.3.5). The method must be the same as used at baseline and throughout the whole study.
- Blood tests for hemoglobin A1c, complete blood count, complete chemistry and coagulation panels (see Section 7.5.3.1). 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 (see Section 6.4.2.2).
  The testing for HbA1c is not required if the previous test was performed within 4 weeks preceding EOT visit.
- Collection of plasma for tumor genetics and non-genetic biomarker analyses (see Section 7.6.1).
- 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 discontinues due to PD which has been radiologically evaluated within the 4 weeks preceding EOT (see Section 7.3.2).
- 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
- A tumor biopsy is encouraged at the time of progression (optional) to allow investigation of copanlisib resistance. In addition, if a tumor biopsy/excision occurs during the course of the study based on medical need, a sample should be submitted (though no biopsy is required during treatment).

7.1.2.5 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).

HbA1C testing should be performed approximately 3 months after the EOT visit whenever possible.

7.1.2.5.1 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.

This visit includes:

- Toxicity/AE assessment (see Section 7.5.1.3)
- Concomitant medication review

If clinically indicated:

- Brief physical examination, including ECOG performance status, vital signs (temperature, pulse and blood pressure), examination of pertinent organ systems, and brief interim history (change of symptoms) (see Section 7.5.3.2)
- Complete blood count (see Section 7.5.3.1)
- Complete chemistry and coagulation panels (see Section 7.5.3.1)

If a patient has begun treatment with another anti-cancer agent and 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.

7.1.2.5.2 Active follow-up

Patients who 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, including bone marrow analysis to confirm the first CR in patients with previous bone marrow infiltration during Screening, as outlined in this protocol from the day of randomization until disease progression is documented or new anti-tumor treatment is administered. For further details see Section 7.3.2.

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 PV department.

The end of Active follow-up period is defined as (i) when disease progression is documented or (ii) when a new anti-tumor treatment is administered, whichever occurs first.

7.1.2.5.3 Survival follow-up

All patients will be followed off study for overall survival at 3-monthly intervals during the survival follow-up period (up to 7 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

7.2 Population characteristics

7.2.1 Demographics

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

- Year of birth and age
- Sex
- Race
- Ethnicity

7.2.2 Medical history

Relevant medical history findings (i.e., relevant previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected:

- Not pertaining to the study indication
- Start before signing of the informed consent

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 7.5.1.1.

The CIRS-G scoring sheet will be completed and recorded, if applicable (see Appendix 14.7).

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, peripheral neuropathy, and bone marrow parameters
- 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

7.2.3 Other baseline characteristics

Information on patient’s history of smoking will be collected and recorded.

7.3 Efficacy

7.3.1 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 central review or death from any cause (if no progression is documented).

For secondary and other efficacy variables please refer to Section 8.3.1.

7.3.2 Radiological tumor assessments

Radiologic tumor assessments will include neck, chest, abdomen and pelvis, and will be evaluated locally at the study site.

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 CT/MRI (if a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the screening). Scans done up to 28 days prior to first dose can be used as baseline studies. The method chosen at baseline 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 (IV [and oral, if indicated, per Imaging Manual] contrast-enhanced CT/MRI) tumor assessment will be performed every 8 weeks (± 7 days) during Year 1, every 12 weeks (± 7 days) during Year 2, and every 24 weeks (± 7 days) during Year 3 and onwards. CT/MRI scans are not required at the EOT visit if the patient discontinues due to PD which has been radiologically confirmed within the 4 weeks preceding EOT. Central independent blinded review of tumor scans will not be performed.

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.

The response assessment will be done according to the Lugano Classification. For patients with WM, additional criteria apply (see Section 7.3.3). Detailed instructions on tumor assessment are provided in Appendix 14.4.

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 (and oral, if indicated, per Imaging Manual) 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 treatment phase of the study, should the case examinations be continued without contrast. In certain countries MRI should be used based on local regulations.

7.3.3 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.

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 7.1.2.3).

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

Detailed instructions on tumor assessment are provided in Appendix 14.4.

7.4 Pharmacokinetics / pharmacodynamics

7.4.1 Sampling

PK sampling will be performed in all patients as follows (see also Table 7–2):

For copanlisib + metabolite (M-1), and other metabolites, if needed:	on Cycle 1 Day 8: pre-infusion copanlisib/placebo, 5-15 min and 55 min (within 5 min prior to end of infusion) on Cycle 1 Day 15: pre-infusion and end of rituximab infusion (within 5 min prior to the end of infusion)
For rituximab:	on Cycle 1 Day 15: pre-infusion and end of rituximab infusion (within 5 min prior to the end of infusion) on Cycle 1 Day 22: pre-infusion and end of rituximab infusion (within 5 min prior to the end of infusion)

If sampling for copanlisib/placebo and/or rituximab is not feasible at Cycle 1, samples may be collected at Cycle 3 (on the corresponding days with the matched medication). A separate IV line should be used for PK draws.

Deviations from the specified time points will be documented and taken into account when calculating the PK parameters. Those deviations do not qualify as protocol violation. All blood samples should be collected, processed, stored, and shipped according to procedures outlined in the Laboratory Manual.

PK samplings are not applicable to sites who cannot obtain approval by competent Health Authority.

7.4.2 Analysis

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

Concentration data of copanlisib, its metabolite M-1, and other metabolites, if 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, if needed, in this Phase III population. A population pharmacokinetic approach will be used for the analysis and reported in a standalone report.

7.5 Safety

7.5.1 Adverse events

7.5.1.1 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 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.

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
  (i.e. elective or scheduled surgery arranged prior to the start of the study)
- 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 medically important serious event as judged by the investigator

7.5.1.2 Classifications for adverse event assessment

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

7.5.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 7.5.1.1.

7.5.1.2.2 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

7.5.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the CRF.

The causality assessment should be done separately for each study treatment as detailed on the CRF.

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 clear 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 there is a reasonable suspicion that the AE is 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 patients response after re-challenge should be considered in the 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 may be suspected to cause the event in question.
- 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.

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”

7.5.1.2.4 Action taken with study treatment

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

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

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

7.5.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

7.5.1.2.6 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

7.5.1.3 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. AEs will be documented in an event-based manner, using NCI-CTCAE v.4.03 guidelines.

The observation phase for AEs will start with signing the ICF and shall end 30 days after the last dose of study drug. The safety follow-up visit shall occur 30 days (window of +5 days allowed) after the last dose of study medication. AEs still present at the end of the observation phase should be followed until resolution or stabilization unless, in the investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

AEs to be documented include all AEs that were ongoing at the end of treatment as well as new AEs that, in the opinion of the investigator, could be related to study treatment (information may be obtained via phone call). Documentation must be supported by an entry in the patient's file.

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 PV department.

The investigator is responsible for the grading of each category mentioned in Section 7.5.1.2. For all SAEs the sponsor is to carry out a separate assessment for expectedness, seriousness and causal relationship to the test drug.

If any patient dies in the safety follow-up period 30 days (window of +5 days allowed) after last dose of study medication, the investigator will inform the sponsor and record the cause of death in detail within 24 hours on an SAE form.

A laboratory test abnormality considered clinically relevant, e.g., causing the patient to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant 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.

7.5.1.4 Reporting of serious adverse events

The definition of SAEs is given in Section 7.5.1.1.

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.

All SAEs occurring during the observation period defined in Section 7.5.1.3 must immediately (within 24 hours of the investigator's awareness) be reported to the recipient detailed in the manual. An SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the designated recipient. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

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 7.5.1.1), 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".**

In the event of a fatal or life-threatening reaction, the investigator must seek relevant follow-up information and must complete a follow-up report to be faxed 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.

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 International Conference on Harmonization (ICH) criteria for an SAE (see SAE definition in Section 7.5.1.1).

Once data regarding survival and remission status are no longer required by the protocol, only additional primary tumors regarded as related to study treatment should be reported.

Progressive disease should not be reported.

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.

7.5.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the IB for copanlisib and prescribing information / SmPC for rituximab.

Overview listings of frequent events that have occurred so far in the clinical development 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.

7.5.1.6 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 unexpected AEs, including hypersensitivity reactions.

Based on data from Phase I studies with copanlisib, as soon as there is reasonable suspicion of the following AE, the investigator should immediately notify the sponsor as outlined in section 7.5.1.4, regardless of whether the investigator assessed the AE as serious or non-serious:

- Non-infectious pneumonitis

7.5.2 Pregnancies

The investigator must report to the sponsor any pregnancy occurring in a study patient during the patient's participation in this study. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE.

For a study patient, the outcome of the pregnancy should be followed up carefully, and any outcome of the mother or the child should be reported.

The sponsor usually does not gather information of drug exposure via the father, however, if such cases are reported, all efforts should 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.

7.5.3 Further safety

7.5.3.1 Laboratory

All laboratory analyses will be performed locally according to the schedule summarized in the flow chart of Section 7.1.1.

- Complete blood count: hemoglobin, hematocrit, RBC, and WBC (with differential to include neutrophil, lymphocyte, monocyte, basophils and eosinophil counts), and platelet count. Differential blood count in percentage can be provided when absolute count is not available per standard of care of the local lab.
- 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, BUN (or urea if BUN is not routinely measured at the site), creatinine, uric acid, total bilirubin, creatine kinase, ALT, AST, 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 according to local standards prior to sampling. For patients who cannot adhere to these fasting requirements the evaluation of lipid-panels including triglycerides is considered not feasible.
- Coagulation panel: INR or PT, and PTT.
- Serum pregnancy test in women of childbearing potential. 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).
- Quantification of proteinuria by either a 24 h 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 on the same sample. Dipstick analysis is **not** acceptable to assess proteinuria.
- Measurement of GFR according to the MDRD abbreviated formula.
- Blood test for HBV and HCV (HBsAg, HBcAb and anti-HCV antibody; if HBsAg or HBcAb positive also HBV DNA; if anti-HCV antibody positive also HCV RNA).
- Hemoglobin A1c.
- CD4 (for patients with signs of infection), blood cultures if febrile neutropenia occurs or when ANC of CTCAE grade 4, PCR for CMV.
- For patients with identified risk factors and those who developed OI, additional laboratory assessments will include (see Section 6.4.2.7.1):
    - 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 7.5.1.1). 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.

7.5.3.2 Physical examinations

Physical examinations will be performed according to the schedule summarized in the flow chart of Section 7.1.

7.5.3.2.1 Complete physical examination

Complete physical examination includes ECOG performance status assessment, NYHA classification (see Appendix 14.3), height (only at Screening), weight, vital signs (see Section 7.5.3.3), and 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 (paleness, jaundice, redness/rash, acneiform changes) including clinical assessment of hydration status via hand extensor surface skin turgor
- Hand and feet (signs of hand-foot-skin-syndrome/ hand-foot skin reaction)
- Eyes (accommodation, double images, abnormal sensitivity to light, jaundice)
- Ears, nose, throat (presence of petechial bleeding, gingival bleeding) including inspection of oral mucosa for hydration status
- Head and neck
- Lungs: evaluation of new onset or worsening of pulmonary symptoms, and lung examination
- Heart
- Abdomen (pain, tenderness, peristaltism, ascites, organomegaly)
- Lymph nodes
- Musculoskeletal system and spine
- Lower legs (petechial bleedings, ulcer, signs of thrombosis)
- Neurologic findings

7.5.3.2.2 Brief physical examination

Brief physical examination includes ECOG performance status, vital signs (see Section 7.5.3.3), examination of pertinent organ systems, and brief interim history (change of symptoms).

The examination of pertinent organ systems should investigate at minimum:

- Skin (paleness, jaundice, redness/rash, acneiforme changes) including clinical assessment of hydration status via hand extensor surface skin turgor
- Hand and feet (signs of hand-foot-skin-syndrome)
- Throat (presence of petechial bleeding, gingival bleeding) including inspection of oral mucosa for hydration status
- Lungs: evaluation of new onset or worsening of pulmonary symptoms, and lung examination
- Abdomen (pain, tenderness, peristaltic, ascites, organomegaly)
- Neurologic findings

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

7.5.3.3 Vital signs

Pulse, blood pressure and temperature will be assessed according to the schedule summarized in the flow chart of Section 7.1. If clinically indicated, it is at the investigator's discretion to perform these measurements more frequently.

Blood pressure measurement on infusion 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 min before blood pressure is recorded.

- On copanlisib/placebo infusion days: blood pressure will be measured at pre-dose. Blood pressure can be measured during or after copanlisib/placebo infusion if clinically indicated/based on the investigator´s discretion.

For details on the management of arterial hypertension, see also Sections 6.4.1 (dose modification) and 6.4.2.3 (treatment of blood pressure increases).

7.5.3.4 12-lead ECG

12-lead ECGs will be performed according to the schedule summarized in the flow chart in Section 7.1. 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 min 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.

7.5.3.5 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.

7.5.3.6 ECOG performance status

Grading definitions are given in Appendix 14.2.

7.5.3.7 Glucose measurement on copanlisib/placebo infusion days

- 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 rituximab infusion. Additional measurements to be performed at the clinic as clinically indicated.
- On subsequent copanlisib/placebo infusion days: glucose will be measured prior to copanlisib/placebo infusion. Additional measurements to be performed at the clinic as clinically indicated.
- On all copanlisib/placebo infusion days: time window of ± 10 min is allowed for glucose measurements (except for the pre-dose measurement).

7.6 Other procedures and variables

7.6.1 Biomarker investigations

Overview

There will be several parts to biomarker testing in this study:

1) tumor-genetic testing of fresh (preferred) or archival tumor tissue, and possibly of circulating tumor DNA isolated from plasma
2) non-genetic biomarker testing
3) genetic biomarker research

Genetic biomarker research of the whole blood requires 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

Biomarker samplings are not applicable to sites who cannot obtain approval by competent Health Authority.

Optional Tumor Tissue

One or more of the following pre-treatment tumor tissue samples should 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 study enrollment) is mandatory when available.

A tumor biopsy is also encouraged at the time of progression (optional) to allow investigation of copanlisib resistance. In addition, if a tumor biopsy/excision occurs during the course of the study based on medical need, a sample should be submitted (though no biopsy is required during treatment)

Archival 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 in addition 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 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 Table 7–1). Plasma may be used to quantify the circulating levels of various proteins.

Plasma for tumor genetics: Blood samples will be obtained and used for plasma preparation at the time points as indicated in the study flow chart (see Table 7–1). Plasma may be used as a source of circulating tumor DNA for the evaluation of mutations in tumor-related genes of interest.

Whole blood (only applicable for patients who provided 'genetic' research consent): At Screening, 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, if the evaluations are performed.

In addition to the proteins and genes 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.

7.6.2 Quality of life questionnaire

No further data collection is required for the QoL questionnaires, and electronic PRO devices will no longer be used.

7.7 Appropriateness of procedures / measurements

The efficacy assessments used in this study include those considered standard of care to evaluate objective tumor response rate in patients with iNHL. Although the recently published Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (27) strongly support the use of PET-CT for staging and response assessment of routinely FDG-avid histologies, especially in clinical trials, it was decided to use in this study only a CT-based response. CT/MRI-based response remains in fact preferred for histologies with low or variable FDG avidity and in regions of the world where PET-CT is unavailable. Moreover, in trials exploring new agents in multiply relapsed disease where data are lacking regarding PET-CT and where assessment of disease control is more important than likelihood of cure, CT/MRI-based response may also be more relevant.

The safety assessments are appropriate and standard to monitor safety and assess toxicity.

8. Statistical methods and determination of sample size

8.1 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).

Further details on the statistical analyses including handling of missing data will be provided in the SAP that will be approved before database release.

8.2 Analysis sets

The statistical analysis sets are defined as follows:

Full analysis set (FAS): all patients randomized.

Safety analysis set (SAF): all FAS patients with at least one intake of copanlisib/placebo or rituximab.

All patients with valid PK data will be included in the evaluation of PK concentrations and parameters.

The efficacy variables will be analyzed in the FAS.

The SAF will be used for the analyses of the safety variables. The FAS will be used for the display of all other variables.

8.3 Variables

8.3.1 Efficacy variables

Disease progression (PD) in the context of statistical efficacy evaluation is considered to be radiological progression, as assessed by central review. For WM patients without radiologically measureable disease, clinical progression will be used.

8.3.1.1 Primary efficacy variable

- Progression-free survival (PFS), defined as the time (in days) from randomization to PD or death from any cause (if no progression is documented). The actual date of tumor assessments will be used for this calculation. PFS for patients without PD or death at the time of analysis will be censored at the date of their last tumor evaluation. PFS for patients who have neither tumor assessments nor death after baseline will be censored at Day 1.

8.3.1.2 Secondary efficacy variables

- Objective tumor response rate (ORR) assessed in all patients up to the time of analysis of PFS. ORR is defined as the proportion of patients who have a best response rating over the whole duration of the study (i.e. until time of analysis of PFS) of complete response (CR) or partial response (PR) according to the Lugano Classification and for patients with WM a response rating of CR, very good partial response (VGPR), PR, or minor response (MR) according to the Owen Criteria. Detailed instructions on tumor assessment are provided in Appendix 14.4.
- Duration of response (DOR), 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. DOR will only be defined for patients with at least one CR, VGPR, PR, or MR. Patients without PD or death at the time of analysis will be censored at the date of their last tumor evaluation.
- Complete response rate (CRR), assessed in all patients up to the time of analysis of PFS.
- Time to progression (TTP), defined as the time from randomization to PD or death related to PD, whichever is earlier. The actual dates of tumor assessments will be used for this calculation. 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 evaluation. TTP for patients who have neither tumor assessments nor death related to PD after baseline will be censored at Day 1. Death related to PD is considered to be any death except for:
    - Death due to an AE unrelated to progression
    - Death with a specification of “other” as reason (which excludes PD)
- Overall survival (OS), defined as the time (in days) from randomization until death from any cause. OS of patients alive at the time of analysis will be censored at the last date they were known to be alive.

- Time to deterioration in DRS-P of at least 3 points, as measured by the FLymSI-18 questionnaire. Patients will be considered as “censored” at the date of their last tumor evaluation, if the reason for stopping treatment is not related to PD. Patients dropping out due to progression-related reason or experiencing a PD event or death due to any reason will be considered as having had their decline in DRS-P at the date of their last tumor evaluation.
- Time to improvement in DRS-P of at least 3 points, as measured by the FLymSI-18 questionnaire, 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). Patients will be considered as "censored" at the date of their last tumor evaluation, if the reason for stopping treatment is not related to PD. Patients dropping out due to progression-related reason or experiencing a PD event or deaths due to any reason will be considered censored at the largest observation time (of events and censoring in all patients evaluated for improvement), plus 1 day.

Further sensitivity analyses for the DRS-P analyses will be described in the SAP (e.g. might involve different handling of the last response status for that patient or considering PD and death as censored). 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.

8.3.1.3 Other efficacy variables

- AUC across all data of FLymSI-18 DRS-P subscale score
- FLymSI-18 total and subscale scores (DRS-P, DRS-E, TSE, FWB), and time to onset of physical symptoms of lymphoma based on the DRS-P subscale
- Performance status (ECOG)

8.3.2 Safety variables

Safety variables will include treatment-emergent AEs, SAEs, laboratory parameters, and vital signs. The severity of AEs will be graded using the CTCAE v 4.03 dictionary. AEs will be classified by the investigator as related or not related to test drug. 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 (end of safety follow-up).

8.4 Statistical and analytical plans

8.4.1 Population characteristics

Demographics and baseline characteristics will be summarized by treatment group in the FAS.

A listing for the retrospective evaluation of histopathological diagnosis performed centrally at baseline will be provided. These data are exploratory.

8.4.2 Efficacy

All efficacy analyses will be performed when at least 190 PFS events (PD by central review or death before PD) are observed in the study. Also see minimum number of PFS events that has to be observed in each of the two strata defined by the inclusion criterion (progression-free and treatment-free interval of ≥ 12 months after completion of the last rituximab-containing treatment vs. unwilling/unfit to receive chemotherapy). See Section 8.6.

Evaluations from central blinded review will be used for the primary efficacy analyses of primary and secondary endpoints containing radiological tumor assessments.

8.4.2.1 Primary efficacy analysis

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

In order to evaluate whether copanlisib in combination with rituximab is superior to placebo in combination with rituximab in prolonging PFS in patients with relapsed iNHL who have received one or more lines of treatment, including rituximab, the following null hypothesis will be tested in the FAS:

$H_{0,\,PFS}$: $S_{Copanlisib+Rituximab}(t) = S_{Placebo+Rituximab}(t)$ for all time points $t \geq 0$

The alternative hypothesis will be:

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

where $S_{Copanlisib+Rituximab}$ denotes the survival function of the copanlisib + rituximab group and $S_{Placebo+Rituximab}$ denotes the survival function of the placebo + rituximab group in the total study population.

The following decision rule to test the null hypothesis will be applied:

According to the size of this study it is justified to assume under $H_{0,\,PFS}$ the one-sided log-rank test (36) is a sufficiently close approximation to the normal distribution. If the z-value from the one-sided log-rank test (for the difference $\boldsymbol{S_{Copanlisib+Rituximab} - S_{Placebo+Rituximab}}$, stratified by the factors used for randomization: FL vs. other iNHL histologies, and progression-free and treatment-free interval of ≥ 12 months after completion of the last rituximab-containing treatment vs. unwilling/unfit to receive chemotherapy) is larger than the critical quantile from the normal distribution ($z_{0.975} = 1.96$), the null hypothesis will be rejected in favor of the alternative hypothesis.

The PFS will be tested in the hierarchy test (see Section 8.4.2.3).

Additional analyses of the primary efficacy variable

Kaplan-Meier estimates of median times to PFS (including 95% confidence interval) and Kaplan-Meier curves will be presented for each treatment group.

The hazard ratios (including 95% confidence interval) will be derived from Cox proportional hazards models that are stratified by the same factors as used for the primary efficacy analysis.

The censoring mechanism of subjects without PFS event at the time of analysis is assumed to be non-informative for the primary efficacy analysis. Sensitivity analyses will be performed, assessing the impact of a potential informative censoring of such subjects. These will include

the use of different rules for considering subjects without PFS events as having an event or being censored and will be further outlined in the SAP.

8.4.2.2 Secondary efficacy parameters

All secondary efficacy variables will be analyzed in the FAS at the time of the analysis of the primary variable.

The ORR will be analyzed using the Cochran-Mantel-Haenszel test (37), stratified for the same stratification factors as used for PFS. The null hypothesis is defined as:

$H_{0,\,ORR}$: $ORR_{Copanlisib+Rituximab} \leq ORR_{Placebo+Rituximab}$

The alternative hypothesis is:

$H_{1,\,ORR}$: $ORR_{Copanlisib+Rituximab} > ORR_{Placebo+Rituximab}$

The following decision rule to test the null hypothesis will be applied:

If the p-value for the two-sided Cochran-Mantel-Haenszel test is smaller than the 0.05 significance level and the estimated difference $ORR_{Copanlisib+Rituximab}$ - $ORR_{Placebo+Rituximab}$ (comparing copanlisib + rituximab vs. placebo + rituximab) is greater than 0.0, the null hypothesis will be rejected in favor of the alternative hypothesis.

The time to deterioration and time to improvement in DRS-P subscale of FLymSI-18 will be analyzed analogously to the PFS, using similar hypotheses, decision rules, and significance level.

OS, CRR, TTP as well as DOR will be analyzed supportively only.

OS, TTP, and DOR will be analyzed using stratified log-rank tests analogue to the analysis for the primary endpoint, PFS.

CRR will be analyzed using the Cochran-Mantel-Haenszel test and estimated difference analogous to the analysis of ORR. The test will be adjusted for the same stratification factors as used for PFS.

The first analysis of OS will be performed at the time of analysis of the primary endpoint, PFS. The survival status will further be collected quarterly during the survival follow-up period up to 7 years after the last patient started study treatment.

A follow-up analysis of OS will be performed. Details will be described in the SAP.

8.4.2.3 Confirmatory statistical test strategy

Separate statistical test strategies will be conducted for the United States and Europe as outlined below.

United States

For the United States, to control the study-wise alpha, a fixed-sequence multiple testing strategy will be implemented. The sequence of the testing of primary and secondary endpoints will be as follows and is shown in Figure 8–1.

The primary efficacy variable PFS will be tested in the FAS population (tested at one-sided alpha=0.025).

If the PFS test in the FAS population is successful,

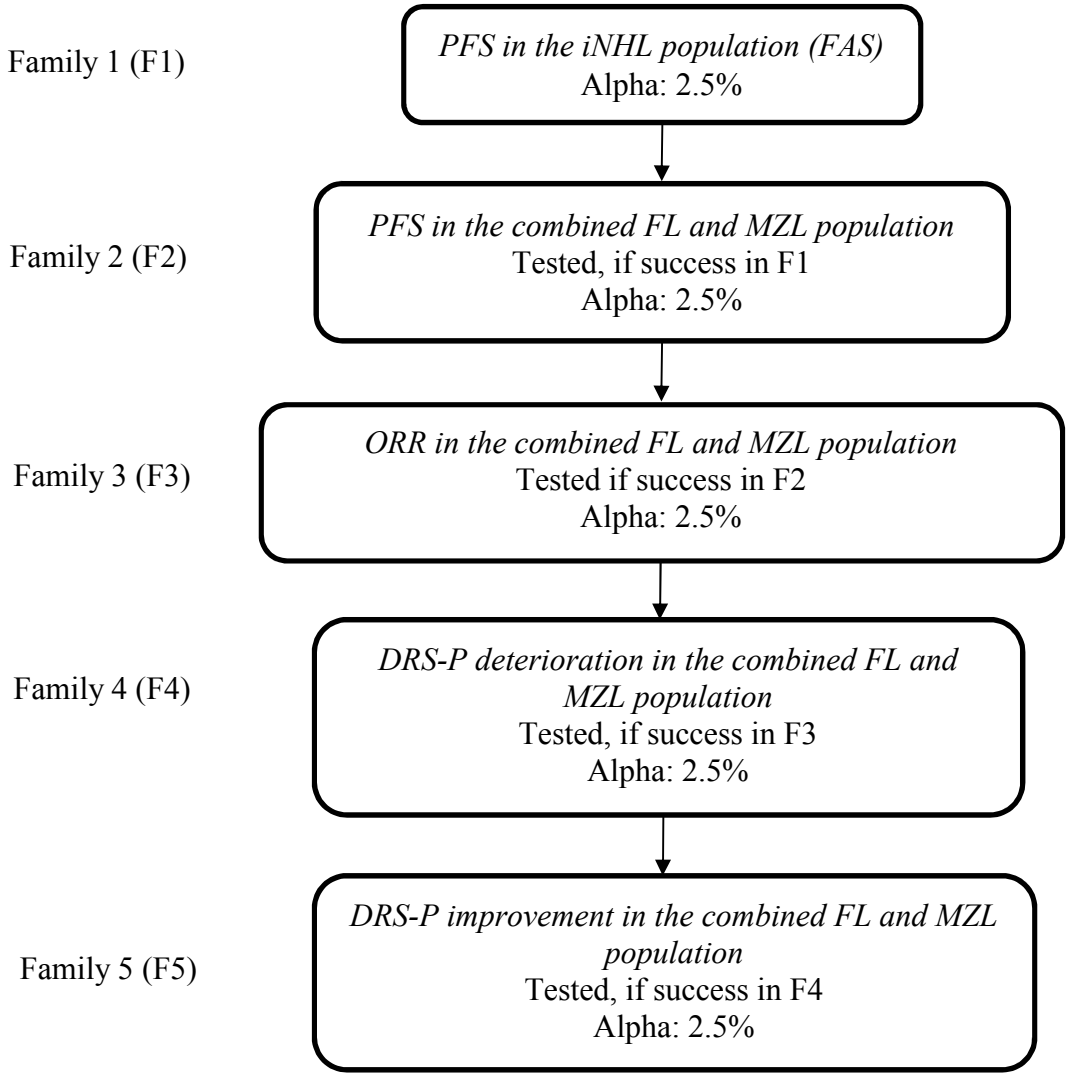
a) a second test on the PFS will be performed (tested at one-sided alpha=0.025), evaluating the subpopulation of combined FL and MZL population, if this is successful

b) a test on the ORR in the combined FL and MZL population will be performed (tested at one-sided alpha=0.025), if this is successful

c) a test on the time to deterioration in DRS-P in the combined FL and MZL population will be performed (tested at one-sided alpha=0.025), if this is successful

d) a test on the time to improvement in DRS-P in the combined FL and MZL population will be performed (tested at one-sided alpha=0.025), it would conclude the confirmatory test procedure.

Figure 8–1 Confirmatory test strategy based on five test families for United States



For testing Families 1 to 2 of this confirmatory test strategy, an assessment of power based on Schoenfeld's formula (52) was performed for two scenarios as listed in Table 8–1:

- Scenario 1: HR=0.61 in the FAS population (according to the re-planned sample size planning)
- Scenario 2: HR=0.53 in the FAS population (less conservative assumption)

Table 8–1 Assessment of statistical power for PFS test in the overall FAS population and combined FL and MZL population

	Total patients	Dropout rate	Events to be expected (E)	Hazard ratio	Power
Scenario 1:					
Family 1: overall FAS population	458	30%	190	0.61	89.5%
Family 2: combined FL and MZL population	370	30%	140	0.61	78.7%
Scenario 2:					
Family 1: overall FAS population	458	30%	190	0.53	98.5%
Family 2: combined FL and MZL population	370	30%	140	0.53	94.3%

The number of total patients in Table 8–1 is the number of patients having been randomized in the study.

Europe

For Europe, to control the study-wise alpha, a fixed-sequence multiple testing strategy will be implemented. In this strategy, the sequence of the testing of primary and secondary endpoints is as follows and is shown in Figure 8–2:

The primary endpoint PFS will be tested in the FAS population (tested at one-sided alpha=0.025).

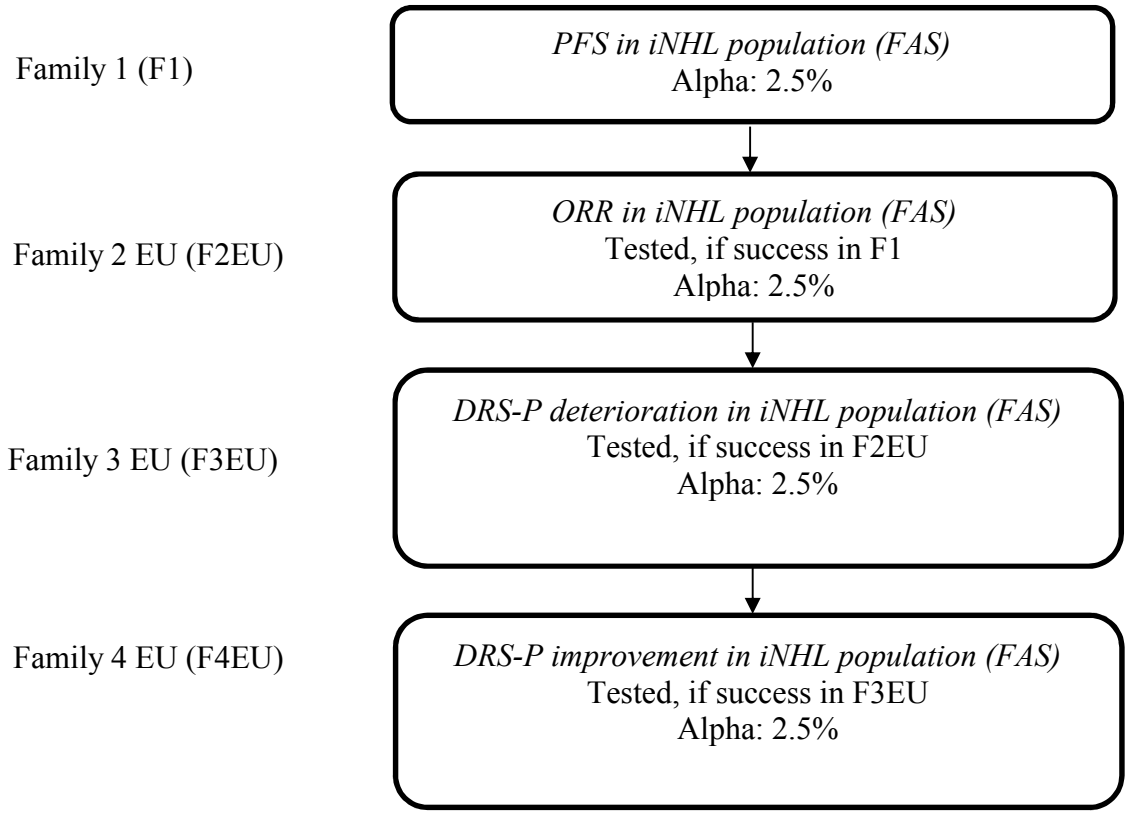
If the PFS test in the FAS population is successful,

a) a second test on the ORR in the FAS population will be performed (tested at one-sided alpha=0.025), if this is successful,

b) a test on the DRS-P deterioration in the FAS population will be performed (tested at one-sided alpha=0.025), if this is successful,

c) a test on the DRS-P improvement in the FAS population will be performed (tested at one-sided alpha=0.025), it would conclude the confirmatory test procedure.

Figure 8–2 Confirmatory test strategy based on four test families for Europe



Note: EU refers to Europe

8.4.2.4 Other efficacy evaluations

An additional analysis of the physical symptoms of lymphoma (as measured using the FLymSI-18 DRS-P subscale) will be performed to assess differences between treatment arms in the FAS based on AUC. Total FLymSI-18 and subscales will be evaluated descriptively. Further details on PRO data analysis will be provided in the SAP.

Performance status (ECOG) will be summarized for the original score, as well as for the change from baseline score by treatment group.

8.4.3 Subgroup Analyses

Countries will be combined into regions US vs. Europe vs. rest of the world in order to define regional subgroups.

Subgroup analyses will include forest plots as well as treatment-interaction analyses, both for the region subgroups as well as further subgroups (e.g. based on stratification factors and/or baseline characteristics) and will be provided both for the primary efficacy endpoint as well as other relevant efficacy and/or safety endpoints. The treatment-interaction analysis will be conducted for the primary efficacy endpoint (PFS), and the secondary efficacy endpoints time to worsening of DRS-P and time to improvement in DRS-P.

8.4.4 Safety Analyses

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

All AEs, treatment-emergent and hematological/biochemical toxicities based on laboratory measurements, as well as drug-related AEs and SAEs, will be summarized by CTCAE version 4.03 category and worst grade.

In addition, results of physical examination, vital signs, and ECG will be summarized.

8.4.5 Pharmacokinetic Data

Individual concentration-time data will be provided in a clinical study report appendix.
A population pharmacokinetic approach will be used for the analysis, and the results will be reported separately in a modeling and simulation report. Rituximab concentrations will be listed and the pharmacokinetics compared to the published rituximab PK data in the modeling and simulation report. All patients who provide valid PK samples are valid for population PK.

8.5 Planned interim analyses

No interim efficacy analyses are planned for this study. A DMC meeting will take place after the 30th randomized patient has completed the first cycle of treatment and provide recommendation on whether it is safe to continue recruitment into the combination arm.

8.6 Determination of sample size

EAST 6.4 is used to calculate sample size. Sample size estimation is based on the evaluation of the primary efficacy endpoint, PFS, in the FAS.

The two treatment arms copanlisib in combination with rituximab and placebo in combination with rituximab will be compared. Superiority of the copanlisib + rituximab arm over the placebo + rituximab arm will be tested for the FAS.

Sample size justification for primary efficacy test on PFS in the total study population

A recent study (AUGMENT, 51) reported a hazard ratio of 0.46 (95% CI 0.34-0.62) for the PFS, and a median PFS of 14.1 months in the rituximab + placebo arm in the indication of second line iNHL. Based on the results from this study, Bayer has decided to update the sample size justification.

With at least 190 PFS events (progression based on central review or death if death occurs before progression), a randomization ratio of 2:1 between the experimental and control arms, a 1-sided alpha of 0.025, a hazard ratio of 0.61 (i.e., median PFS of 23 months for copanlisib + rituximab arm and 14 months for placebo + rituximab arm) can be detected with a power of at least 89%.

Based on the planned 450 patients for this study and the observed and projected recruitment as well as blinded monitoring of event times, the expected study duration to reach at least 190 events is 59 months (with maximum accrual rate being approximately 10 patients per month). The percentage of dropouts (ie. lost to survival follow-up or withdrawal of consent before their PFS event) rate is assumed to be 135 (30%) dropout patients over the duration of the study through the primary PFS analysis.

The primary analysis will be performed when at least 190 centrally evaluated PFS events are observed in the study.

As an additional criterion, a sufficient number of PFS events has to be observed in each of the two strata defined by the inclusion criterion (progression-free and treatment-free interval of ≥ 12 months after completion of the last rituximab-containing treatment vs. unwilling/unfit to receive chemotherapy) before the study is unblinded for primary evaluation. This especially ensures the contribution of events also from patients who have previously shown a good response to rituximab.

The required minimum number of PFS events in these strata will depend on the relative proportion of patients recruited into the respective cohorts and is shown in Table 8–2 The observed proportions and event numbers will be determined during blind data review after the end of recruitment.

Table 8–2 Required number of PFS events per entry criteria stratum

Proportion of patients randomized in one strata	Required number of PFS events	Proportion of patients randomized in the other strata	Required number of PFS events
0% - 5%	no required numbers (in both strata)	95% - 100%	no required numbers (in both strata)
>5% - 10%	10	90% - <95%	122
>10% - 20%	20	80% - <90%	112
>20% - 30%	33	70% - <80%	99
>30% - 40%	46	60% - <70%	86
>40% - 50%	59	>50% - <60%	73

As an example: In case 32% of patients would be recruited in the “progression-free and treatment-free interval of ≥ 12 months after completion of the last rituximab-containing treatment” stratum, then at least 46 PFS events are required in this stratum. In addition, at least 86 PFS events from the complement stratum “considered unwilling/unfit to receive chemotherapy by the CIRS-G” are required. To fulfill the overall criterion of at least 190 PFS events, approximately 58 additional events from any of the two strata are required.

In case of an extreme proportion of censored/discontinued patients in a stratum that severely impacts the relation of "Proportion of recruited patients" ≈ "Proportion of PFS events", the study team might decide to deviate from the above rule during blind data review.

Sample size assumptions for the first DMC meeting.

When the first 30 patients are recruited in this blinded study, the probability to have at least 15 patients in the copanlisib+rituximab arm is greater than 95%. These 15 patients are considered to be adequate for initial assessment of safety of the combination drug by the DMC.

9. Data handling and quality assurance

9.1 Data recording

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site. The site must implement processes to ensure this happens. A source document checklist will be used at the site to identify the source data for all data points collected and the monitor will work with the site to complete this.

Data recorded from "only screened patients (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, data to be recorded on the CRF are demographic information (patient number, year of birth/age, sex, race and ethnicity), the reason for premature discontinuation and date of last visit. These data will be transferred to the respective database.

For screening failures with an SAE, the following additional data should be collected on the CRF, in addition to demographic information, primary reason for discontinuation and date of last visit:

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

9.2 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
- 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.

9.3 Data processing

The data collection tool for this study will be a validated electronic system called RAVE. Patient data necessary for analysis and reporting will be entered/ transmitted into a validated database or data system (e.g. TOSCA; SAS). Clinical data management will be performed in accordance with applicable sponsor'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, ePRO).

For data coding internationally recognized and accepted dictionaries will be used; Medical Dictionary for Regulatory Activities (MedDRA) and the CTCAE version 4.03 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.

9.4 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.

9.5 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.

10. 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
  - Results of parallel animal studies
    (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).

- 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 given by the sponsor for destruction.
- In case 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 5.2.1.

11. Ethical and legal aspects

11.1 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 GCP guidelines and under 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 10.

11.2 Patient information and consent

All relevant information on the study will be summarized in an integrated patient information sheet ICF provided by the sponsor or the study center. A sample patient information and ICF is provided as a document separate to this protocol. Separate patient information sheets/ ICFs will be provided to the patients on a voluntary basis for the following:

- Pharmacogenetic ICF
- ICF for collection of data on pregnancy and birth
- ICF on study updates

Based on the patient information sheet, the investigator or designee will explain all relevant aspects of the study to each patient, 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 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 data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the SAP.
- 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 SAP. The patient has the right to object to the generation and processing of this post-withdrawal data. The patient's oral objection may be documented in the patient's source data.

Each patient will have ample time and opportunity to ask questions.

Only if the patient voluntarily agrees to sign the informed consent form and has done so, may he/she enter the study. Additionally, the investigator and other information provider (if any) will personally sign and date the form. The patient 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.

The informed consent form and any other written information provided to patients 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 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.

11.3 Publication policy

The sponsor is interested in the publication of the results of every study it performs.

All relevant aspects regarding publication will be part of the contract between the sponsor and the investigator/institution.

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

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 EU regulation, 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.

11.4 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.

11.5 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 on 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.

12. Reference list

1. Shankland KR, Armitage JO, Hancock BW. Non-Hodgkin lymphoma. Lancet. 2012;380(9844):848-57.
2. Ferlay J, Bray F, Forman D, Mathers C, Parkin D. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet] Available from: http://globocan.iarc.fr.

3. Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood. 2011;117(19):5019-32.
4. A clinical evaluation of the International Lymphoma Study Group classification of non-Hodgkin's lymphoma. The Non-Hodgkin's Lymphoma Classification Project. Blood. 1997;89(11):3909-18.
5. DeVita VT, Lawrence TS, Rosenberg SA. DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology 9th ed.
6. Travis LB, Curtis RE, Glimelius B, Holowaty E, Van Leeuwen FE, Lynch CF, et al. Second cancers among long-term survivors of non-Hodgkin's lymphoma. Journal of the National Cancer Institute. 1993;85(23):1932-7
7. Mudie NY, Swerdlow AJ, Higgins CD, Smith P, Qiao Z, Hancock BW, et al. Risk of second malignancy after non-Hodgkin's lymphoma: a British Cohort Study. J Clin Oncol. 2006;24(10):1568-74.
8. Hequet O, Le QH, Moullet I, Pauli E, Salles G, Espinouse D, et al. Subclinical late cardiomyopathy after doxorubicin therapy for lymphoma in adults. J Clin Oncol. 2004;22(10):1864-71.
9. Limat S, Demesmay K, Voillat L, Bernard Y, Deconinck E, Brion A, et al. Early cardiotoxicity of the CHOP regimen in aggressive non-Hodgkin's lymphoma. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2003;14(2):277-81.
10. SEER Stat Fact Sheets: Non-Hodgkin Lymphoma. Available from: http://seer.cancer.gov/statfacts/html/nhl.html.
11. Ihle NT, Powis G. Take your PIK: phosphatidylinositol 3-kinase inhibitors race through the clinic and toward cancer therapy. Molecular cancer therapeutics. 2009;8(1):1-9.
12. Yuan TL, Cantley LC. PI3K pathway alterations in cancer: variations on a theme. Oncogene. 2008;27(41):5497-510.
13. Saal LH, Johansson P, Holm K, Gruvberger-Saal SK, She QB, Maurer M, et al. Poor prognosis in carcinoma is associated with a gene expression signature of aberrant PTEN tumor suppressor pathway activity. Proceedings of the National Academy of Sciences of the United States of America. 2007;104(18):7564-9.
14. Prevo R, Deutsch E, Sampson O, Diplexcito J, Cengel K, Harper J, et al. Class I PI3 kinase inhibition by the pyridinylfuranopyrimidine inhibitor PI-103 enhances tumor radiosensitivity. Cancer research. 2008;68(14):5915-23.
15. Gopal AK, Kahl BS, de Vos S, Wagner-Johnston ND, Schuster SJ, Jurczak WJ, et al. PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014;370(11):1008-18.
16. Hiddemann W, Kneba M, Dreyling M, Schmitz N, Lengfelder E, Schmits R, et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood. 2005;106(12):3725-32.

17. Marcus R, Imrie K, Solal-Celigny P, Catalano JV, Dmoszynska A, Raposo JC, et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. J Clin Oncol. 2008;26(28):4579-86.
18. Rummel M, Kaiser U, Balser C. Bendamustine plus rituximab versus fludarabine plus rituximab in patients with relapsed follicular, indolent and mantle cell lymphomas - final results of the randomized phase III study NHL 2-2003 on behalf of the StiL (Study Group Indolent Lymphomas, Germany) Blood. 2010(116).
19. Hainsworth JD, Litchy S, Burris HA, 3rd, Scullin DC, Jr., Corso SW, Yardley DA, et al. Rituximab as first-line and maintenance therapy for patients with indolent non-hodgkin's lymphoma. J Clin Oncol. 2002;20(20):4261-7.
20. McLaughlin P, Grillo-Lopez AJ, Link BK, Levy R, Czuczman MS, Williams ME, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. J Clin Oncol. 1998;16(8):2825-33.
21. Johnston A, Bouafia-Sauvy F, Broussais-Guillaumot F, Michallet AS, Traulle C, Salles G, et al. Retreatment with rituximab in 178 patients with relapsed and refractory B-cell lymphomas: a single institution case control study. Leuk Lymphoma. 2010;51(3):399-405.
22. Hainsworth JD, Litchy S, Shaffer DW, Lackey VL, Grimaldi M, Greco FA. Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma – a randomized phase II trial of the Minnie Pearl Cancer Research Network. J Clin Oncol. 2005;23(6):1088-95.
23. Coiffier B, Osmanov EA, Hong X, Scheliga A, Mayer J, Offner F, et al. Bortezomib plus rituximab versus rituximab alone in patients with relapsed, rituximab-naive or rituximab-sensitive, follicular lymphoma: a randomised phase 3 trial. The lancet oncology. 2011;12(8):773-84.
24. Ghielmini M, Rufibach K, Salles G, Leoncini-Franscini L, Leger-Falandry C, Cogliatti S, et al. Single agent rituximab in patients with follicular or mantle cell lymphoma: clinical and biological factors that are predictive of response and event-free survival as well as the effect of rituximab on the immune system: a study of the Swiss Group for Clinical Cancer Research (SAKK). Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2005;16(10):1675-82.
25. Ghielmini M, Schmitz SF, Cogliatti SB, Pichert G, Hummerjohann J, Waltzer U, et al. Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule. Blood. 2004;103(12):4416-23.
26. Martinelli G, Schmitz SF, Utiger U, Cerny T, Hess U, Bassi S, et al. Long-term follow-up of patients with follicular lymphoma receiving single-agent rituximab at two different schedules in trial SAKK 35/98. J Clin Oncol. 2010;28(29):4480-4.
27. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol. 2014; 32(27):3059-3067.

28. Miller MD, Towers A. A Manual of Guidelines for Scoring the Cumulative Illness Rating Scale for Geriatrics (CIRSG). Pittsburg, PA: University of Pittsburg; 1991.

29. Visani G, Ferrara F, Alesiani F, Ronconi S, Catarini M, D'Adamo F, et al. R-COMP 21 for frail elderly patients with aggressive B-cell non-Hodgkin lymphoma: a pilot study. Leuk Lymphoma. 2008;49(6):1081-6.

30. Tucci A, Ferrari S, Bottelli C, Borlenghi E, Drera M, Rossi G. A comprehensive geriatric assessment is more effective than clinical judgment to identify elderly diffuse large cell lymphoma patients who benefit from aggressive therapy. Cancer. 2009;115(19):4547-53.

31. Busaidy NL, Farooki A, Dowlati A, Perentesis JP, Dancey JE, Doyle LA, et al. Management of metabolic effects associated with anticancer agents targeting the PI3K-Akt-mTOR pathway. J Clin Oncol. 2012;30(23):2919-28.

32. Lacouture ME, Wu S, Robert C, Atkins MB, Kong HH, Guitart J, et al. Evolving strategies for the management of hand-foot skin reaction associated with the multitargeted kinase inhibitors sorafenib and sunitinib. Oncologist. 2008;13(9):1001-11.

33. *Reference removed by amendment 12*.

34. *Reference removed by amendment 12*.

35. Owen RG, Kyle RA, Stone MJ, Rawstron AC, Leblond V, Merlini G, et al. Response assessment in Waldenstrom macroglobulinaemia: update from the VIth International Workshop. British journal of haematology. 2013;160(2):171-6.

36. Collett D. Modelling Survival Data in Medical Research: Chapman and Hall; 2003.

37. Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. 'Categorical Data Analysis' in Statistical methodology in the pharmaceutical sciences /edited by Berry DA, Marcel Dekker; 1990.

38. *Reference removed by amendment 9.*

39. *Reference removed by amendment 9.*

40. *Reference removed by amendment 9.*

41. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine 2007 Available from: http://medicine.iupui.edu/clinpharm/ddis/clinical-table.

42. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9 ed: Boston: Little Brown & Co; 1994.

43. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999; 30(6):461-70.

44. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247-54.

45. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Part 4. Definition and

classification of stages of chronic kidney disease. Am J Kidney Dis. 2002;39(2, Suppl 1):S46-S75.

46. *Reference removed by amendment 9*.
47. National Comprehensive Cancer Network (NCCN): NCCN Guidelines version 2.2015, Prevention and treatment of cancer-related infections. Available online: http://www.nccn.org/professionals/physician_gls/pdf/infections.pdf.
48. Food and Drug Administration (FDA), Guidance for Industry, Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations Center for Drug Evaluation and Research (CDER), Draft Guidance (2012). Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm292362.pdf.
49. FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Available from: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm.
50. Metabolism and Transport Drug Interaction Database, University of Washington, Department of Pharmaceutics (2008) www.druginteractioninfo.org (Last update: July, 2014).
51. Leonard JP, Trneny M, Izutsu K, Fowler NH, Hong X, Zhu J, et al. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. J Clin Oncol. 2019;37(14):1188-1199.
52. Schoenfeld D. The asymptotic properties of nonparametric tests for comparing survival distributions. Biometrika. 1981;68(1): 316–319.

13. Protocol amendments

13.1 Amendment 1

Amendment 1 is dated 23 JAN 2015.

13.1.1 Overview of changes

13.1.1.1 Modification 1 – inclusion criteria changed

Inclusion criteria were supplemented with the following condition: patients must either have had a treatment-free interval of 12 months or longer after completion of the last rituximab-containing treatment, or be considered unfit to receive chemotherapy for reasons of age, concomitant morbidities and/or residual toxicity from previous treatments. Contraindications to chemotherapy were added, as well as an appendix on Cumulative Illness Rating Scale for Geriatrics (CIRS-G). Based on this criterion the stratification factors were also updated (see Section 13.1.1.4). Rationale: patients considered unfit for chemotherapy for reasons of comorbidities, residual toxicity, or advanced age may respond less well to study treatment.

To adjust to the new patient profile the following changes were made to inclusion criteria:

- Laboratory entry criteria were changed: amylase and serum creatinine were removed from the inclusion criteria, and entry values for hemoglobin and ANC were decreased (hemoglobin from 9 g/dL to 8 g/dL, ANC from 1,500 mm^3 to 1,000 mm^3).
- Criterion for left ventricular ejection fraction was specified to be no less than 45%.

Consequently, the following changes were made in other protocol sections:

- Dose modification in the event of NIP was adjusted, as well as text related to NIP in prohibited medications section, and a separate chapter was added, for patients who are unfit to receive chemotherapy.
- One more MUGA/echocardiogram test was added for patients with LVEF below lower level of normal for the institution, with flexibility regarding the time point (any time between 5 hours after the first dose and before the next administration).

In addition, the inclusion criteria were changed as follows:

- The possibility for the second evaluation of GFR was added, if it is not on target at the first screening, and either MDRD or 24-hour sampling can be used to fulfill the inclusion criterion. This was added because GFR can be more accurately calculated by comparative measurements of creatinine in blood and urine than by using a formula and to give a chance for reevaluation of the patient.
- Eligibility threshold of platelet and neutrophil counts was reduced for patients with confirmed lymphomatous bone marrow infiltration ($\geq$ 50,000 /mm^3 and $\geq$ 750/mm^3 for platelet and neutrophil counts, respectively). Therefore, laboratory test criteria for Days 1, 8 and 15 of subsequent cycles were updated. This change was made because in patients whose cytopenias are due to lymphomatous bone marrow infiltration as histologically proven during screening, the benefit from treatment is expected to exceed the risk of drug-induced marrow depletion.

Sections affected by this modification: Synopsis, 1.1 Background, 1.2 Rationale for the study, 1.3 Benefit-risk assessment, 2 Study objectives, 4 Study design, 5.1.1 Inclusion criteria, 5.1.3 Justification of selection criteria, 6.4 Dosage and administration, 6.4.1.1 Hematological toxicity, 6.4.1.2 Non-hematological toxicity, 6.4.2.6 Special considerations for patients unfit for chemotherapy, 6.9.1 Prohibited concomitant therapy, 7.1.1 Tabulated overview, 7.1.2.1 Screening period, 7.1.2.2.1 Treatment – Cycle 1, 7.1.2.2.2 – Treatment – Cycle 2 and higher, 7.1.2.4 End-of-treatment visit, 7.2.2 Medical history, 8.6 Determination of sample size, 12 Reference list, 14.6 Glomerular filtration rate and Appendix 14.7 (appendix added).

13.1.1.2 Modification 2 – exclusion criteria updated

To adjust to the new patient profile the following changes were made to the exclusion criteria:

- Criterion “renal failure requiring hemo- or peritoneal dialysis” was removed.
- More exceptions were added to the following exclusion criteria: previous or concurrent cancer (asymptomatic prostate cancer without known metastatic disease) and unresolved toxicity higher than CTCAE Grade 1 (peripheral neuropathy and bone marrow parameters).
- Cut-off time period for excluded myeloid growth factors and blood or platelet transfusion was changed from 14 days to 7 days before the start of treatment

After consultation with regulatory authorities prior exposure to PI3K inhibitors was removed as an exclusion criterion, and documented progression to PI3K inhibitors was added instead (patients pre-exposed, but not resistant, to PI3K inhibitors, can be accrued to the study). Consequently, prior treatment with PI3K inhibitor was added as a new stratification factor (see Section 13.1.1.4).

Definition of rituximab refractoriness was replaced by a condition excluding patients whose last rituximab infusion was within 12 months of the start of the next treatment, and, for patients unfit to receive chemotherapy – within 6 months after the last rituximab-containing regimen. This change was done because many patients are most often referred after relapse, and regional centers do not have access to the imaging examinations checking the progression within 6 months of the last course of rituximab-containing regimen. A long-term response with rituximab is used instead, verifying that rituximab is an active agent against the selected disease.

Patients who show evidence of progression since last treatment were exempt of the required minimum time for the following criteria:

- Treatment with investigational drugs other than PI3K inhibitors less than 28 days before start of treatment
- Radiotherapy or immuno-/chemotherapy less than 4 weeks before start of treatment
- Radioimmunotherapy or autologous transplant less than 3 months before start of treatment

This was done to allow accrual of patients in whom the effect of previous treatment can safely be excluded and because evidence of progression brings urgency to the treatment of this elderly population.

Sections affected by this modification: Synopsis, 5.1.1 Inclusion criteria, 5.1.2 Exclusion criteria and 7.2.2 Medical history.

13.1.1.3 Modification 3 – target population for efficacy analysis changed

Following advice received by regulatory authorities, the study target population for efficacy analysis was changed from iNHL patients to FL patients, with a possibility to also recruit other iNHL patients. However, the study will be powered for FL patients. Consequently, the number of PFS events and the number of patients were re-calculated, with patients divided into FL subgroup and other iNHL group.

Likewise, the confirmatory statistical test strategy was revised to include separate tests in the FL subgroup and total population, respectively. In accordance with the target population of FL patients, the study-wise alpha is initially split with 80% to the primary analysis in the FL subgroup. Furthermore, any potential alpha propagation is initially done within the FL subgroup or from the total population to the FL subgroup as well.

Sections affected by this modification: Synopsis, 4 Study design, 8.4.1 Population characteristics, 8.4.2 Efficacy, 8.6 Determination of sample size and 12 Reference list.

13.1.1.4 Modification 4 – randomization ratio and stratification changed

Randomization ratio was changed from 1:1 to 2:1. Stratification factors were changed to comprise iNHL histology (FL histology vs. other iNHL histology), newly added inclusion criterion (treatment-free interval after rituximab treatment vs. contraindication for chemotherapy), presence of bulky disease (yes vs. no) and prior exposure to PI3K inhibitors. FLIPI score and time between the last therapy and the most frequent progression were removed as stratification factors. Rationale: randomization was changed to 2:1 in order to increase the patients' odds of being randomized to the study treatment arm, and to increase the level of experience with the study drug. Stratification was changed because histology, patient's profile as defined by the entry criteria and bulky disease could influence the magnitude of the effect of treatment. The FLIPI prognostic score was deleted at the suggestion of FDA because the usefulness of the FLIPI score in patients who have had multiple relapses to balance randomization is not known.

Sections affected by this modification: Synopsis, 4 Study design, 6.3 Treatment assignment, 7.2.2 Medical history, 8.4.2 Efficacy and 8.6 Determination of sample size.

13.1.1.5 Modification 5 – time to improvement in DRS-P added as secondary efficacy variable

Because of a change in the patient population, time to improvement in disease-related symptoms - physical (DRS-P) was added as an additional secondary efficacy variable, to be measured for patients with a baseline DRS-P score of 30 points or less (i.e. patients who still have room for improvement in symptoms). Consequently, study objectives and fixed sequence test hierarchy were updated.

Sections affected by this modification: Synopsis, 2 Study objectives, 7.6.2 Quality of life questionnaire, 8.3.1.2 Secondary efficacy variables and 8.4.2 Efficacy.

13.1.1.6 Modification 6 – subgroup analyses added

In accordance with the EMA draft guideline on the investigation of subgroups in confirmatory clinical trials, a section describing a pre-defined region definition, as well as briefly describing subgroup analyses for regions and other subgroups (e.g. based on stratification factors and other baseline characteristics), was added to the protocol.

Section affected by this modification: 8.4.3 Subgroup analyses.

13.1.1.7 Modification 7 – patient enrollment and DMC review of safety data changed

After the 30th randomized patient has completed the first cycle treatment, enrollment will not be stopped. Data Monitoring Committee will review the safety data of all patients treated up to that time point.

Rationale: If no safety-relevant events occur in the first 30 patients treated, there will not be any need to stop accrual. If such an event occurs, accrual will be stopped anyway.

Sections affected by this modification: Synopsis, 4 Study design.

13.1.1.8 Modification 8 – language on informed consent, re-screening and re-testing revised

Wording related to the re-consent of the re-screened patients was corrected. Text about screening was updated to clarify which test results can be accepted even if performed as part of routine practice provided that they fall into the protocol-specified time window and the patient has given informed consent to use them.

Sections affected by this modification: Synopsis, 4 Study design, 5.1.1 Inclusion criteria, 5.2.1 Withdrawal, 7.1.1 Tabulated overview and 7.1.2.1 Screening period.

13.1.1.9 Modification 9 – language on study drug reconstitution modified

The volume of copanlisib and placebo solution was removed and reference to the Pharmacy manual was added instead, to avoid discrepancies between the protocol and the Pharmacy Manual.

Sections affected by this modification: 6.4 Dosage and administration.

13.1.1.10 Modification 10 – guidelines on management of hyperglycemia updated

Recommendations regarding management of hyperglycemia were changed in order to simplify and harmonize guidance between planned clinical studies. Modifications are based on review of the latest data on Phase I studies and Phase II study 16349 (part A). These modifications include changes in patient's fasting requirements and subsequent modifications on glucose measurement time points on Cycle 1 Day 1 as these time points are tailored based on fasting. It is considered safe and beneficial to shorten the time-interval of both fasting requirements and blood glucose assessments.

Guidance for home blood glucose monitoring for non-diabetic patients on Cycle 1 Day 1 was harmonized with guidance in place for days of infusion from Cycle 1 Day 8 onwards. Therefore only those non-diabetic patients will be required to monitor their blood glucose at home who develop hyperglycemia > 250 mg/dL or require insulin administration.

In addition, diary was added to record home glucose measurement and insulin administration, if applicable.

Sections affected by this modification: 5.2.1.1 Withdrawal of study treatment, 6.4 Dosage and administration, 6.4.2.1 Management of hyperglycemia that can occur with copanlisib, 7.1.1 Tabulated overview, 7.1.2.2.1 Treatment – Cycle 1 and 7.1.2.2.2 Cycle 2 and higher.

13.1.1.11 Modification 11 – laboratory evaluations revised

HDL measurement was removed from the complete chemistry panel; only total cholesterol and LDL cholesterol will be checked following recommendations of Busaidy et al.(31). Turbidity was removed from urinalysis, GFR calculation was added to Day 1 of Cycle 2 and higher.

Sections affected by this modification: 7.1.1 Tabulated overview, 7.1.2.1 Screening period and 7.5.3.1 Laboratory.

13.1.1.12 Modification 12 – blood pressure and ECG measurements revised

Number of blood pressure measurements on Cycle 1 Day 1 was reduced, because safety data from part A of study 16349 showed that there was no substantial amount of patients with new onset of Grade 3 hypertension after 3 hours of monitoring on Cycle 1 Day 1. Therefore, monitoring at 30 minutes, 1 hour, 2 hours and 3 hours after the start of copanlisib infusion on Cycle 1 Day 1 is comparable to 6 hours monitoring to detect at least one Grade 3 event.

ECG measurement timing was changed to be performed within 28 days of Cycle 1 Day 1 (instead of 14 days) and on Cycle 1 Day 1. Measurement on Day 15 of every third cycle was removed (tests on Day 1 of every third cycle and EOT remained unchanged). This was done to monitor patients' ECG parameters.

The required position for the patient before blood pressure and ECG measurement was changed from "lying down" to "rest" as being more common in clinical practice.

Sections affected by this modification: 7.1.1 Tabulated overview, 7.1.2.1 Screening period, 7.1.2.2.1 Treatment – Cycle 1, 7.1.2.2.2 Treatment – Cycle 2 and higher, 7.5.3.3 Vital signs and 7.5.3.4 12-lead ECG.

13.1.1.13 Modification 13 – tumor assessments clarified

Starting time point for tumor assessment was added for clarity (Cycle 1 Day 1), as well as tumor assessments guidance for WM patients. Oral contrast agent for radiological tumor assessment was added to IV contrast for consistency with the Imaging Manual. Footnote explaining the reason for performing MRI instead of CT in Germany was deleted as being too specific to be described in a protocol.

Sections affected by this modification: Synopsis, 4 Study design, 7.1.1 Tabulated overview, 7.1.2.1 Screening period, 7.1.2.3 Tumor assessments, 7.1.2.4 End-of-treatment visit, 7.3.2 Radiological tumor assessments, 7.3.3 Tumor assessments in patients with WM (added) and 8.3.1 Efficacy variables.

13.1.1.14 Modification 14 – completion of PRO information sheet clarified

Responsible persons for completing the PRO information sheet (nurse/investigator) were replaced by "study personnel" to allow more flexibility.

Section affected by this modification: 7.6.2 Quality of Life questionnaire.

13.1.1.15 Modification 15 – blinding details removed

Detailed information about the measures to preserve the blinding was removed because it will be described in the Pharmacy Manual.

Section affected by this modification: 6.5 Blinding.

13.1.1.16 Modification 16 – collection of biomarker and PK samples revised

Requirements about collection of tumor tissue were specified further to make sure the best material is received if available but at the same time not to restrict patients from participating in the study if sufficient sample is not available for biomarkers (tumor tissue for central pathology review is still mandatory). Timing of plasma collection for tumor genetics and non-genetic biomarker analysis was changed to only be performed at Cycles 1, 2 (non-genetic sample only), and end-of-treatment visit, i.e. sampling on Day 1 of subsequent cycles was removed.

PK sampling on Day 15 of Cycle 2 and higher was removed. The number of required samples on Day 8 of Cycle 1 was decreased to three samples.

This was done to reduce the burden on the patients and the sites, and to reduce the overall number of samples to be shipped and processed.

Sections affected by this modification: 4 Study design, 7.1.1 Tabulated overview, 7.1.2.2.2 Treatment – Cycle 2 and higher,7.1.2.4 End-of-treatment visit, 7.4.1 Sampling and 7.6.1 Biomarker investigations

13.1.1.17 Modification 17 – tumor response criteria udpated

Criteria for assessing tumor response were updated following the most recent publication by Cheson (27); assessment of response and disease progression will be done according to the Lugano Classification. According to the new criteria organomegaly is only defined by CT imaging therefore splenomegaly/hepatomegaly will no longer be checked at physical examinations. Ann Arbor terminology will no longer use suffixes A and B for symptoms related to NHL (they will only be included for Hodgkin Lymphomas), therefore B symptoms will not be collected. The change in CT-based criteria resulted in an updated table for tumor response definitions (Appendix 14.4). However, even though PET CT was formally incorporated into standard staging for FDG-avid lymphomas, the current study will only use CT scan for response assessment (see Section 7.7). Criteria for assessing tumor response in WM patients were also updated.

Sections affected by this modification: Synopsis, List of abbreviations, Definition of terms, 4 Study design, 5.1.1 Inclusion criteria, 5.2.1.1 Withdrawal of study treatment, 7.1.1 Tabulated overview, 7.1.2.1 Screening period, 7.1.2.2.2 Treatment – Cycle 2 and higher, 7.1.2.3 Tumor assessments, 7.1.2.4 End-of-treatment visit, 7.3.2 Radiological tumor assessments, 7.5.3.2 Physical examinations, 7.7 Appropriateness of procedures / measurements, 8.3.1.2 Secondary efficacy variables, 12 Reference list and 14.4 Evaluation of tumor response.

13.1.1.18 Modification 18 – copanlisib clinical experience udpated

Data related to study 16349 (part A) were updated based on the most recent clinical study report. Wording regarding population PK analysis was updated accordingly.

Section affected by this modification: 1.1.2 Clinical experience.

13.1.1.19 Modification 19 – administrative information udpated

Study medical expert changed therefore the contact details were updated. Contact details of another coordinating co-investigator were added. The study received an abbreviated name CHRONOS-3 that was added to the study title.

Sections affected by this modification: Title page, 3 Investigator and other study personnel

13.1.1.20 Modification 20 – other clarifications and corrections

In addition to the modifications specified above there have been minor corrections for better clarity and consistency.

Sections affected by this modification: Synopsis, 1.1 Background, 1.3 Benefit-risk assessment, 2 Study objectives, 3 Investigator and other study personnel, 4 Study design, 5.2.1.1 Withdrawal of study treatment, 5.3 Patient identification, 6.1 Treatments to be administered, 6.2 Identity of investigational medicinal products, 6.4.1 Dose modification, 6.4.1.1 Hematological toxicity, 6.4.1.2 Non-hematological toxicity, 6.4.2.1 Management of hyperglycemia that can occur with copanlisib, 6.4.2.5 Treatment of dermatologic toxicity, 6.9.1 Prohibited concomitant therapy, 7.1.1 Tabulated overview, 7.1.2.2.1 Treatment – Cycle 1, 7.1.2.5 Follow-up periods (added), 7.1.2.5.1 Safety follow-up, 7.1.2.5.3 Survival follow-up, 7.3.2 Radiological tumor assessments, 7.4.1 Sampling, 7.4.2 Analysis, 7.5.1.1 Definitions, 7.5.3.1 Laboratory, 7.6.3 Electronic patient-reported outcomes evaluation, 8.1 General considerations, 8.3.1.2 Secondary efficacy variables, 10 Premature termination of the study and 14.6 Glomerular filtration rate.

13.1.2 Changes to the protocol text

Changes to the protocol text done in Amendment 1 are provided in Section 13.1.2 of Amendment 1.

13.2 Amendment 6

Amendment 6 is dated 18 FEB 2016.

13.2.1 Overview of changes

13.2.1.1 Modification 1 – update of clinical experience with copanlisib

Introductory information on patients treated with copanlisib was updated based on most recent data. In addition, the results from copanlisib studies 12871 and 16349 part A were updated.

Section affected by this modification: 1.1.2 Clinical experience

13.2.1.2 Modification 2 – previous exposure to alkylating agents removed

Mandatory exposure to alkylating agents was removed since only the assessment of rituximab effectiveness is evaluated by the inclusion/exclusion criteria of this protocol and the mandatory use of alkylating agents could potentially exclude part of the population who is considered unfit for chemotherapy.

Sections affected by this modification: Synopsis, 1.2 Rationale for the study, 2 Study objectives, 5.1.1 Inclusion criteria, 8.4.2.1 Primary efficacy analysis

13.2.1.3 Modification 3 – clarification of inclusion criterion related to WM patients

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 (≥ 2 x 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.

Sections affected by this modification: Synopsis, 5.1.1 Inclusion criteria

13.2.1.4 Modification 4 – 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 ≤ 1.5 x ULN. The modification was done because previous language (INR ≤ 1.5 x 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: 5.1.1 Inclusion criteria and 7.5.3.1 Laboratory

13.2.1.5 Modification 5 – modification of contraception and pregnancy testing requirements

Text was added in the inclusion criteria to clarify the required time period of contraceptive use, to provide a detailed description of effective contraception and to provide definition of a woman of childbearing potential (WOCBP) and a post-menopausal state. 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.

Serum pregnancy test was added to be performed at the EOT visit in countries where it is required by local regulations. The list of specific countries where pregnancy test is mandatory after Cycle 1 was removed to avoid confusion and to present a general statement applicable to all countries with such a requirement.

These changes were made according to recommendations related to contraception and pregnancy testing in clinical trials by the Clinical Trial Facilitating Group.

Sections affected by this modification: 5.1.1 Inclusion criteria, 7.1.1 Tabulated overview, 7.1.2.2.2 Treatment – Cycle 2 and higher, 7.1.2.4 End-of-treatment visit.

13.2.1.6 Modification 6 – clarification of the requirements for baseline laboratory analyses

Inclusion criteria related to adequate baseline laboratory values were modified to clarify that platelet transfusion, packed red blood cells or erythropoietin; and myeloid growth factors should not be given less than 7 days before the exam collection for platelet count, hemoglobin and ANC, respectively. The use of these treatments could act as confounding factors in order to establish evidence of minimal bone marrow function, hence the limitation of treatment period providing an improved assessment.

Section affected by this modification: 5.1.1 Inclusion criteria

13.2.1.7 Modification 7 – modification of conditions for rituximab use and alignment of time frame reference

Progression of disease after the last rituximab infusion within defined time period before next treatment was added as an exclusion condition to ensure that rituximab had been previously proven to be beneficial to the target population. For patients considered unfit to receive chemotherapy the timeframe reference was also realigned to match that of the overall population.

Sections affected by this modification: Synopsis, 5.1.2 Exclusion criteria

13.2.1.8 Modification 8 – modification of exclusion criterion related to arterial hypertension

The conservative requirement for blood pressure levels during the evaluation of patient's eligibility was removed due to feedback from the investigators and lymphoma specialists. Appropriate blood pressure levels prior to study treatment and available prophylactic treatments are considered to be the most important safety points.

Section affected by this modification: 5.1.2 Exclusion criteria

13.2.1.9 Modification 9 – exclusion of patients based on plasma glucose levels removed

Exclusion of patients with fasting plasma glucose > 160 mg/dL at Screening was removed to implement the advisory board recommendations. 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.

Sections affected by this modification: Synopsis, 5.1.2 Exclusion criteria

13.2.1.10 Modification 10 – prophylaxis for HBV and monitoring of HBV and HCV added

Requirement was added that prophylactic antiviral therapy should be given 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, 5.1.2 Exclusion criteria, 5.2.1.1 Withdrawal of study treatment, 7.1.1 Tabulated overview, 7.1.2.1, Screening period, 7.5.3.1 Laboratory, 12 Reference list

13.2.1.11 Modification 11 – 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.

Following the investigator's feedback on the study feasibility, the criterion was amended to make the patient evaluation more flexible and feasible.

Section affected by this modification: 5.1.2 Exclusion criteria,7.1.1 Tabulated overview,7.1.2.1 Screening period,7.5.3.1 Laboratory

13.2.1.12 Modification 12 – 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. 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.

Sections affected by this modification: 5.1.2 Exclusion criteria and 6.9.1 Prohibited concomitant therapy

13.2.1.13 Modification 13 – modification of exclusion criterion related to evidence of resistance to PI3K inhibitors

The exclusion criterion was modified since the definition of resistance should be progression within 6 months starting from the treatment with PI3K inhibitors instead of within 6 months from the end of therapy.

Sections affected by this modification: Synopsis, 5.1.2 Exclusion criteria

13.2.1.14 Modification 14 – prior treatment with copanlisib added to the exclusion criteria.

Copanlisib was included to the list of prohibited previous therapies and medications. Modification was done because prior treatment with copanlisib could jeopardize the clinical assessment of the study drug.

Sections affected by this modification: Synopsis, 5.1.2 Exclusion criteria

13.2.1.15 Modification 15 – 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.

Section affected by this modification: 6.2 Identity of investigational medicinal products

13.2.1.16 Modification 16 – updated guidance for glucose increase management and monitoring

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 4 symptomatic hyperglycemia or glucose intolerance*" was revised to align with a new guidance for the transient glucose increases management.Appendix 14.8 was added based on the new guidance for the transient glucose increases management and to clarify average glycemic index of common foods derived from multiple studies by different laboratories.

Sections affected by this modification: 5.2.1.1 Withdrawal of study treatment, 6.4 Dosage and administration, 6.4.1 Dose modification, 6.4.1.2 Non-hematological toxicity, 6.4.2.1 Management of transient post-infusion glucose increases that can occur with copanlisib, 6.4.2.6 Special considerations for patients unfit for chemotherapy, 7.1.1 Tabulated overview, 7.1.2.2.1 Treatment – Cycle 1, 7.1.2.2.2 Treatment – Cycle 2 and higher, 7.1.2.4 End-of-treatment visit, 7.5.3.7 Glucose measurements on copanlisib/placebo infusion days, Appendix 14.8 The average glycemic index of common foods derived from multiple studies by different laboratories

13.2.1.17 Modification 17 – 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: 6.4.1 Dose modification, 6.4.1.2 Non-hematological toxicity, 6.4.2.3 Treatment of blood pressure increases associated with copanlisib, 7.1.1 Tabulated overview, 7.1.2.2.1 Treatment – Cycle 1, 7.1.2.2.2 Treatment – Cycle 2 and higher, 7.5.3.3 Vital signs

13.2.1.18 Modification 18 – minimum exposure to rituximab added

The only proven medication to establish an effect on the cancer is rituximab. For ethical reasons, it was required that a minimum exposure of 4 doses until Cycle 3 Day 1 (included) is mandatory for patients to be able to continue on the study.

Section affected by this modification: 6.4.1 Dose modification

13.2.1.19 Modification 19 – fasting requirement for lipid panels revised

The 11 h fasting requirement before evaluation of 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: 6.4.2.2 Management of hyperlipidemia, 7.1.1 Tabulated overview, 7.1.2.1 Screening period, 7.1.2.2.2 Treatment – Cycle 2 and higher, 7.1.2.4 End-of-treatment visit, 7.5.3.1 Laboratory

13.2.1.20 Modification 20 – 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, after the first complete response if the baseline sample was positive, and for suspicion of progressive disease restricted to bone marrow infiltration without radiological findings; assuring that central pathology review confirms the disease response status.

Sections affected by this modification: Synopsis, 4 Study design, 7.1.1 Tabulated overview, 7.1.2.1 Screening period, 7.1.2.3 Tumor assessments

13.2.1.21 Modification 21 – clarification of tumor response language

The language related to radiological tumor assessments was modified to clarify the process for central review that the evaluation of tumor response will be done retrospectively only for those patients who did not experience PD.

Modifications were also done to harmonize the language across the protocol and with other copanlisib protocols, e.g. language regarding tumor assessment in patients with WM was clarified.

In general, CT/MRI needs to be performed with IV 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.

Table for the CT and/or MRI response assessment criteria was also clarified:

- Original wording from the Lugano Classification 2014 (27) was inserted to the column "bone marrow" for PD.
- 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 (27). 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.

Sections affected by this modification: Synopsis, 4 Study design, 7.1.1 Tabulated overview, 7.3.2 Radiological tumor assessments,7.3.3 Tumor assessments in patients with WM, 14.4 Evaluation of tumor response

13.2.1.22 Modification 22 – 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: 6.4.2.3 Treatment of blood pressure increases associated with copanlisib

13.2.1.23 Modification 23 – PK sampling time modified

The possible PK sampling time for copanlisib/placebo was changed from Cycle 2 to Cycle 3 in case the sampling is not feasible on Cycle 1. The wording was added that also sampling for rituximab can be done on Cycle 3 if not feasible at Cycle 1.

The modification was done to be able to characterize the PK of copanlisib when coadministered with rituximab and there is no rituximab administration on Cycle 2.

Section affected by this modification: 7.4.1 Sampling

13.2.1.24 Modification 24 – clarification of SAE reporting language

The language regarding reporting of SAEs that occur after the protocol-defined observation was modified to meet the current regulations.

Section affected by this modification: 7.5.1.4 Reporting of serious adverse events

13.2.1.25 Modification 25 – language related to hemoglobin A1c measurements clarified

It was clarified in the protocol that test for HbA1c is not required at the EOT visit if the previous test was performed within 4 weeks preceding EOT visit. The rationale for this change was to implement the consideration of erythrocyte lifecycle.

HbA1c was added to the list of laboratory evaluations in further safety section for consistency.

Sections affected by this modification: 7.1.1 Tabulated overview, 7.1.2.4 End-of-treatment visit, 7.5.3.1 Laboratory

13.2.1.26 Modification 26 – assessment of hydration status added

Language on clinical assessment of hydration status was included to be part of complete and brief physical examinations. This change was made to emphasize the importance to check a hydration status during patient physical examination.

Sections affected by this modification: 7.5.3.2.1 Complete physical examination and 7.5.3.2.2 Brief physical examination

13.2.1.27 Modification 27 – paper PRO questionnaire removed

The possibility to use paper PRO surveys was removed since only electronic devices will be used in this study. If electronic device is not available at the site, or technical problems prevent it from working properly, the PRO questionnaire will not be completed at that visit.

Section affected by this modification: 7.6.3 Electronic patient-reported outcomes evaluation

13.2.1.28 Modification 28 – 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. Patient information and content section was updated based on current protocol template text.

Sections affected by this modification: 5.2.1.1 Withdrawal of study treatment, 11.2 Patient information and consent

13.2.1.29 Modification 29 – administrative change

The sponsor's medically responsible person was changed.

Section affected by this modification: Signature of the sponsor's medically responsible person.

13.2.1.30 Modification 30 – other clarifications and corrections

In addition to the modifications specified above there have been minor corrections for better clarity and consistency.

- The clarification was made that the study drug is to be administered in an approximate timeframe of 1 h to allow for a little time window. The change was done following the feedback from the investigators.
- It was clarified that the laboratory test results can be assessed by the investigator and/or appropriate site personnel before administration of study drug.
- The symbol "≥" was added to dosing criteria section to clarify that dosing criteria apply to neutrophil count decreased, platelet count decreased and anemia of CTCAE grade ≥ 3, not only for events of CTCAE grade 3.
- A footnote was added to Table 6–4 clarifying that treatment with transfusion or growth factors is allowed at the investigator's discretion.
- Table 6–5 was clarified to harmonize the language with other dose modification tables.
- Cyclosporin was removed from the list of permitted concomitant medications since the protocol prohibits concomitant therapy with immunosuppressive agents.
- PRO information sheet was added to Table 7–1 for clarification.
- Brief physical examination was removed from tabulated overview (Day 22 of Cycle 2 and higher) for consistency.
- Reference to PK section was added to Table 7–2.
- Clarification was made in the screening period section that procedures need to be performed **within** x days before start of study treatment instead of **less than** x days.

Sections affected by this modification: 6.4 Dosage and administration, 6.4.1.1 Hematological toxicity, 6.4.1.2 Non-hematological toxicity, 6.9.2 Permitted concomitant therapy, 7.1.1 Tabulated overview, 7.1.2.1 Screening period

13.2.2 Changes to the protocol text

Changes to the protocol text done in Amendment 6 are provided in Section 13.2.2 of Amendment 6.

13.3 Amendment 7

Amendment 7 is dated 28 JUL 2016.

13.3.1 Overview of changes

13.3.1.1 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.

Section affected by this modification: 1.1.2 Clinical experience

13.3.1.2 Modification 2 – modification of inclusion criteria

- Definition of relapse was clarified. In addition a clarification was added that patients with prior intolerance to PI3K inhibitors are eligible although patients with resistance to PI3K inhibitors are not.
- It was clarified that chemotherapy is contraindicated also in patients who are unwilling to be treated with chemotherapy.

Section affected by these modifications: Synopsis, 5.1.1 Inclusion criteria

13.3.1.3 Modification 3 – modification of exclusion criteria

- Language on exclusion after rituximab therapy was modified to ensure that the last assessment of rituximab therapy was proven to be beneficial for the subjects; this change also clarifies the timeframe for the conditions to be verified.
- Exclusion criterion regarding HbA1c levels in patients with diabetes mellitus was changed. It was clarified that the HbA1c >8.5% level concerns all patients at screening, not only patients with diabetes mellitus.
- The exclusion criterion related to evidence of resistance to PI3K inhibitors was corrected. The proposed definition is a more appropriate definition of resistance to PI3K inhibitors and aligned with the program language
- See Modification 7 for exclusion of patients with cytomegalovirus (CMV) infection.

Sections affected by these modifications: Synopsis, 5.1.2 Exclusion criteria

13.3.1.4 Modification 4 – change of extended period for 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: 6.3 Treatment assignment, 7.1.1 Tabulated overview, 7.1.2.2.1 Treatment – Cycle 1

13.3.1.5 Modification 5 – 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 ≥500/mm^3 for Day 8 and 15. 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 6–4 "Dose modification of copanlisib/placebo for hematological toxicity" was also modified accordingly.

Sections affected by this modification: 6.4 Dosage and administration, 6.4.1.1 Hematological toxicity

13.3.1.6 Modification 6 – guidance for management of toxicities added

Guidance in Table 6–4 "Dose modification of copanlisib/placebo for hematological toxicity" was updated: reference to patients with lymphomatous bone marrow infiltration was removed due to the new lowered ANC threshold (500 from 1000). INR and PTT ranges are clarified since they are not mentioned in Table 6–2.

Sections affected by this modification: 6.4 Dosage and administration, 6.4.1.1 Hematological toxicity

13.3.1.7 Modification 7 – addition of guidance for monitoring and prophylaxis of opportunistic infections (OI)

Following Health Authority alerts related to safety issues with Zydelig (idelalisib, a PI3K inhibitor) treatment in clinical trials, Section 6.4.2.7 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.

The guidance includes additional CD4, CD8, CMV and blood culture laboratory tests, and lung examinations to be monitored during study treatment in patients who are at risk of development of infections. Schedule of procedures were modified to be consistent with the OI guidance.

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. Reactivation means that acute infection needs treatment. Patients with chronic infection could be eligible as long as they do not exhibit symptoms of acute infection which should be confirmed by negative CMV PCR test at baseline.

These criteria were modified to avoid worsening of CMV infection in patients with active CMV and to harmonize the protocol with other copanlisib studies.

Sections affected by this modification: Synopsis, 5.1.2 Exclusion criteria, 5.2.1.1 Withdrawal of study treatment, 6.4.1.2 Non-hematological toxicity, 6.4.2.7 Guidance for monitoring and prophylaxis of opportunistic infection, 7.1.1 Tabulated overview, 7.1.2.1 Screening period, 7.1.2.2 Treatment period, 7.1.2.2.1 Treatment Cycle 1, 7.1.2.2.2 Treatment – Cycle 2 and higher, 7.5.3.1 Laboratory, 7.5.3.2.1 Complete physical examination, 7.5.3.2.2 Brief physical examination

13.3.1.8 Modification 8 – reference to patient's paper blood glucose tracking diary was added

Reference to patient's paper blood glucose tracking diary instructions was added to give guidance for glucose monitoring at home. The definition of glucose goal values was deleted since it is disclosed in the aforementioned document.

Section affected by this modification: 6.4.2.1 Management of transient post-infusion glucose increases that can occur with copanlisib

13.3.1.9 Modification 9 – clarification on procedure schedule

This modification clarifies when the ECG shall be measured on the days of rituximab infusion.

Section affected by this modification: 7.1.1 Tabulated overview

13.3.1.10 Modification 10 – change in agenda of procedures

The time for diagnostic procedure was increased to allow more flexibility for the sites and patients to collect diagnostic exams for patients with LPL/WM or WM and FL.

Sections affected by this modification: 7.1.1 Tabulated overview, 7.1.2.1 Screening period

13.3.1.11 Modification 11 – 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. A safety follow-up visit may occur 30 days (window of +5 days is allowed) after last treatment.

Sections affected by this modification: 4 Study design, 7.1.1 Tabulated overview, 7.1.2.5.1 Safety Follow-up, 7.5.1.3 Assessments and documentation of adverse events, 8.3.2 Safety variables

13.3.1.12 Modification 12 – clarification of language regarding ePRO devices

Language regarding the ePRO devices was modified for clarification.

Sections affected by this modification: 7.6.3 Electronic patient-reported outcomes evaluation

13.3.1.13 Modification 13 – clarification for prohibited concomitant therapy

The clarification for use of short-term systemic corticosteroids above 15 mg prednisolone or equivalent will be allowed prior to for radiological contrast infusion.

Section affected by this modification: 6.9.1 Prohibited concomitant therapy

13.3.1.14 Modification 14 - other clarifications and corrections

- Due to sponsor name change, sponsor information and sponsor logo were changed.
- Text was modified in Section 7.5.3.1 "Laboratory" and in Table 7–1 footnote "j" to allow site to provide differential blood count in percentage when absolute count is not available per standard of care of the local lab.
- It was clarified in Section 5.2.1.1 "Withdrawal of study treatment" that patients must (not may) be withdrawn from the study at the specific request of the sponsor and in liaison with the investigator.

- The dose modification guidance for the management of Hypertension of grade 3 was clarified in Table 6–8. If subjects developed grade 3 hypertension during infusion, it was clarified that study drug infusion may be resumed immediately when blood pressure has returned to < 150/90 mmHg, otherwise this dose will be skipped.
- Minor modifications regarding verapamil and diltiazem use were added to Section 6.9.2"Permitted concomitant therapy" to be consistent with Section 6.4.2.3 "Treatment of blood pressure increases associated with copanlisib"

Sections affected: Title page, 5.2.1.1 Withdrawal of study treatment, 6.4.1.2 Non-hematological toxicity, 6.9.2Permitted concomitant therapy, 7.1.1Tabulated overview, 7.5.3.1 Laboratory

13.3.2 Changes to the protocol text

Changes to the protocol text done in Amendment 7 are provided in Section 13.3.2 of Amendment 7.

13.4 Amendment 9

Amendment 9 is dated 02 FEB 2018.

13.4.1 Overview of changes

13.4.1.1 Modification 1 – 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 567 patients to 450 patients and primary efficacy analysis will be performed in the FAS instead of both FAS and FL subgroup.

Based on more updated site information, the recruitment ramp up period was increased from 6 months to 29 months and the dropout rate was increased from 20% to 30%.

In addition, minor clarifications were done in the statistical sections. The language regarding deaths that are related to PD was transferred from Section 8.3.1 to Section 8.3.1.2 since it is only applicable for the secondary efficacy variable "time to progression". Also, the definition of PFS was further clarified and the reference related to minimum number of PFS events was included in Section 8.4.2.

Sections affected by this modification: Synopsis, 4 Study design , 8.3.1 Efficacy variables, 8.3.1.2 Secondary efficacy variables, 8.4.1 Population characteristics, 8.4.2 Efficacy, 8.4.2.1 Primary efficacy analysis, 8.4.2.2 Secondary efficacy analysis, 8.4.2.3 Confirmatory statistical test strategy *(section removed)*, 8.4.2.4 Other efficacy evaluations, 8.4.3 Subgroup analyses, 8.4.4 Safety analyses, 8.6 Determination of sample size, 12 Reference list

13.4.1.2 Modification 2 – clarifications/modifications of inclusion criteria

Although introduced changes do not alter the essence of the protocol, some modifications were considered necessary to improve clarity of the protocol procedures.

Inclusion criterion 2 was clarified to provide less chance for misinterpretation. The definition of SLL was also adjusted to utilize more updated diagnostic definition of the pathology as well defining the requirements only for study entry.

Inclusion criterion 3 was modified to clarify that the requirement is applied for the last line of rituximab-containing therapy ensuring that the treatment was effective. Regarding the definition of a previous regimen, the specific requirement for rituximab monotherapy was included to ensure the alignment with the current clinical practice.

Inclusion criterion 4 was clarified. A footnote describing the minimum values for measurable disease according to the Lugano Classification was added. The requirement for splenic MZL was also clarified 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.

It was added that archival tumor tissue was to be obtained within 5 years of the consent date in inclusion criterion 9. The modification was done for further clarification.

Inclusion criterion 13 was adjusted to be consistent with exclusion criterion 4. In addition, following wording was harmonized throughout the protocol since there were minor variations although the meaning was the same: progression-free and treatment-free interval of ≥ 12 months after completion of the last rituximab containing treatment.

Sections affected by the modification: Synopsis, 1.2 Rationale for the study, 4 Study design, 5.1.1 Inclusion criteria, 6.3 Treatment assignment, 8.4.2.1 Primary efficacy analysis, 8.6 Determination of sample size

13.4.1.3 Modification 3 – clarifications/modifications of exclusion criteria

The requirement of "histologically confirmed diagnosis" was removed from exclusion criterion 3. A suspicion of FL grade 3b or transformed disease, or chronic lymphocytic leukemia should preclude the enrolment to the study. If confirmation is required, there is a potential risk of enrolling this unwarranted population.

For exclusion criterion 4, see Modification 13.4.1.4.

A reference to inclusion criterion 2 was added to exclusion criterion 5 to further clarify indolent B-cell NHL histologies that are allowed in the study.

Based on drug-drug interaction data, it was clarified that the use of **strong** inducers of CYP3A4 is prohibited (exclusion criterion 39). See also Modification 13.4.1.9.

Sections affected by the modification: Synopsis, 5.1.2 Exclusion criteria

13.4.1.4 Modification 4 – clarification of stratification factors related to entry criteria

The definition of stratification factor related to entry criteria was adjusted according to the clarification of inclusion criterion 13 (see Modification 13.4.1.2). Since inclusion criterion 13 was modified to be consistent with exclusion criterion 4, following wording was also harmonized in the definition of the entry criteria stratification factor: progression-free and treatment-free interval of ≥ 12 months after completion of the last rituximab containing treatment.

The patients considered unwilling/unfit to receive chemotherapy were bundled to differentiate them in a subgroup different from the long-term responders (i.e. progression-free and

treatment-free interval of ≥ 12 months after completion of the last rituximab containing treatment). In case a patient fulfills both entry criteria the preferential assignment should be for the group labeled as “unwilling/unfit to receive chemotherapy” providing a resolution to a possible impasse.

In addition, all applicable protocol sections were updated to clarify that patients may be unwilling or unfit to receive chemotherapy.

Sections affected by the modification: Synopsis, 1.2 Rationale for the study, 2 Study objectives, 4 Study design, 5.1.2 Exclusion criteria, 6.3 Treatment assignment, 8.4.2.1 Primary efficacy analysis, 8.6 Determination of sample size

13.4.1.5 Modification 5 – 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 (at the lowest study drug dose level) for persistent occurrence of post-infusion blood glucose was modified from > 400 mg/dL to > 500 mg/dL.

The language related to meal timing on infusion days was revised. Based on available safety data, fasting status has no significant clinical impact on post-infusion blood glucose. 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 language was changed to allow investigator to determine if home glucose monitoring is needed 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 site compliance. 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/demonstrate that HbA1C elevations revert to baseline after stopping copanlisib.

Sections affected by this modification: 5.2.1 Withdrawal, 5.2.1.1 Withdrawal of study treatment, 6.4 Dosage and administration, 6.4.1.2 Non-hematological toxicity, 6.4.2.1 Management of transient post-infusion glucose increases that can occur with copanlisib, 7.1.1 Tabulated overview, 7.1.2.1 Screening period, 7.1.2.2.1 Treatment – Cycle 1, 7.1.2.2.2 Treatment – Cycle 2 and higher, 7.1.2.5 Follow-up periods, 7.5.3.7 Glucose measurement on copanlisib/placebo infusion days, 12 Reference list, 14.8 The average glycemic index of common foods derived from multiple studies by different laboratories (*section removed*)

13.4.1.6 Modification 6 – modification of the monitoring guidelines for OI

To facilitate the patient adherence to the protocol requirements, 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 a suggestion and should be addressed by the standard of care followed by the institution.

Sections affected by the modification: 6.4.2.7.1 Monitoring guidelines for OI, 7.1.1 Tabulated overview, 7.1.2.2 Treatment period

13.4.1.7 Modification 7 – updated guidance for blood pressure measurements on infusion days

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.

Sections affected by this modification: 7.1.1 Tabulated overview, 7.1.2.2.1 Treatment – Cycle 1, 7.1.2.2.2 Treatment – Cycle 2 and higher, 7.5.3.3 Vital signs

13.4.1.8 Modification 8 – clarification of bone marrow assessments

It was clarified that bone marrow biopsy should be evaluated first locally and the surplus material, if available, should be provided to central pathology review. The text was aligned with other copanlisib protocols.

Protocol was also modified to remind about the need for bone marrow evaluation for those patients who had previous lymphoma in the bone marrow.

Sections affected by the modification: Synopsis, 4 Study design, 7.1.1 Tabulated overview, 7.1.2.1 Screening period, 7.1.2.3 Tumor assessments, 7.1.2.5.2 Active follow-up

13.4.1.9 Modification 9 – changes based on drug-drug interaction data

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.

The list of strong CYP3A4 inhibitors and inducers was updated and it was further clarified that the use of strong inhibitors of CYP3A4 and strong inducers of CYP3A4 is not permitted.

To be aligned at the project-level, the guidance text for the use of substrates of the renal drug transporter MATE2K was included to the protocol.

Sections affected by this modification: 5.1.2 Exclusion criteria, 6.4.2.3 Treatment of blood pressure increases associated with copanlisib, 6.9.1 Prohibited concomitant therapy, 6.9.2 Permitted concomitant therapy, 12 Reference list, 14.1 CYP3A4 inhibitors and inducers

13.4.1.10 Modification 10 – introduction of dose interval for rituximab

Due to differences between different body surface area calculation methods the final rituximab dose may present variation. To acknowledge these differences, which are not medically significant, an interval was granted.

Sections affected by the modification: 6.4 Dosage and administration

13.4.1.11 Modification 11 – clarifications of the tumor assessment/response evaluation

The response criteria in patients affected by WM were clarified: “lowest nadir” was changed to “nadir confirmed by a repeat assessment” since nadir is already the definition of the lowest point and the assessment must be confirmed.

Sections affected by the modification: 14.4 Evaluation of tumor response

13.4.1.12 Modification 12 – clarification of PK sampling and analysis

It was clarified that PK sampling should be done on the corresponding days with the matched medication if samples are collected at Cycle 3 (rituximab infusion is performed on Day 1 of Cycle 3).

It was also clarified that a population pharmacokinetic analysis will be reported in a standalone report.

Sections affected by the modification: 7.4.1 Sampling, 7.4.2 Analysis

13.4.1.13 Modification 13 – clarification of QoL questionnaire schedule

The timing of the completion of FLymSI-18 questionnaire was further clarified. The questionnaire should be completed at the visits where it is scheduled to be completed i.e. during the treatment period, the questionnaire is completed at the start of the infusion day and not during visits on previous days.

Sections affected by the modification: 7.1.2.2.1 Treatment – Cycle 1, 7.1.2.2.2 Treatment – Cycle 2 and higher, 7.6.2 Quality of life questionnaire

13.4.1.14 Modification 14 – administrative changes

The sponsor’s medically responsible person was changed as a result of study personnel change.

The Coordinating Co-Investigator was changed.

Sections affected by this modification: Signature of the sponsor’s medically responsible person, 3 Investigator and other study personnel

13.4.1.15 Modification 15 – other clarifications and corrections

- The term "unblinded monitor" was changed to "independent monitor" in Section 6.5 Blinding
- Oudated recommendation (a fresh biopsy is recommended in patients with clinical suspicion of transformed disease) was deleted from Synopsis since this recommendation had been removed from the main protocol already in Amendment 1.
- The way changes are indicated throughout the protocol body was updated for better readability. Instead of indicating all changes separately in the protocol text, a general statement and a cross-reference to the respective amendment section was included to each amended section.

13.4.2 Changes to the protocol text

Changes to the protocol text done in Amendment 9 are provided in a separate track changes version.

13.5 Amendment 10

13.5.1 Overview of changes

Amendment 10 is dated 08 OCT 2019.

Section(s)	Description of change	Rationale
4 Study design 8.4.2 Efficacy 8.6 Determination of sample size 12 Reference list	The statistical assumptions for the primary efficacy analysis of PFS were modified. The required number of PFS events was changed from 288 to 190.	A recent study (AUGMENT, 51) has reported a hazard ratio of 0.46 (95% CI 0.34-0.62) for PFS and median PFS of 14.1 months in Rituximab + Placebo arm in the indication of second line iNHL. Based on the results from this study, it was decided to update the sample size justification
Synopsis 8.4.2.1 Primary efficacy analysis 8.4.2.2 Secondary efficacy parameters 8.4.2.3 Confirmatory statistical test strategy	The confirmatory testing hierarchy was modified to include a sequential test of PFS in the overall iNHL population, PFS in the combined FL and MZL population, ORR in the combined FL and MZL population, PFS in the SLL population, DRS-P deterioration and DRS-P improvement in the combined FL and MZL population.	• FL + MZL are the most common types of indolent non-Hodgkins lymphomas. • Rituximab-based treatment is standard for both FL and MZL lymphomas. • FL + MZL are responsive to PI3K inhibition. Combination of both lymphomas into one analysis cohort would increase the statistical power of the result.
Synopsis Definitions of terms 5.1.1 Inclusion criteria	The protocol was modified to allow prior anticancer therapies with rituximab biosimilars, and/or anti-CD20 monoclonal	The change was done considering the current iNHL treatment landscape and following the investigator's

5.1.2 Exclusion criteria	antibody (e.g. obinutuzumab).	feedback.
Synopsis 4 Study design 7.1.1 Tabulated overview 7.1.2.3 Tumor assessments 7.3.2 Radiological tumor assessments	The language related to the schedule of radiological tumor assessments was modified.	To allow the collection of tumor imaging data for beyond 3 years since patients may continue in the study for more than 3 years.
Synopsis 4 Study design 7.3.2 Radiological tumor assessments	It was clarified that radiological real-time confirmation of disease progression will only be performed until the database cut-off for the primary analysis.	To allow retrospective reading of the scans after the primary completion.
6.9.1 Prohibited concomitant therapy	The use of biotin was 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 produces high levels of the vitamin, these can interfere with the result of the immunoassay test.
Synopsis 4 Study design 5.1.1 Inclusion criteria 7.1.1 Tabulated overview 7.4.1 Sampling 7.6.1 Biomarker investigations	It was clarified that PK and biomarker samplings are not applicable to sites who cannot obtain approval by competent Health Authority.	To add flexibility for the sample availability from China due to the limitation from CHGRAO.
5.2.1.1 Withdrawal of study treatment 6.4.1.2 Non-hematological toxicity	NIP of any grade is no longer a withdrawal criterion, only grade ≥3 (or recurrent grade 2).	Actions to be taken regarding the AESI NIP were updated to reflect the approved label and to align with other program protocols.
Title page Signature of the sponsor's medically responsible person 3 Investigator and other study personnel	Sponsor's medical expert and medically responsible person were changed.	Administrative change.
13.1.2, 13.2.2 and 13.3.2 Changes to the protocol text	The detailed old vs. new text comparisons for protocol amendments 1, 6 and 7 were replaced with a reference to the respective protocol amendment.	To improve readability, and to reduce complexity of the protocol.

13.5.2 Changes to the protocol text

Changes to the protocol text done in Amendment 10 are provided in a separate track changes version.

13.6 Amendment 11

13.6.1 Overview of changes

Amendment 11 is dated 22 MAY 2020.

Section(s)	Description of change	Rationale
4. Study design 8.4.2 Efficacy 8.6 Determination of sample size	Text for time point of primary analyses was slightly revised for more flexibility.	A minimum of 190 events in iNHL population is needed. However, by the time of database lock, there will be more than 190 events expected. The study power of the results increases with the number of events. If the study is closed with at least 190 PFS events, there is no negative impact on study outcome.
2. Synopsis 8.4.2.1 Primary efficacy analysis	Stratification factors “bulky disease [yes vs. no]” and “previous treatment with PI3K inhibitors [yes vs. no]” are removed in the statistical analysis	In order to avoid a too low number of events, only stratification factors “NHL history” and “entry criterion” will be adjusted at the same time in the statistical analyses.
2. Synopsis 8.4.2.2 Secondary efficacy parameters 8.4.2.3 Confirmatory statistical test strategy	The testing of PFS in SLL population is removed from the confirmatory statistical test strategy for the United States.	The treatment effect may not be detected due to the small sample size in SLL.
2. Synopsis 8.4.2.3 Confirmatory statistical test strategy	A separate confirmatory statistical test strategy for Europe is added.	To maximize the study power, all statistical tests will be conducted in the FAS population.
8.4.2.3 Confirmatory statistical test strategy 8.6 Determination of sample size	Power estimation is updated based on blinded study information using Schoenfeld’s formula	To confirm the study has enough power to reject null hypothesis for the testing of primary efficacy endpoint and key secondary efficacy endpoints.
2. Synopsis 4. Study design 6.8 Post-study therapy	The option for patients currently receiving treatment in this study to continue treatment in a roll-over study was added.	To enable patients receiving copanlisib treatment in the current study to continue to receive copanlisib treatment when the study is completed.
Title page Signature of the sponsor’s medically responsible person	The signature of the Sponsor’s medically responsible person was removed from the clinical study protocol.	Administrative change of Bayer process
	Editorial changes and clarifications	

13.6.2 Changes to the protocol text

Changes to the protocol text done in Amendment 11 are provided in a separate track changes version.

13.7 Amendment 12

13.7.1 Overview of changes

Amendment 12 is dated 09 FEB 2023.

Section(s)	Description of change	Rationale
Synopsis 4. Study design 5.2.1.2 Withdrawal from follow-up period 7.1.1 Tabulated overview 7.1.2.5.3 Survival follow-up 8.4.2.2 Secondary efficacy parameters	Survival follow-up period extended up to 7 years after the last patient started study treatment.	The extension of survival follow-up period from 3 years up to 7 years would allow long-term assessment of OS as both a safety and efficacy endpoint. The follow-up period may be extended based on emerging clinical data by the sponsor after consultation with the investigators and notification of IECs / IRBs. Once the study is analyzed for survival at 7 years after the last patient started study treatment, any patients still on treatment may continue to be treated under a separate provision to be determined.
Synopsis 3. Investigator and other study personnel 4. Study design 7.1.1 Tabulated overview 7.1.2 Timing of assessment 7.3 Efficacy 7.5.3 Further safety 7.6.2 Quality of life questionnaire 7.6.3 Electronic patient reported outcomes evaluation (deleted section) 12. Reference list 14.5 Quality of life questionnaire: FLymSI-18	Reduced efficacy and safety assessments: • Central assessment of tumor images will no longer be performed • Central assessment of bone marrow biopsy will no longer be performed • No further data collection is required for the QoL questionnaires • Glucose and blood pressure measurements required prior to copanlisib/placebo infusion • Urinalysis no longer required	Study 17067 achieved primary completion as well as 1-year and 2-year follow-up. The study met its primary endpoint and, therefore, central review of tumor images is no longer deemed necessary. In addition, sufficient PRO data have been collected for the analyses in this study, and no further data collection is considered necessary. Some safety assessments have also been simplified to decrease patient burden, since the safety profile of copanlisib in combination with rituximab was established and is known by the investigators (i.e., reduction in blood pressure and glucose assessment frequency, and removal of urinalysis assessment).
6.2 Identity of investigational medicinal products	Added guidance for study drug storage, accountability, reconciliation, and record maintenance	Clarification to comply with the requirement of the EU CTR 536/2014.
4. Study design	Reference to sponsor's Global	Clarification: SAE forms are

7.1.2.5.2 Active follow-up 7.5.1.3 Assessments and documentation of adverse events	Pharmacovigilance (GPV) changed to sponsor's Pharmacovigilance (PV).	submitted to the local PV department.
6.5 Blinding	Deletion of independent monitor text.	Following the primary completion, the pharmacy monitoring responsibilities were transferred from an independent unblinded monitoring team to a blinded monitoring team. The rationale for this was based on advances in the chemical development of copanlisib (lighter color) leading to a reduced need for blinding measures, a very low number of unblinding incidents reported during the study, and the risk of unblinding during monitoring being considered extremely low.
Synopsis 4. Study design 6.8 Post study therapy	Text updated re. ROS and other mechanism to supply study drug post study.	Clarification on mechanisms to supply study drug post study.
8.4.1 Population characteristics	A clarification was added regarding the information on central pathology evaluation of tumor histology. The data are exploratory and therefore will be provided as a listing.	Clarification.
11.3 Publication policy	Text re. disclosure of the study results added.	Clarification to comply with the requirement of the EU CTR 536/2014.
14.6 Glomerular filtration rate	A link to www.kidney.org online calculator removed.	The online calculator is no longer available on the website.
3. Investigator 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.
Cover page 13.8 Country/region-specific requirements	Country-specific already approved modifications listed in the newly added section.	To comply with the requirement of the EU CTR 536/2014.
Across the document	Minor 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 including EU CTR 536/2014.

13.7.2 Changes to the protocol text

Changes to the protocol text done in Amendment 12 are provided in a separate track changes version.

13.8 Country/region-specific requirements

13.8.1 Ireland, Germany and Belgium

Local Amendment 2 dated 11 MAY 2015 specific for Ireland, Germany and Belgium only.

13.8.1.1 Overview of Changes

13.8.1.1.1 Modification 1: Clarification of adequate contraception

Text was added in the inclusion criteria to specify adequate contraception, to provide definition of a woman of childbearing potential (WOCBP) and to clarify the required time period of contraceptive use for women and men of reproductive potential. In addition, it was clarified that the use of condoms by patients or their partners is required unless the woman has had a hysterectomy. These changes were made because the local health authorities require to include a detailed description of contraception.

Clinical study protocol section affected by this modification:

5.1.1 Inclusion criteria

13.8.1.2 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.

13.8.1.2.1 Section 5.1.1 Inclusion criteria

This section was changed as a result of Modification 1.

Old text:

10. Women ~~of childbearing potential~~ and men must agree to use adequate contraception when sexually active. This applies ~~since~~ signing of the informed consent form ~~until at least 3 months~~ after the last ~~study drug administration~~. The investigator or a designated associate is requested to advise the patient ~~how to achieve~~ ~~an adequate~~ birth control. ~~Adequate contraception is defined in the study as any medically recommended method (or combination of methods) as per standard of care.~~

New Text:

10. Women and men of reproductive potential must agree to use adequate contraception when sexually active. This applies for the time period between signing of the informed consent form and 12 months (for women of childbearing potential) and 3 months (for fertile men) after the last administration of study treatment.
A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent

sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 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. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.
The investigator or a designated associate is requested to advise the patient (WOCBP or men who have not undergone bilateral orchidectomy) on the use of highly effective birth control methods (i.e. those with failure rates of less than 1%). Such methods include: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable and implantable), intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomised partner and sexual abstinence. In addition, the use of condoms by patients or their partners is required unless the woman has had a hysterectomy.

13.8.2 France

Local Amendment 3 dated 25 AUG 2015 specific for France only.

13.8.2.1 Overview of Changes

13.8.2.1.1 Modification 1: Clarification of contraception requirements

Text was added in the inclusion criteria to specify adequate contraception, to provide definition of a woman of childbearing potential (WOCBP) and of a fertile man, and to clarify the required time period of contraceptive use for women and men of reproductive potential. In addition, it was clarified that the use of condoms by male patients is required unless the female partner is permanently sterile. These changes were made because of the need to integrate request from the French health authority ANSM, and to reach compliance with the current recommendations related to contraception use. These changes will be later implemented into a global amendment.

Clinical study protocol section affected by this modification:

5.1.1 Inclusion criteria

13.8.2.1.2 Modification 2: Pregnancies

Text was added in Section 7.5.2 to specify the action to be taken by the investigators in the event that a pregnancy occurs during the study participation. These changes were made because of the need to integrate request from the French Ethics Committee.

Clinical study protocol section affected by this modification:

7.5.2 Pregnancies

13.8.2.1.3 Modification 3: Clarification of copanlisib/placebo treatment

To fulfill the request by the French Ethics Committee, it was clarified in the protocol that copanlisib/placebo will be provided free of charge to patients until the occurrence of PD (per central independent blinded radiology review) as defined in the Lugano Classification (for

patients with WM according to the Owen Criteria), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment.

Clinical study protocol section affected by this modification:

Section 4 Study design – End of study

13.8.2.1.4 Modification 4: Administrative change

The sponsor's medically responsible person was changed.

Clinical study protocol section affected by this modification:

Signature of the sponsor's medically responsible person

13.8.2.2 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.

13.8.2.2.1 Section 4 Study design

This section was changed as a result of Modification 3.

Old text:

End of study

For each participating European Union (EU) country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last patient for all centers in the respective country has occurred.

The end of study as a whole will be reached as soon as the end of the study according to the above definition has been reached in all participating countries (EU and non-EU).

New text:

End of study

Treatment with copanlisib or placebo will be continued free of charge until the occurrence of PD (per central independent blinded radiology review) as defined in the Lugano Classification (for patients with WM according to the Owen Criteria), unacceptable toxicity, or until another criterion is met for withdrawal from the study treatment (see Section 5.2.1.1).

For each participating European Union (EU) country, the end of the study according to the EU Clinical Trial Directive will be reached when the last visit of the last patient for all centers in the respective country has occurred.

The end of study as a whole will be reached as soon as the end of the study according to the above definition has been reached in all participating countries (EU and non-EU).

13.8.2.2.2 Section 5.1.1 Inclusion criteria

This section was changed as a result of Modification 1.

Old text:

10. Women ~~of childbearing potential~~ and men must agree to use adequate contraception when sexually active. This applies ~~since~~ signing of the informed consent form ~~until at least 3 months~~ after the last ~~study drug administration~~. The investigator or a designated associate is requested to advise the patient how to achieve ~~an adequate~~ birth control. ~~Adequate contraception is defined in the study as any medically recommended method (or combination of methods) as per standard of care.~~

New text:

10. Women and men of reproductive potential must agree to use adequate contraception when sexually active. This applies for the time period between signing of the informed consent form and 12 months (for women of childbearing potential) and 5 months (for fertile men) after the last administration of study treatment. A woman is considered of childbearing potential (WOCBP), 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 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. A man is considered fertile after puberty unless permanently sterile by bilateral orchiectomy.

    The investigator or a designated associate is requested to advise the patient (WOCBP or men who have not undergone bilateral orchiectomy) how to achieve highly effective birth control method (failure rate of less than 1%), e.g. hormonal contraception associated with inhibition of ovulation, intrauterine device (IUD), intrauterine hormone-releasing system (IUS), bilateral tubal occlusion, vasectomized partner, sexual abstinence.

    In addition, the use of condoms by male patients is required unless the female partner is permanently sterile.

13.8.2.2.3 Section 7.5.2 Pregnancies

This section was changed as a result of Modification 2.

Old text:

[…]

The sponsor usually does not gather information of drug exposure via the father, however, if such cases are reported, all efforts should 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.

New text:

[…]

The sponsor usually does not gather information of drug exposure via the father, however, if such cases are reported, all efforts should 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.

Due to the mechanism of action of copanlisib as a PI3K inhibitor, adverse effects on reproduction and development are expected. This was confirmed in a developmental toxicity study in rats.

As a consequence, if a pregnancy occurs during the critical period of conceiving, i.e. the treatment period plus 5 months (for male patients) and 12 months (for female patients, according to manufacturer's recommendations for rituximab) after treatment, the investigator should inform the pregnant patient or the pregnant partner of the patient of the potential risk for the unborn child in order for the patient to make an informed decision about the continuation or the termination of pregnancy.

13.8.2.2.4 Signature of the sponsor's medically responsible person

This section was changed as a result of Modification 4.

Old text:

Name: PPD Role: PPD

New text:

Name: PPD Role: PPD

13.8.3 Denmark

Local Amendment 4 dated 01 SEP 2015 specific for Denmark only.

13.8.3.1 Overview of Changes

13.8.3.1.1 Modification 1: Clarification of SAE reporting language

To fulfill the request by the Danish Health and Medicines Authority (DHMA), the language regarding reporting of SAEs occurring after the protocol-defined observation was modified to meet the current EU regulations. This change will be later implemented into a global amendment.

Clinical study protocol section affected by this modification:

7.5.1.4 Reporting of serious adverse events

13.8.3.1.2 Modification 2: Administrative change

The sponsor's medically responsible person was changed.

Clinical study protocol section affected by this modification:

Signature of the sponsor's medically responsible person

13.8.3.2 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.

13.8.3.2.1 Section 7.5.1.4 Reporting of serious adverse events

This section was changed as a result of Modification 1.

Old text:

Investigator's notification of the sponsor

[…]

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.

~~It is not mandatory to report SAEs occurring after the protocol defined observation period (see Section 7.5.1.3); however, at the investigator's discretion these may be reported if considered potentially relevant. In such cases, the SAEs will be processed by the sponsor according to all applicable regulations.~~

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 International Conference on Harmonization (ICH) criteria for an SAE (see SAE definition in Section 7.5.1.1).

[…]

New text:

Investigator's notification of the sponsor

[…]

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.

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 International Conference on Harmonization (ICH) criteria for an SAE (see SAE definition in Section 7.5.1.1).

[…]

13.8.3.2.2 Signature of the sponsor's medically responsible person

This section was changed as a result of Modification 2.

Old text:

Name: PPD Role: PPD

New text:

Name: PPD Role: PPD

13.8.4 Turkey

Local Amendment 5 dated 13 OCT 2015 specific for Turkey only.

13.8.4.1 Overview of Changes

13.8.4.1.1 Modification 1: Plasma for non-genetic biomarker tests

To fulfill the request by the Turkish Ethics Committee, the language describing the use of plasma for non-genetic biomarker tests was clarified.

Clinical study protocol section affected by this modification:

7.6.1 Biomarker investigations

13.8.4.1.2 Modification 2: Administrative change

The sponsor's medically responsible person was changed.

Clinical study protocol section affected by this modification:

Signature of the sponsor's medically responsible person

13.8.4.2 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 <u>underlined</u> in the "*new text*". Corrections of typos or omissions are not highlighted.

13.8.4.2.1 Signature of the sponsor's medically responsible person

This section was changed as a result of Modification 2.

Old text:

Name: PPD Role: PPD

New text:

Name: PPD Role: PPD

13.8.4.2.2 Section 7.6.1 Biomarker investigations

This section was changed as a result of Modification 1.

Old text:

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 Table 7-1). Plasma may be used to quantify the circulating levels of various proteins.

New text:

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 Table 7-1). Plasma may be used to quantify the circulating levels of various proteins including cancer markers, cytokines, chemokines, metabolic markers, hormones, growth factors, tissue remodeling proteins, angiogenesis markers, acute phase reactants, kidney damage markers and other important circulating proteins to understand biological activity, efficacy, and safety profile of the drug as well as the disease. The list of markers is provided in the local informed consent form.

13.8.5 Japan

Local Amendment 8 dated 18 APR 2017 specific for Japan only.

13.8.5.1 Overview of Changes

13.8.5.1.1 Modification 1: 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 PMDA, IECs/IRBs and investigators. A new section was added to include this requirement.

Clinical study protocol sections affected by this modification:

Section 7.5.3.8 Reporting of medical device failures (new section was added).

13.8.5.2 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, additions are underlined in the "*new text*".

New text:

Section 7.5.3.8 Reporting of medical device failures

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.

14. Appendices

14.1 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, troleoandomycin, 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: 41, 48, 49 and 50.

14.2 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all pre-diseases performance without restriction. (Karnofsky 90-100)
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). (Karnofsky 70-80)
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. (Karnofsky 50-60)
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)

14.3 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 (42)

14.4 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 (27).

	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 not assessable: IHC negative
PR	Decrease ≥ 50% in the SPD from baseline		All normal or stable	Spleen must have regressed by 50% in extent beyond normal at baseline (=value over 13 cm)	No	Not relevant
Stable disease	• Decrease < 50% in the SPD from baseline • No criteria for PD		All normal or stable	Normal size or stable size	No	Not relevant
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 = disease progression; PPD = product of perpendicular diameters; PR = partial response; SDi = shortest diameter; SPD = sum of the product of the diameters

* If LDi ≤ 2 cm 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.

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	• ≥ 25% increase in serum IgM level from nadir confirmed by a repeat assessment (an absolute value increase 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

Source: Adapted from Owen RG et al, 2013 (35)

14.5 Quality of life questionnaire: FLymSI-18

Appendix removed by amendment 12.

14.6 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, 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).

The above result should be multiplied by 1.212 for African-Americans.

Patients with a baseline GFR < 30 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 acceptable range, it may be used to fulfill the inclusion criteria instead.

For further information on assessing renal function using GFR estimates, see references 43, 44 and 45.

14.7 Cumulative Illness Rating Scale for Geriatrics (CIRS-G)

Scoring Sheet

CUMULATIVE ILLNESS RATING SCALE FOR GERIATRICS (CIRS-G)

Miller, Paradis, and Reynolds 1991

PATIENT_____**AGE**_____

RATER_____**AGE**_____

Instructions: Please refer to the CIRS-G Manual. Write brief descriptions of the medical problem(s) that justified the endorsed score on the line following each item. (Use the reverse side for more writing space).

RATING STRATEGY

0 - No Problem
1 - Current mild problem or past significant problem
2 - Moderate disability or morbidity/requires "first line" therapy
3 – Severe/constant significant disability / "Uncontrollable" chronic problems
4 - Extremely Severe/immediate treatment required/end organ failure/severe impairment in function

	SCORE
HEART	_____
VASCULAR	_____
HEMATOPOIETIC	_____
RESPIRATORY	_____
EYES, EARS, NOSE AND THROAT AND LARYNX	_____
UPPER GI	_____
LOWER GI	_____
LIVER	_____
RENAL	_____
GENITOURINARY	_____
MUSCULOSKELETAL/INTEGUMENT	_____
NEUROLOGICAL	_____
ENDOCRINE/METABOLIC AND BREAST	_____
PSYCHIATRIC ILLNESS	_____
TOTAL NUMBER CATEGORIES ENDORSED	_____
TOTAL SCORE	_____
Severity Index: (total score/total number of categories endorsed)	_____
Number of categories at level 3 severity	_____
Number of categories at level 4 severity	_____

Source: (28), GI = Gastrointestinal

14.8 The average glycemic index of common foods derived from multiple studies by different laboratories section removed

Appendix removed by amendment 9.